The Selection and Use of Essential Medicines

Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2023 (including the 23rd WHO Model List of Essential Medicines and the 9th WHO Model List of Essential Medicines for Children)

World Health Organization

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Executive summary

The meeting of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines took place in person in Geneva, Switzerland, from 24 to 28 April 2023. The aim of the meeting was to review and update the 22nd WHO Model List of Essential Medicines (EML) and the 8th WHO Model List of Essential Medicines for Children (EMLc) (the "Model Lists").

Essential medicines are those that satisfy the priority health care needs of a population. They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety, and comparative cost–effectiveness. They are intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford.

The WHO Model Lists are updated every two years, intended as a guide for countries or regional authorities to adopt or adapt in accordance with local priorities and treatment guidelines for the development and updating of national essential medicines lists. Selection of a limited number of medicines as essential, taking into consideration national disease burden and clinical need, can lead to improved access through streamlined procurement and distribution of quality-assured medicines, support more rational or appropriate prescribing and use, and lower costs for both health care systems and for patients.

The Expert Committee considered a total of 85 applications, including 52 proposals for the addition of new medicines or medicine classes, nine proposals for new indications for 22 currently listed medicines, nine proposals for the addition of new formulations of currently listed medicines, six proposals for the removal of 13 medicines, formulations or indications, and nine proposals for other changes to current listings on the Model Lists. In accordance with applicable procedures[1], the Expert Committee reviewed and evaluated the scientific evidence for the effectiveness, safety and comparative cost–effectiveness of the medicines in question. The Committee also considered a review of the age-appropriateness of formulations of essential medicines for children on the EMLc.

In summary, the Expert Committee:

- recommended the addition of 25 new medicines to the EML (16 to the core list and nine to the complementary list);

- recommended the addition of 13 new medicines to the EMLc (nine to the core list and four to the complementary list);

- recommended adding additional indications for 16 currently listed medicines;

- recommended the addition of new formulations of 22 medicines on the EML and of medicines on the EMLc;

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[1] https://apps.who.int/gb/ebwha/pdf_files/EB109/eeb1098.pdf

- recommended the deletion of three medicines from the EML and three medicines from the EMLc and of specific formulations of a further 13 medicines from the EML and 23 medicines from the EMLc; and

- did not recommend proposals for inclusion, change or deletion for 32 medicines, medicine classes or formulations.

The recommended changes bring the total number of medicines (including fixed-dose combinations) on the EML to 502 (from 479 in 2021), including 361 on the EMLc (from 350 in 2021).

Changes to the Model Lists are shown in Tables 1–3. Applications for proposed changes to the Model Lists that were not recommended are shown in Table 4.

Section 1: Anaesthetics, preoperative medicines and medical gases
Section 1.1.1 Inhalational medicines

The Expert Committee recommended the inclusion of sevoflurane as an inhalational anaesthetic on the core list of the EML and EMLc based on evidence of similar efficacy and safety to currently listed isoflurane. The Committee noted that sevoflurane has a lower global warming potential than other volatile anaesthetics, particularly desflurane, which is not listed as an essential medicine, but also halothane and isoflurane, which are both currently included. More efficient use of sevoflurane, in preference to other inhalational anaesthetics, can contribute to reducing greenhouse gas emissions and the environmental impact of climate change.

Section 2: Medicines for pain and palliative care
Section 2.2 Opioid analgesics

The Expert Committee did not recommend the inclusion of fast-acting oral transmucosal formulations of fentanyl citrate on the EML for the treatment of breakthrough cancer pain based on significant incremental costs compared to immediate-release oral morphine, which were considered disproportionate to the marginal incremental benefits. The Committee also noted that fentanyl has much higher potency and more drug-interactions than other opioids, which limit its manageability. The Committee was also concerned that transmucosal fentanyl formulations have greater potential for misuse and addiction.

Section 5: (renamed) Medicines for diseases of the nervous system

This section of the Model Lists has been renamed from "Anticonvulsants/antiepileptics" to "Medicines for diseases of the nervous system" and includes new subsections for antiseizure medicines, medicines for multiple sclerosis and medicines for parkinsonism (formerly listed in Section 9).

The Expert Committee did not recommend inclusion of donepezil on the EML for the treatment of dementia due to Alzheimer disease. The Committee noted that moderate-certainty evidence suggested donepezil may be associated with short-term improvements in cognitive outcome scores compared with placebo. However, these improvements are unlikely to be clinically

meaningful. The Committee noted that the evidence suggests that the effect on activities of daily living is limited and there is no impact on behavioural symptoms and quality of life and a lack of longer-term clinical cognitive benefits. The Committee noted that adverse effects of donepezil are generally mild, but the risk increases with higher doses, (those associated with greater cognitive benefits in the short term), and there is potential for numerous drug-drug and drug-disease interactions. The Committee considered that the patients included in dementia trials are generally younger and characterized by a better performance than patients seen in routine dementia care, affecting the generalizability of trial results. Consequently, the Committee considered the overall benefit-to-harm profile of the medicine to be unfavourable.

The Expert Committee did not recommend inclusion of risdiplam on the core list of the EML and EMLc for treatment of spinal muscular atrophy. The Committee noted that the body of evidence for efficacy and safety of risdiplam in spinal muscular atrophy is still limited, with only a small number of patients exposed to long-term treatment. The Committee, therefore, considered that the overall magnitude and long-term duration of benefits and potential harms were still uncertain. The Committee noted that based on the available evidence in patients with symptomatic disease, improvements in motor function were observed in younger children (younger than 5 years) but that these improvements became increasingly less prominent in older children, adolescents and adults. The Committee took note of ongoing clinical trials of risdiplam in presymptomatic infants up to 6 weeks of age and the introduction of routine newborn screening for spinal muscular atrophy in some settings and considered that the outcomes of these trials and screening programmes would be informative for future consideration of risdiplam for inclusion on the Model Lists.

Section 5.1 (new sub-section) Antiseizure medicines

The Expert Committee recommended the inclusion of oral levetiracetam on the core list of the EML and EMLc for the treatment of focal-onset and generalized-onset seizures in adults in children. The Committee also recommended the inclusion of parenteral levetiracetam on the complementary list of the EML and EMLc for use in the management of benzodiazepine-refractory status epilepticus. These recommendations were made based on evidence of effectiveness and safety, and in recognition of the need for treatment strategies for people with epilepsy to be individualized taking into account multiple factors including, but not limited to, pregnancy and patient preferences, seizure type, comorbidities, and concomitant use of other medications. These recommendations are also aligned with expected recommendations in the updated WHO Mental Health Gap Action Programme (mhGAP) guidelines.

Section 5.2 (new sub-section) Medicines for multiple sclerosis

The Expert Committee recommended the inclusion of cladribine, glatiramer acetate and rituximab as individual medicines on the complementary list of the EML for the treatment of multiple sclerosis. The Committee did not recommend the inclusion of ocrelizumab for this indication, either as an individual medicine, or as a therapeutic alternative to rituximab under a square box listing.

The Committee noted that multiple sclerosis is the most common non-traumatic cause of neurological disability in young adults, with approximately 2.8 million people living with multiple

sclerosis worldwide. Until now, the EML has not included any medicines for the treatment of multiple sclerosis. The Committee considered that the inclusion of effective and safe treatments for multiple sclerosis on the EML would address an important public health need and support global advocacy efforts to reduce the global burden of multiple sclerosis, especially in low- and middle-income countries.

The Committee acknowledged the availability of a large number of disease-modifying medicines for multiple sclerosis (particularly for the treatment of relapsing and remitting forms of the disease) and the need to prioritize the most effective, tolerable and affordable options. The Committee considered that the approach taken in the application submitted by the Multiple Sclerosis International Federation (MSIF) to identify which medicines to prioritize for EML listing from among the many available was comprehensive, up-to-date, transparent, robust and evidence based. The Committee recognized the value of involving different organizations and stakeholders at the global level, including consultation with people living with multiple sclerosis. The Committee considered that the application's selection of cladribine, glatiramer acetate and rituximab as priority medicines for EML inclusion was well justified and supported by evidence of clinical benefit and safety across different settings, as well as suitability for use in different patient populations (e.g. pregnant women) and feasibility. The inclusion on the EML of three medicines, with different routes of administration, different prices (including the availability of generics and biosimilars) and different recommended uses, would provide valuable options for patients and national selection decisions and could facilitate improved access to treatment for people living with multiple sclerosis. The Committee acknowledged that rituximab does not have market authorization by regulatory authorities for treatment of multiple sclerosis and is thus used "off-label" for this indication. The Committee reiterated that the Model List can play an important role in identifying those medicines for which off-label use is supported by convincing evidence, complementing the assessment and labelling by jurisdictional authorities.

The Committee acknowledged the benefits of ocrelizumab in the management of relapsing and primary progressive forms of multiple sclerosis. However, there was no compelling evidence of its superiority over other alternatives, specifically rituximab, which has the same target (CD20) and a similar peptide sequence, is widely used, more affordable and reimbursed for use in multiple sclerosis in several countries. The Committee considered the option of listing ocrelizumab as an alternative to rituximab, but also recognized the large difference in current prices of the two products which decreases ocrelizumab competitiveness. The Committee concluded that including ocrelizumab as a therapeutic alternative to rituximab could result in considerable additional expenditure at the country level for patients and health systems, without offering additional clinical benefit.

Section 6: Anti-infective medicines
Section 6.2.1 Access group antibiotics

The Expert Committee recommended the inclusion of a new strength, child-friendly dispersible tablet formulation of amoxicillin + clavulanic acid (200 mg + 28.5 mg) as an Access group antibiotic on the core list of the EMLc for treatment of bacterial infections in children – specifically those infections for

which amoxicillin + clavulanic acid is already recommended on the EMLc. The Committee noted that the 7:1 ratio of amoxicillin to clavulanic acid is associated with similar efficacy to the 4:1 ratio but has a reduced frequency of gastrointestinal adverse effects. The Committee endorsed the importance of age-appropriate formulations to better meet the dosing needs of children.

Section 6.2.2 Watch group antibiotics

The Expert Committee did not recommend inclusion of flomoxef sodium as a Watch group antibiotic on the EML and EMLc for empiric treatment of community acquired mild/moderate intraabdominal and upper urinary tract infections caused by extended-spectrum β-lactamase-producing Enterobacterales because of uncertainty in the available evidence.

Section 6.2.3 Reserve group antibiotics

The Expert Committee recommended the inclusion of ceftolozane + tazobactam as a Reserve group antibiotic on the complementary list of the EML and EMLc for the treatment of infections caused or suspected to be caused by carbapenem-resistant *Pseudomonas aeruginosa*, a "critical" priority pathogen on the 2017 WHO list of priority pathogens. The Committee acknowledged that the clinical evidence for efficacy of ceftolozane + tazobactam against this specific pathogen is limited but considered that the availability of carbapenem-sparing alternatives for treatment of drug-resistant *Pseudomonas aeruginosa* was important as part of the strategy to limit/prevent further emergence and spread of carbapenem-resistant organisms.

The Committee did not recommend inclusion of imipenem + cilastatin + relebactam as a Reserve group antibiotic on the complementary list of the EML and EMLc for the treatment of infections caused by multidrug-resistant organisms. The Committee noted that imipenem + cilastatin + relebactam lacks in vitro activity against the carbapenemase genotypes most commonly associated globally with carbapenem resistance in Enterobacterales and that other antibiotics with similar spectrum of activity (e.g. cefiderocol, ceftazidime + avibactam and meropenem + vaborbactam) are already included as Reserve antibiotics on the Model Lists.

The Committee recommended inclusion of tedizolid phosphate on the complementary list of the EML as a Reserve group antibiotic for the treatment of infections caused or suspected to be caused by multidrug-resistant Gram-positive pathogens (methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci), as an alternative to linezolid under a square box listing. The recommendation was based on evidence indicating that tedizolid is non-inferior to linezolid for the treatment of acute bacterial skin and skin structure infections, with a lower incidence of adverse events. However, the Committee observed that tedizolid phosphate is currently less widely available and considerably more expensive than linezolid.

Update to the AWaRe (Access, Watch, Reserve) classification of antibiotics

No changes were recommended to the classification of antibiotics as Access, Watch or Reserve. The 2023 AWaRe classification database will be updated to reflect the recommended inclusion of ceftolozane + tazobactam on the EML and EMLc and of tedizolid phosphate as a therapeutic alternative to linezolid on the EML. The AWaRe classification database is available at Web Annex C.

Section 6.2.5 Antituberculosis medicines

The Expert Committee recommended the inclusion of ethionamide on the core list of the EML and EMLc for the new indication for treatment of drug-susceptible tuberculosis meningitis in children and adolescents, as part of a 6-month intensive regimen in combination with isoniazid, rifampicin and pyrazinamide. The Committee also recommended the inclusion of pretomanid on the complementary list of the EML for treatment of multidrug-resistant or rifampicin-resistant tuberculosis, in a combination regimen with bedaquiline, linezolid with or without moxifloxacin.

The Committee recommended deletion from the EML and/or EMLc of various formulations and strengths of amikacin, ethambutol, ethionamide, isoniazid, linezolid, p-aminosalicylic acid and pyrazinamide, noting that they are not optimal formulations and strengths for tuberculosis treatment. A new strength formulation of p-aminosalicylic acid (as p-aminosalicylate sodium) was recommended for inclusion to replace the previously listed one which has been discontinued by the only manufacturer. The Committee also recommended that the age restrictions associated with the listings for bedaquiline and delamanid on the EML and EMLc should be removed.

These recommendations are fully aligned with recommendations in current WHO guidelines for tuberculosis.

Section 6.4.4.2 Medicines for hepatitis C

The Expert Committee recommended the inclusion of ravidasvir on the core list of the EML as a therapeutic alternative under the square box listing for pangenotypic direct-acting antivirals for the treatment of chronic hepatitis C virus infection in adults. Ravidasvir is pangenotypic when used in combination with sofosbuvir. The recommendation was made based on evidence of effectiveness and safety, similar to that seen with other pangenotypic direct-acting antiviral regimens.

The Committee also recommended deletion of non-pangenotypic treatment options for hepatitis C virus infection (dasabuvir, ombitasvir + paritaprevir + ritonavir, and pegylated interferon alfa 2a and 2b) from the core list of the EML. These treatments are no longer recommended in WHO guidelines for treatment of hepatitis C.

Section 6.7 (new sub-section) Medicines for Ebola virus disease

The Expert Committee recommended the addition of the monoclonal antibodies ansuvimab and atoltivimab + maftivimab + odesivimab to the core list of the EML and EMLc for the treatment of confirmed Ebola virus disease caused by *Zaire ebolavirus* in adults and children, and in neonates of unconfirmed infection status aged 7 days or younger, born to mothers with confirmed infection. The Committee noted that Ebola virus disease is a life-threatening disease with a high case-fatality rate, for which effective treatments are of public health importance. The Committee considered that the available clinical trial evidence for ansuvimab and atoltivimab + maftivimab + odesivimab has demonstrated important reductions in mortality compared to standard supportive care alone. The Committee considered that their inclusion on the Model Lists would represent a strong equity and advocacy message, fully aligned with WHO guidelines, that could contribute to broader actions being undertaken to ensure reliable, affordable access to quality-assured therapeutics for Ebola virus disease.

Section 6.8 (new sub-section) Medicines for COVID-19

Taking account of the global recognition of the need for effective therapeutics to prevent and treat coronavirus disease 2019 (COVID-19), as well as the need to ensure adequate and affordable access globally to these treatments, the Expert Committee recommended that effective and safe therapeutics for COVID-19 be considered as essential medicines and therefore be prioritized by countries for national selection and procurement. However, the Committee also recognized the continued rapid evolution of the evidence base for COVID-19 therapeutics, which contrasts with the 2-year update cycle of the Model Lists. Furthermore, the evolution of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), combined with changing population immunity may influence disease severity and thus have an impact on the relative and absolute benefits associated with COVID-19 therapeutics. The Committee considered that in the context of public health emergencies, there is a risk in listing medicines on the WHO Model Lists that later must be removed because they are no longer relevant for the reasons outlined above, a scenario that ideally should be avoided. The Committee recommended that countries should refer to WHO and national guidelines as tools to orient prioritization of medicines during public health emergencies.

The Expert Committee recommended a new section be added to the EML and EMLc for COVID-19 therapeutics, but that specific, individual medicines should not be listed at this time. Rather, the Committee recommended that this section of the Model Lists should direct national decision-makers to the WHO living guidelines for COVID-19 therapeutics, noting that these are being revised and updated regularly. Importantly, these living guidelines also include recommendations for use of other medicines already included on the Model Lists (e.g. dexamethasone, oxygen), as well as recommendations against the use of medicines that are included on the Model Lists for other indications (e.g. hydroxychloroquine, lopinavir-ritonavir).

Section 8: Immunomodulators and antineoplastics

Section 8.1 Immunomodulators for non-malignant disease

The Expert Committee did not recommend the inclusion of subcutaneous injection formulations of methotrexate on the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and arthritic psoriasis, and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate. The Committee noted that methotrexate is one of the mainstays of treatment for these conditions, but that data on clinical efficacy and safety of subcutaneous methotrexate compared to oral or intramuscular formulations are limited and are based mostly on studies in patients with rheumatoid arthritis. Overall, the Committee considered the possible benefits of subcutaneous compared to oral methotrexate were unclear, and with limited available evidence suggesting only modest benefits in a small proportion of patients, at a considerably higher price.

Section 8.2 Antineoplastic and supportive medicines

A total of 12 applications for cancer medicines were considered by the Expert Committee. These included requests for addition of new cancer medicines, and requests for new indications for already listed cancer medicines. Three applications (programmed cell death protein 1 (PD-1) and

programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors for non-oncogene-addicted locally advanced and metastatic non-small-cell lung cancer, osimertinib for epidermal growth factor receptor (EGFR)-mutated locally advanced or metastatic non-small-cell lung cancer, and cyclin-dependent kinase 4/6 inhibitors for hormone-receptor positive/HER2-negative advanced breast cancer) were resubmissions following recommendations not to list them made by the 2021 Expert Committee. All applications were reviewed by the EML Cancer Medicines Working Group prior to the meeting, who provided written comments to inform the Expert Committee's considerations.

Expert Committee recommendations to include new cancer and supportive medicines

– The inclusion of pegylated liposomal doxorubicin on the complementary list of the EML and EMLc for the treatment of Kaposi sarcoma. The Committee noted evidence that pegylated liposomal doxorubicin is associated with similar or improved survival benefits and reduced harms in comparison to non-liposomal doxorubicin and other routinely used chemotherapies, and pegylated doxorubicin is a preferred therapeutic alternative to paclitaxel in children as the experience with paclitaxel in this setting is still limited.

– The inclusion of pegfilgrastim (including quality-assured biosimilars) on the complementary list of the EML and EMLc for primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy, and for secondary prophylaxis in patients who have experienced neutropenia following prior myelotoxic chemotherapy. The Committee noted that a single dose of pegfilgrastim (once every 2 weeks) is an efficacious and safe alternative to daily injections of filgrastim. The Committee considered that pegfilgrastim may offer advantages over filgrastim in settings where refrigerated storage outside of secondary treatment centres is limited. In these settings, patients being treated with filgrastim face longer hospital stays or daily clinic visits and this has been associated with lower adherence to treatment and increased risk of life-threatening infections. The Committee noted that filgrastim remains a relevant treatment option for patients in whom a treatment duration of less than 2 weeks is indicated.

Expert Committee recommendations to include new indications for existing listed cancer and supportive medicines

– The extension of current listings of cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, methotrexate, prednisolone and vinblastine on the complementary list of the EML and EMLc to include the new indication of anaplastic large-cell lymphoma. These medicines are recognized as part of the standard of care for anaplastic large cell lymphoma. Their benefits and harms were accepted as being well established from use in other indications in children and in adults.

– The extension of current listings of cytarabine, immunoglobulin, mercaptopurine, methotrexate, prednisolone, vinblastine and vincristine on the complementary list of the EML and EMLc to include the new indication of Langerhans cell histiocytosis. While Langerhans cell histiocytosis is considered a rare disease, the Committee acknowledged that treatment is associated with very high survival rates in many cases. These medicines are recognized as part of the standard of care for children with Langerhans cell histiocytosis. Their benefits and harms were accepted as being well established from use in other indications in children and in adults.

– The extension of the current listing for rituximab on the complementary list of the EML and EMLc to include the new indication of Burkitt lymphoma. The Committee noted that rituximab, when added to standard chemotherapy, is associated with meaningful benefits in terms of event-free and overall survival in children and adolescents, with a well known and acceptable safety profile.

The Expert Committee did not recommend listing for the following new medicines and/or new indications

– Cladribine for the treatment of refractory Langerhans cell histiocytosis with involvement of risk organs (a high-risk subgroup) in children and adolescents. The Committee noted that cladribine is associated with serious haematological toxicities limiting its safe use to specialist tertiary care centres and impacting the feasibility of use.

– Crizotinib for the treatment of relapsed/refractory anaplastic large-cell lymphoma in children and adolescents because of insufficient evidence and toxicity concerns.

– Cyclin-dependent kinase 4/6 inhibitors (abemaciclib, palbociclib and ribociclib) for the treatment of hormone receptor positive/HER2-negative advanced breast cancer. The Committee acknowledged that clinical trial results for this class of medicines in the first- and second-line settings suggest a meaningful survival benefit when added to endocrine therapy compared with endocrine therapy alone. However, the Committee considered that uncertainties still exist regarding the optimal, most active and best tolerated dose, noting that many patients had to reduce the dose in the pivotal trials. The Committee also considered that there were uncertainties regarding the duration of treatment, positioning as first or second line in the metastatic setting, and whether clinically significant differences exist between agents within the pharmacological class. As in 2021, the Committee noted the enduring high prices of these medicines, which would pose serious affordability challenges, especially in low- and middle-income countries. The Committee recommended that data for these medicines continue to be evaluated as they evolve and reiterated the recommendation of the 2021 Expert Committee that this class of medicines be flagged to the Medicines Patent Pool as potential candidates for voluntary licensing agreements.

– Osimertinib for first-line treatment of EGFR-mutated locally advanced or metastatic non-small cell lung cancer. The Committee acknowledged that current data show meaningful survival benefits for osimertinib, a third-generation tyrosine kinase inhibitor, compared to first- and second-generation EML-listed alternatives for this indication (erlotinib, gefitinib and afatinib). However, the Committee noted that osimertinib remains very highly priced, and as such would still be unaffordable in many low- and middle-income countries. The Committee expressed concern that the inclusion of osimertinib on the EML could worsen health inequity by diverting limited resources from less expensive alternatives (including generics) already listed on the EML for this indication. The Committee requested that data for osimertinib continue to be evaluated as they evolve and encouraged efforts to facilitate affordable access to osimertinib in low- and middle-income settings, for example, through negotiation of public health licensing agreements through the Medicines Patent Pool.

– Zanubrutinib for treatment-naïve or relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma. The Committee noted the results of clinical trials comparing zanubrutinib with bendamustine plus rituximab in previously untreated patients, and with ibrutinib in patients with relapsed/refractory disease, showed promising survival gains. However, the Committee considered that the magnitude of these gains may be limited, and that few long-term data were available. The Committee also noted important toxicity concerns (particularly neutropenia). The Committee considered that at the current high price, zanubrutinib would neither be considered cost-effective nor affordable in most low- and middle-income settings. The Committee considered that substitution of ibrutinib with zanubrutinib would not necessarily be associated with health budget savings as proposed in the application, because lower ibrutinib doses than those described in the application may be used in clinical practice.

– CD-19-directed antigen receptor (CAR) T-cells (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel) for the treatment of adults with relapsed or refractory large B-cell lymphoma. The Committee acknowledged that CAR T-cell treatment outperforms the standard of care with salvage immunochemotherapy in terms of progression free-survival, however the survival data remain immature. The Committee noted variability across trials (with one study suggesting a potential negative effect associated with CAR T-cell therapy) and limited long-term follow-up for all CAR-T therapies proposed, making the actual survival benefit uncertain. The Committee noted significant safety concerns including cytokine release syndrome and neurological toxicity that can occur in a high proportion of patients and which requires highly specialized medical management. The Committee recognized that treatment of patients using CAR T-cell therapy requires dedicated health system resources and infrastructure well beyond those available in most settings. CAR T-cell therapy has generally been found not to be cost-effective with large budget impacts due

to prohibitive production costs for administration and management of toxicities. However, the Committee noted with interest that these therapies are becoming increasingly available in academic settings and closed/semi-automated manufacturing process systems are now available which may substantially reduce prices and likely increase availability. Recognizing the promising role of CAR T-cell therapy for large B-cell lymphoma and potentially also other cancers, the Committee recommended that evidence for these therapies, as well as their growing availability and affordability, should continue to be monitored by WHO.

– PD-1 and PD-L1 immune checkpoint inhibitors for the first-line treatment of non-oncogene-addicted metastatic NSCLC in patients with tumour PD-L1 expression ≥ 50% (pembrolizumab, atezolizumab, cemiplimab) and of non-oncogene addicted locally advanced, unresectable non-small cell lung cancer following chemo-radiotherapy in patients with tumour PD-L1 expression ≥ 1% (durvalumab). As was the case in 2021, the Committee accepted these medicines continue to demonstrate a relevant and meaningful survival benefit for eligible patients, and possible improvements in quality of life compared with platinum-based chemotherapy. The available evidence is particularly strong for pembrolizumab, for which overall survival benefits are maintained over 5 years. Atezolizumab and cemiplimab show similar benefits, although the available follow-up data are shorter. Similarly, durvalumab data are less mature and will require further consideration. The Committee considered that an overall net benefit can be reasonably assumed for the entire class when compared to platinum-based chemotherapies. However, more data are needed regarding the optimal doses and duration of treatment, with some data already suggesting that for several immune checkpoint inhibitors, lower doses and shorter durations may be sufficient. In principle, the Committee considered that the availability of several immune checkpoint inhibitors as therapeutic options can boost competition and facilitate affordable access. These considerations notwithstanding, the Committee noted that prices for immune checkpoint inhibitors remain prohibitively high in most settings, and global access to affordable companion diagnostic tests is limited. Coupled with the high global prevalence of non-small-cell lung cancer, the opportunity costs of providing treatment with immune checkpoint inhibitors would be substantial for many health systems and would divert limited available resources from other public health programmes. The Expert Committee encouraged WHO to continue to work on strategies to address the issue of high prices of effective cancer medicines and identify solutions to facilitate increased affordable access.

– Tislelizumab for the treatment of non-oncogene-addicted locally advanced and metastatic non-small cell lung cancer, without patient preselection based on PD-L1 tumour expression. The Committee noted that survival data from clinical trials comparing tislelizumab plus chemotherapy versus chemotherapy alone were immature, with less than 2 years of follow-up, and therefore, while promising based on the available data, the overall survival benefit was still

uncertain. The Committee acknowledged that the reported price of tislelizumab in China (the only country where tislelizumab is currently approved and available for this indication) was notably lower than the price of other immune checkpoint inhibitors in this setting.

– Toripalimab for the treatment of locally advanced or metastatic nasopharyngeal and oesophageal cancers. The Committee noted that the survival benefit observed when toripalimab is added to chemotherapy for first-line treatment of advanced nasopharyngeal cancer was currently modest, and that toripalimab had been assigned a score of 3 on the European Society for Medical Oncology's Magnitude of Clinical Benefit Scale (below the accepted score for cancer medicines on the EML). For advanced oesophageal cancer, the Committee noted that toripalimab plus chemotherapy compared to chemotherapy alone might meaningfully improve survival, however the available evidence was still preliminary with only a short follow-up. The Committee acknowledged that the reported price of toripalimab in China (the only country where toripalimab is currently approved and available for these indications) was considerably lower than other immune checkpoint inhibitors in this setting.

Section 9: (renamed) Therapeutic foods

The Expert Committee recommended the inclusion of ready-to-use therapeutic food (RUTF) on the core list of the EMLc for the treatment of severe acute malnutrition in children aged 6 months to 5 years based on evidence from systematic reviews that demonstrated that the use of RUTF is associated with important benefits in terms of nutritional recovery and weight gain compared to standard care. The Committee was satisfied with the information provided by the applicants addressing the specific concerns highlighted by the 2019 Expert Committee regarding potential consequences of including RUTF on the Model List and associated risk-mitigation measures. The Committee was also reassured by the publication of Codex Alimentarius guidelines which define the nutritional composition, production and labelling standards for RUTF as a food for special medical purposes.

Section 10: Medicines affecting the blood
Section 10.1 Antianaemia medicines

The Expert Committee recommended the inclusion of a new strength formulation of ferrous salt + folic acid (60 mg elemental iron + 2.8 mg folic acid) on the core list of the EML as a weekly-administered supplement for prevention of anaemia in menstruating women and adolescent girls, and for reducing the risk of pregnancies affected by neural tube defects. The Committee noted that weekly intermittent supplementation with this formulation was associated with similar outcomes as daily iron and folic acid supplementation and is likely to be associated with advantages in terms of adherence. The Committee also noted that weekly iron and folic acid supplementation is recommended in multiple WHO guidelines.

Section 10.3 Other medicines for haemoglobinopathies

The Expert Committee recommended that oral deferasirox be transferred to the core list of the EML and EMLc for use in the treatment of transfusional iron overload in patients with thalassaemia syndromes, sickle-cell disease and other chronic anaemias, with a square box listing specifying oral deferiprone as a therapeutic alternative. The Committee also recommended that intravenous deferoxamine remain listed on the complementary list of the EML and EMLc for these indications, and the square box associated with the current listing be removed. The Committee accepted that the comparative efficacy and safety of deferiprone, deferoxamine and deferasirox were generally similar, and that orally administered treatments may be preferred options. The Committee recognized the value in having multiple iron chelating agents included on the Model Lists to enable countries to make appropriate national selection decisions taking into consideration relevant contextual factors.

Section 11: Blood products of human origin and plasma substitutes

Section 11.1 Blood and blood components

The Expert Committee recommended the inclusion of pathogen-reduced cryoprecipitate on the core list of the EML and EMLc with a square box, indicating non-pathogen-reduced cryoprecipitate as a therapeutic alternative. The Committee noted that cryoprecipitate is used to replace coagulation factors in cases of massive haemorrhage, von Willebrand disease and deficiency of coagulation factor XIII. It may also be used as an alternative to coagulation factor VIII concentrate in haemophilia A in settings where this is unavailable or unaffordable. The Committee also noted that pathogen reduction of cryoprecipitate can reduce the risk of transmission of bloodborne infectious agents and has been associated with lower risks of alloimmunization and allergic transfusion reactions compared to other blood components.

Section 11.2.2 Blood coagulation factors

The Expert Committee did not recommend inclusion of recombinant coagulation factors or bypassing agents as therapeutic alternatives to plasma-derived coagulation factors under the square box listings for coagulation factors VIII and/or IX on the EML and EMLc. The Committee advised that future consideration for the inclusion of these products on the Model Lists will require full applications, compliant with the requirements for EML applications and containing all relevant information, so that the available evidence can be evaluated in line with standard procedures.

The Committee recommended that the square box be removed from the current listing of coagulation factor VIII, noting that other proposed alternatives (desmopressin and cryoprecipitate) are included in the Model Lists as independent listings. The Committee recommended the inclusion of additional strength formulations (250 IU and 1000 IU per vial) of factor VIII, acknowledging that these are the most commonly used and available formulations.

The Committee agreed that coagulation factor IX complex is a suitable therapeutic alternative to coagulation factor IX in situations where purified factor IX is not available. The Committee therefore recommended that coagulation factor IX complex be included as a therapeutic alternative under the current square box listing for factor IX.

The Committee did not recommend removal of dextran from the Model Lists. While it is not used in the treatment of haemophilia, it remains an essential plasma substitute for patients in need of blood volume replacement.

Section 12: Cardiovascular medicines

Section 12.5.1 Anti-platelet medicines

The Expert Committee did not recommend the addition of ticagrelor to the core list of the EML for the prevention of atherothrombotic events in adults with acute coronary syndromes or high-risk patients with a history of myocardial infarction. The Committee considered that there was uncertainty in efficacy outcomes across trials comparing ticagrelor and clopidogrel and among different patient subpopulations. The Committee also noted that ticagrelor was associated with significantly increased risks of some important bleeding outcomes (e.g. fatal intracranial bleeding). Further, while it was noted that generics of ticagrelor are available, it remains more expensive than clopidogrel in many settings.

Section 12.7 (new sub-section) Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease

The Committee recommended the inclusion of three fixed-dose combinations of cardiovascular medicines (acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide; acetylsalicylic acid + atorvastatin + ramipril; atorvastatin + perindopril + amlodipine) on the core list of the EML for use in primary and secondary prevention of atherosclerotic cardiovascular diseases. Components of the combinations are listed with a square box, indicating other medicines within the respective pharmacological classes represent therapeutic alternatives, consistent with the current square box listings for hydrochlorothiazide, antihypertensives and statins. The Committee noted evidence from large randomized controlled trials that indicate that use of these combinations is associated with reduced risks of cardiovascular events, including fatal and non-fatal myocardial infarction and stroke and the need for revascularization in primary and secondary prevention settings. The Committee also noted data that indicates that the combination products are associated with improved adherence and quality of life, at prices equal to or lower than multiple component monotherapies. This recommendation notwithstanding, the Committee emphasized that the ongoing availability of single agent cardiovascular medicines was critical to allow treatment modification where necessary, and that combination products should not displace single components at the country level. The Committee further considered that guidance concerning the most appropriate use of these fixed-dose combinations for different indications should be provided in separate WHO guidance documents.

Section 13: Dermatological medicines

The Expert Committee did not recommend the inclusion of sunscreen on the EML and EMLc for the prevention of skin cancer in people with albinism or xeroderma pigmentosum. The Committee acknowledged the public health relevance and effectiveness of sunscreen in preventing skin cancer especially in high-risk subgroups, such as people with albinism or xeroderma pigmentosum, but

also in the general population. The Committee agreed that the use of sunscreens, as well as other sun-protection and sun-avoidance strategies and behaviours, are important, effective preventive interventions to reduce the incidence and prevalence of skin cancers, including melanoma. The Committee also noted that the global burden of disease of such cancers is increasing, and that their treatment is associated with considerable costs for both individuals and health systems.

The Committee considered that before being able to recommend sunscreen products for inclusion on the Model Lists, it would be necessary to define relevant standards and specifications for therapeutic (as distinct from cosmetic) sunscreen products protecting against both ultraviolet A and B rays (i.e. broad spectrum). This would include details of specific active ingredients and their concentration, and the range of sun protection factor rating. This information needs to be supported by evidence and implications for labelling standards, to provide clear and reliable guidance for countries for selection of the most appropriate sunscreen products.

13.4 Medicines affecting skin differentiation and proliferation

The Expert Committee acknowledged the global burden of psoriasis and the public health need for effective treatments. Until now, only topical therapies for psoriasis have been included on the Model Lists. The Committee recommended the inclusion of methotrexate on the complementary list of the EML and EMLc for the new indication of psoriasis, based on a favourable balance of desirable to undesirable effects. The Committee did not recommend the inclusion of ustekinumab on the EML for the treatment of severe psoriasis in adults. The Committee recognized the important role of biological disease-modifying agents in the management of moderate to severe psoriasis. The Committee requested that a comprehensive review of all biological disease-modifying medicines in the treatment of moderate-to-severe forms of psoriasis be undertaken to inform future consideration for EML and EMLc listing.

Section 18: Medicines for endocrine disorders

The Expert Committee did not recommend inclusion of the vitamin D analogues alfacalcidol and calcitriol on the complementary list of the EML and EMLc for the proposed indications of hypoparathyroidism, hypophosphataemic rickets, hypocalcaemic vitamin D dependent/ resistant rickets, neonatal hypocalcaemia, chronic kidney disease, and other disorders of vitamin D metabolism or transport. While the application included reference to conditional guideline recommendations for the use of vitamin D analogues in chronic kidney disease, hypophosphataemic rickets and hypoparathyroidism, overall, the Committee noted that the evidence base was uncertain due to risk of bias, indirectness when assessing patient-important outcomes, inconsistencies and imprecision. The Committee considered that the limited likelihood of influencing important clinical outcomes was potentially outweighed by the risks associated with the use of alfacalcidol and calcitriol, such as hypercalciuria, decrease in renal function and cardiovascular risk.

The Expert Committee did not recommend the inclusion of phosphorus on the complementary list of the EMLc, for the treatment of hypophosphataemic rickets in children. The Committee noted evidence from small cohort studies which suggests that early introduction of treatment

with phosphorus and vitamin D in children with hypophosphataemic rickets has beneficial effects in terms of growth, improved bone mineralization and reduced bone deformities. However, the Committee considered that hypophosphataemic rickets is a relatively rare condition which constitutes only a small subgroup of all hypophosphataemic conditions that may benefit from phosphorus supplementation. The Committee therefore considered that a comprehensive review of the evidence for phosphorus treatment across all conditions for which it is indicated should be requested for future consideration.

The Expert Committee did not recommend inclusion of zoledronic acid on the EML and EMLc for the new indication of osteogenesis imperfecta. The Committee noted that available evidence suggests that bisphosphonates may increase bone mineral density but considered that the benefits of bisphosphonate treatment on other important outcomes such as fracture risk, bone pain and physical functioning were unclear.

The Expert Committee did not recommend inclusion of ketoconazole on the EML for the treatment of Cushing syndrome. The Committee noted that the available evidence suggests that a significant proportion of patients have a good response to treatment with ketoconazole, however, the certainty of evidence was low, and there are serious concerns about the safety profile associated with systemic use of ketoconazole, including potentially severe liver toxicity, and the potential for numerous drug–drug interactions.

The Expert Committee did not recommend inclusion of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) to the core list of the EML for weight loss in obesity because of uncertain long-term clinical benefit and safety in this patient population. The Committee noted that GLP-1 RAs have been shown to reduce weight and body mass index in the short term compared to placebo. However, data are lacking on long-term effectiveness, optimal duration of treatment, maintenance of weight reduction once the therapy is stopped and effect on other clinically important outcomes (e.g. hypertension or hyperglycaemia). Long-term safety data are also lacking.

Section 18.3 Estrogens

The Expert Committee did not recommend inclusion of 17-β-estradiol on the complementary list of the EML for the management of pubertal development in adolescents with primary or secondary ovarian failure. The Committee considered that the application reported insufficient information on the evidence supporting the use of estradiol for the proposed indication, including optimal dosages and formulations. The Committee noted that global prevalence of primary ovarian failure or primary ovarian insufficiency varies among different populations but is generally low. The Committee considered that re-evaluation of estradiol should be made taking into account additional indications for which estradiol is routinely used, such as hormone replacement therapy in menopause or following hysterectomy.

Section 18.5.1 Insulins

The Expert Committee recommended that the current listings for human insulin on the core list of the EML and EMLc be extended to include cartridge and prefilled pen delivery systems. The Committee considered that cartridges and prefilled pens may offer advantages for patients over

vials and syringes in terms of ease of use, greater accuracy of dosing and improved adherence. The Committee acknowledged that affordable access to insulin products remains a critical global health priority.

Section 18.6 Medicines for hypoglycaemia

The Expert Committee did not recommend the inclusion of somatropin on the complementary list of the EMLc for the management of hypoglycaemia secondary to growth hormone deficiency in neonates, infants and young children. The Committee acknowledged that the management of hypoglycaemia, of any etiology, in neonates and infants is critical to prevent permanent neurological sequelae. However, the Committee considered that comparative evidence for somatropin versus other medicines for management of hypoglycaemia currently included on the Model Lists (e.g. diazoxide, glucagon, glucose) and information regarding the comparative costs and cost–effectiveness would be necessary to inform any future consideration for somatropin in this indication.

Section 18.8 (new sub-section) Medicines for disorders of the pituitary hormone system

The Expert Committee recommended the inclusion of cabergoline on the core list of the EML for the medical management of hyperprolactinaemia associated with prolactin-secreting pituitary adenomas (prolactinomas). Listing was recommended with bromocriptine as a therapeutic alternative under a square box listing. Overall, the Committee considered that the available evidence suggests medical therapy with dopamine agonists can achieve prolactin normalization in most patients. The Committee noted that dopamine agonist therapy is a preferred first-line intervention for management of hyperprolactinaemia and prolactinomas and may be the only option in settings where specialist neurosurgery is not available, or in patients for whom surgery is not feasible. Cabergoline may be superior to bromocriptine in decreasing the serum prolactin concentration and has fewer adverse effects but is usually more costly.

The Expert Committee recommended the inclusion of octreotide immediate-release and modified-release injections on the complementary list of the EML for use in the management of gigantism and acromegaly in adults with growth hormone-producing tumours. The Committee noted that trans-sphenoidal surgery is the treatment of first choice for this condition but accepted that pharmacological treatment with somatostatin analogues is an effective alternative in situations where surgery is not possible or available. The Committee did not recommend the inclusion of lanreotide depot injection either as an individual listing or as a therapeutic alternative to octreotide, because it was not shown to be superior to octreotide, is more expensive, and unlike octreotide, is not yet available as generics.

Section 19: Immunologicals
Section 19.3 Vaccines

This section was reviewed by the Secretariat for consistency and full alignment with the latest WHO recommendations for routine immunization (March 2023). No changes to the current vaccine listings on the EML and EMLc were required.

Section 21: Ophthalmological preparations

The Expert Committee did not recommend inclusion of hypromellose on the EML and EMLc for the treatment of dry eye disease in adults and children. The Committee accepted that hypromellose is a safe and effective ocular surface lubricant for reducing the signs and symptoms of dry eyes, especially for patients with mild-to-moderate symptoms. However, the Committee considered that the sight-threatening complications of dry eye disease are primarily associated with severe forms of the condition. There was limited evidence comparing hypromellose versus other artificial tear preparations, including combinations, for improvement in relevant clinical outcomes, specifically in patients with severe dry eye disease.

Section 22: Medicines for reproductive health and perinatal care
Section 22.2 Ovulation inducers

The Expert Committee recommended inclusion of letrozole on the complementary list of the EML for the treatment of anovulatory infertility associated with polycystic ovary syndrome or unexplained infertility. Listing was recommended with anastrozole as a therapeutic alternative under a square box listing. The Committee noted evidence that letrozole is associated with a moderate increase in live births and clinical pregnancies compared to clomifene (a medicine currently included in the EML) in patients with infertility due to polycystic ovary syndrome, and similar efficacy to clomifene for live births or biochemically tested pregnancy in couples with unexplained infertility. The Committee noted that WHO guidelines for the prevention, diagnosis and treatment of infertility are in development, and are expected to include recommendations for use of letrozole for ovulation induction in these populations.

Section 22.3 Uterotonics

The Committee recommended that the current listing of mifepristone + misoprostol on the core list of the EML be extended to include the new indication of medical management of intra-uterine fetal demise. The Committee noted evidence that the combination regimen was associated with higher rates of expulsion and shorter expulsion times than misoprostol alone. The Committee considered that adverse effects associated with use of the combination were generally mild, well known and manageable. The Committee also noted that the medical management of intra-uterine fetal demise using this combination regimen has been included in WHO guidelines for medical management of abortion since 2018.

Section 24: Medicines for mental and behavioural disorders

A total of 16 applications for medicines for mental health conditions and substance use disorders were considered by the Expert Committee. Many were developed by, or in consultation with the WHO Department of Mental Health and Substance Use, with the goal of optimizing alignment between the Model Lists and recommendations in relevant WHO guidelines.

Section 24.1 Medicines used in psychotic disorders

The Expert Committee recommended the removal of chlorpromazine immediate-release injection from the core list of the EML for the treatment of schizophrenia and related psychoses because of a lack of high-quality evidence of benefit versus either placebo, or the alternative EML-listed haloperidol immediate-release injection, with a likely increased risk of adverse effects. The Committee recommended inclusion of olanzapine immediate-release injection on the core list of the EML for the acute treatment of schizophrenia and related psychoses based on evidence of similar effectiveness and greater tolerability compared to haloperidol immediate-release injection.

The Expert Committee did not recommend inclusion of paliperidone palmitate 3-month long-acting injection on the EML for maintenance treatment of schizophrenia. The Committee noted that compared to the 1-month formulation, the 3-month formulation has evidence of similar clinical efficacy and safety and may offer advantages to patients in terms of fewer injections. However, the Committee noted that it is not recommended to initiate treatment with the 3-month formulation, rather it is used in patients who demonstrate benefit and tolerance to the 1-month formulation over at least 4 months. In addition, the 3-month formulation is more highly priced, not yet available as a generic and currently has limited availability in low- and middle-income countries.

The Expert Committee recommended the addition of a square box to the listing of risperidone on the EML for treatment of schizophrenia and related chronic psychotic disorders, specifying oral aripiprazole, olanzapine, paliperidone and quetiapine as therapeutic alternatives. The Committee noted that evidence from several high-quality meta-analyses on the acute and maintenance treatment of schizophrenia and other chronic psychoses found most oral second-generation antipsychotics were similarly effective and tolerable.

The Expert Committee recalled the request made by the 2021 Committee that therapeutic alternatives for the square box listings for chlorpromazine, fluphenazine and haloperidol in this section of the EML be reviewed. The Expert Committee accepted the rationale applied by the WHO Department of Mental Health and Substance Use in identifying suitable therapeutic alternatives, and made the following recommendations:

- – chlorpromazine (oral formulations only) should be included as a therapeutic alternative to oral haloperidol (This recommendation, coupled with the recommendation above to remove chlorpromazine injection, effectively removes the independent listing for chlorpromazine from the EML);
- – haloperidol decanoate and zuclopenthixol decanoate should be included as therapeutic alternatives to fluphenazine (decanoate/enantate).

The Expert Committee recommended the deletion of chlorpromazine and haloperidol (all dosage forms) from the complementary list of the EMLc. The Committee noted that schizophrenia and other chronic psychotic disorders are rare in children younger than 12 years. The Committee agreed that the available evidence for these medicines in the treatment of psychoses in children was inconclusive and insufficient to support their ongoing inclusion on the EMLc.

Section 24.2.1 Medicines used in depressive disorders

The Expert Committee recommended that the square box be removed from the current listing for amitriptyline for the treatment of depressive disorders on the EML. The Committee considered that there are insufficient data to support the inclusion of other tricyclic antidepressants as therapeutic alternatives for amitriptyline. The Committee considered that amitriptyline is the tricyclic antidepressant with the larger evidence base and other molecules have insufficient evidence, or are likely to be inferior to amitriptyline in some relevant areas (e.g. clomipramine is likely to be less acceptable to patients than amitriptyline and placebo).

The Expert Committee recommended the deletion of fluoxetine for the treatment of depressive disorders in children from the complementary list of the EMLc. The Committee accepted that fluoxetine may be used in children younger than 12 years in some setting where there is limited access to mental health facilities and non-pharmacological interventions and may be recommended in some consensus guidelines. However, the Committee noted that the reported prevalence of depression in children younger than 12 years is low and considered that the current evidence for use of fluoxetine in this age group was inconclusive and insufficient to support its ongoing inclusion the EMLc. This recommendation therefore also applies to the listing of fluoxetine on the EMLc in Section 2.3 Medicines for other common symptoms in palliative care. The Committee noted that the prevalence of depression substantially increases throughout adolescence and into adulthood and confirmed that fluoxetine will remain on the EML for the treatment of depression in adults.

The Expert Committee did not recommend the inclusion of phenelzine on the complementary list of the EML for use in treatment-resistant depression because of uncertain evidence for benefit in the proposed patient population and increased risk of harms. The Committee noted that the systematic reviews and meta-analyses presented in the application which evaluated the comparative efficacy of phenelzine versus placebo or other antidepressants did not include participants with treatment-resistant depression. The Committee also noted that phenelzine is associated with potentially serious adverse effects and has high potential for drug–drug and drug–food interactions. Treatment with phenelzine therefore would require careful and specialized monitoring and management, which may not be available in many low- and middle-income settings.

Section 24.2.2 Medicines used in bipolar disorders

The Expert Committee recommended the inclusion of quetiapine, with a square box indicating aripiprazole, olanzapine and paliperidone as specified therapeutic alternatives, on the core list of the EML for treatment of bipolar disorders. The Committee considered that the evidence presented in the application demonstrated the effectiveness of the proposed second-generation antipsychotics in the acute treatment and long-term prevention of mania/hypomania and/or depression in bipolar disorders was similar to that of classic mood stabilizers currently included on the EML (carbamazepine, lithium carbonate and valproic acid). All proposed medicines were shown to be either superior or non-inferior to placebo for acceptability (determined by all-cause discontinuations). The Committee agreed that second-generation antipsychotics have an important role in bipolar disorders in patients who do not adequately respond to or experience adverse events from mood stabilizers. Moreover, the Committee noted that the two classes of medicines may be used in combination in selected patients in clinical practice.

Section 24.3 Medicines for anxiety disorders

The Expert Committee recommended the addition of a note to the listing of diazepam in this section of the EML to indicate use is only recommended for the short-term emergency management of acute and severe anxiety symptoms as the balance of benefits and risks of diazepam use under these circumstances is considered favourable. The Committee also recommended that lorazepam be specified as the only therapeutic alternative under the square box listing for diazepam for this indication. These recommendations are aligned with expected recommendations in updated mhGAP guidelines.

The Expert Committee recommended the inclusion of fluoxetine on the EML for the new indications of use in generalized anxiety disorder, panic disorder and social anxiety disorder. Listing is recommended with a square box specifying citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives. The Committee considered that the evidence presented in the application supported the use of fluoxetine and the proposed alternative selective serotonin reuptake inhibitors (SSRIs) for these indications as they were shown to be more effective than placebo in reducing anxiety symptoms and have a well known and acceptable safety profile.

Section 24.4 Medicines used for obsessive–compulsive disorders

The Expert Committee recommended the inclusion of fluoxetine on the EML for the new indication of obsessive–compulsive disorder in adults. Listing is recommended with a square box specifying citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives. The Committee considered that the evidence presented in the application supported the use of fluoxetine and the proposed alternative SSRIs for the treatment of obsessive–compulsive disorder, indicating that SSRIs are more effective than placebo in reducing obsessive–compulsive symptoms, and have a more favourable safety profile than tricyclic antidepressants.

Section 24.5 Medicines for disorders due to psychoactive substance use

This section of the Model Lists has been updated to include separate subsections for medicines for alcohol, nicotine and opioid use disorders.

Section 24.5.1 (new sub-section) Medicines for alcohol use disorders

The Expert Committee recommended the inclusion of acamprosate and naltrexone on the core list of the EML for the treatment of alcohol use disorder in adults. The Committee considered that the available evidence showed these medicines to be associated with moderate improvements in abstinence rates, which would translate to meaningful impact at the population level. Both medicines are generally well tolerated and are recommended in WHO guidelines. The Committee considered that the availability of different medicines for alcohol use disorder would provide valuable options and choice for patients and clinicians, and could facilitate increased market competition, reduce costs and improve affordable access for national health systems.

Section 24.5.2 (new sub-section) Medicines for nicotine use disorders

The Expert Committee recommended the inclusion of nicotine lozenges and mouth spray on the core list of the EML as additional forms of nicotine replacement therapy for tobacco and smoking

cessation. The Committee noted high-quality evidence from multiple randomized controlled trials that all licensed forms of nicotine replacement therapy are effective at increasing cessation rates. The Committee considered that the availability of different forms of nicotine replacement therapy would provide options and choice for patients and clinicians, and could facilitate increased market competition, reduce costs and improve affordable access for national health systems.

Section 29: Medicines for diseases of joints
Section 29.3 Juvenile joint diseases

The Expert Committee recommended the inclusion of triamcinolone hexacetonide on the complementary list of the EML and EMLc for use in the treatment of juvenile idiopathic arthritis. Listing is recommended with a square box with triamcinolone acetonide as a therapeutic alternative for national selection in situations where triamcinolone hexacetonide is not available. The Committee noted that the evidence indicates that triamcinolone hexacetonide is superior to triamcinolone acetate in terms of efficacy and duration of response but it has been subject to supply shortages worldwide. As was the case in 2021, the Committee considered that the available evidence was still limited and of suboptimal quality, but accepted that use of intra-articular glucocorticoid injections with triamcinolone (hexacetonide, and to a lesser extent acetonide) may be associated with improvements in joint inflammation in oligoarticular forms of juvenile idiopathic arthritis and have advantages over long-term systemic corticosteroid use in terms of harms.

The Expert Committee did not recommend the inclusion of anakinra for treatment of systemic-onset juvenile idiopathic arthritis with macrophage activation syndrome, nor of tocilizumab for treatment of systemic-onset juvenile idiopathic arthritis on the EML and EMLc. As was the case when these medicines were considered in 2021, the Expert Committee considered that the clinical benefits and safety of these medicines (including risk of infection) remain uncertain based on the limited available evidence. The Committee also considered that the feasibility of use of these medicines, particularly in low-resource settings was unlikely given their current high prices, and requirements for specialized care and monitoring and management of adverse events.

Section 30: (renamed) Dental medicines and preparations

The Expert Committee recalled the request made by the 2021 Committee for WHO to identify alternative fluoride-containing formulations recommended for use in the prevention of dental caries so they can be clearly defined in the Model Lists to provide clear guidance to countries. The Committee considered that the evidence presented in the applications for fluoride gel, mouthrinse and varnish supported the effectiveness and safety of these products in the prevention of dental caries, and therefore recommended their inclusion on the core list of the EML and EMLc, as specific fluoride-containing formulations.

The Committee also recommended the inclusion of resin-based composites on the core list of the EML and EMLc for use as dental sealants (low-viscosity forms) and as filling materials (high-viscosity forms) in the prevention and treatment of dental caries. The Committee noted that these products are effective and safe and have functional and aesthetic advantages compared to glass ionomer cement, however they require more specialized expertise and facilities for application. The Committee noted that the availability of effective alternatives to dental amalgam is important

to enable parties to the Minamata Convention on Mercury to achieve the mandated phase-down of dental amalgam use, decreasing environmental mercury pollution.

Other matters considered by the Expert Committee
Age-appropriateness of formulations of essential medicines for children

In consideration of the review of the age-appropriateness of formulations of medicines on the EMLc, and the comparison report of the EML versus EMLc, the Expert Committee recommended changes to the EMLc for addition of new, age-appropriate formulations and strengths of existing essential medicines, deletion of unavailable or age-inappropriate formulations and strengths, and other listing modifications as proposed in the application. The Committee also endorsed the proposals for further review of the public health relevance and evidence of specific medicines for use in children for potential future consideration for inclusion on the EMLc. The Committee noted and welcomed the ongoing review being coordinated by the Secretariat for the remaining sections of the EMLc for consideration by the 2025 Expert Committee.

Off-label use of medicines

The Expert Committee noted the comments received from the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) regarding off-label use of medicines included on the Model Lists. The Committee reiterated the views expressed by the 2015 Expert Committee regarding consideration of medicines for inclusion on the Model Lists for off-label uses or indications – namely, that labelling is the responsibility of national regulatory authorities, and there may consequently be different labels for the same product in different countries, and that there is thus no global standard for what is considered "off-label". Furthermore, updating approved labels for older products may not be pursued by market authorization holder(s) if doing so is not determined to be commercially viable, and that there are many examples of older products whose regulatory labels are inconsistent with current clinical evidence and current clinical practice. Consequently, the Expert Committee reaffirmed that off-label status of a medicine need not be a reason to exclude it from the Model Lists if it otherwise meets the criteria for inclusion. Because of the intended global audience of the Model Lists and the differences in national regulatory labelling, the Committee recommended that off-label status should not be specifically marked in the Model Lists. The Committee recognized that it is a responsibility of relevant national decision-makers to consider national labelling and legal requirements in the selection and use of medicines at the country level. The Committee considered that the inclusion on the Model Lists of those off-label medicines that are associated with relevant clinical benefits and financial advantages can play an important role in informing national selection and facilitating progress towards universal health coverage.

Rare diseases

Medicines to treat rare diseases have been included on the Model Lists since the first EML was published in 1977. The Expert Committee acknowledged that rare diseases are a diverse group of conditions that individually affect a small portion of the population. However, collectively, they can affect millions of people worldwide. There is no universally agreed definition of "rare",

with prevalence-based national and regional definitions of rare diseases (often in the context of orphan medicine legislation) varying considerably. Furthermore, a disease may be considered rare in one population or setting, while being highly prevalent in another, as disease prevalence can vary depending on various population-specific, environmental and geographic factors. The Committee also noted that with increasing advancements in precision medicine and targeted treatments in some areas (e.g. oncology), small/rare subcategories of otherwise more common diseases are emerging. The Committee noted that many, but not all, medicines for rare diseases are highly priced and may be unaffordable for many patients and health care systems, particularly in resource-constrained settings.

The Expert Committee recognized the role of the Model Lists in providing an evidence-based blueprint to inform decision-making for national essential medicines lists, including selection of medicines for rare diseases. The Committee also recognized the important advocacy role that inclusion on the Model Lists can play in fostering further actions that can lead to increased access to and affordability of essential medicines for rare diseases. The Committee considered that the low prevalence of a disease need not be a reason to exclude medicines for its treatment from the Model Lists if they otherwise meet the criteria for inclusion.

Procedures for updating the WHO Model Lists

The Expert Committee noted that the procedure for updating the Model Lists has only been updated once since the publication of the first EML in 1977. The Committee also took note of the fact that since the revised procedures were introduced in 2001 (as outlined in Executive Board document EB109/8) the medicine evaluation landscape has become increasingly complex and that some aspects of the procedure may benefit from revision. Issues that were discussed by the Committee and can be considered as part of a broader discussion with Member States are: the actual application process, including how to balance the quality of the applications against the openness of the process that accepts applications without filtering them for quality; the issues surrounding effective but highly priced medicines which pose difficulties as feasibility and acceptability could be low; the role of products commonly not classified as medicines on the list such as condoms, oxygen and toothpastes; the role of the Model Lists in the clinical areas where WHO does not have guidelines; the dissemination of the Model Lists; the role of national lists to facilitate progress towards universal health coverage; and the role of the Model Lists in the context of public health emergencies of international concern. The Committee therefore recommended that WHO consider initiating a process to reassess the procedure for updating WHO's Model Lists of Essential Medicines. This should be an inclusive collaboration with Member States and other relevant stakeholders, including for example other United Nations (UN) organizations, WHO Collaborating Centres, universities and scientific societies, international procurement agencies, nongovernmental organizations, professional associations, representatives of national essential medicines programmes, representatives from the pharmaceutical industry, and patient organizations.

All applications and documents reviewed by the Expert Committee are available on the WHO website at: https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/24th-eml-expert-committee

Table 1
Recommended changes on the 2023 EML

EML – New medicines added	
Medicine	**Indication**
Acamprosate	Alcohol use disorder
Acetylsalicylic acid + atorvastatin + ramipril	Prevention of atherosclerotic cardiovascular diseases
Acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide	Prevention of atherosclerotic cardiovascular diseases
Ansuvimab	Ebola virus disease
Atoltivimab + maftivimab + odesivimab	Ebola virus disease
Atorvastatin + perindopril + amlodipine	Prevention of atherosclerotic cardiovascular diseases
Cabergoline	Hyperprolactinaemia
Ceftolozane + tazobactam	Multidrug-resistant bacterial infections
Cladribine	Multiple sclerosis
Cryoprecipitate, pathogen-reduced	Bleeding disorders
Deferasirox	Iron overload
Glatiramer acetate	Multiple sclerosis
Letrozole	Infertility
Levetiracetam	Partial- and generalized-onset seizures, status epilepticus
Naltrexone	Alcohol use disorder
Octreotide	Gigantism and acromegaly
Olanzapine	Schizophrenia and related psychoses
Pegfilgrastim	Febrile neutropenia prophylaxis
Pegylated liposomal doxorubicin	Kaposi sarcoma
Pretomanid	Multidrug-resistant tuberculosis
Quetiapine	Bipolar disorder
Resin-based composites	Dental caries
Ravidasvir	Hepatitis C virus infection
Sevoflurane	General anaesthesia
Triamcinolone hexacetonide	Juvenile idiopathic arthritis

Table 1 *continued*

EML – New indications	
Medicine	**Indication**
Cyclophosphamide	Anaplastic large-cell lymphoma
Cytarabine	Anaplastic large-cell lymphoma, Langerhans cell histiocytosis
Dexamethasone	Anaplastic large-cell lymphoma
Doxorubicin	Anaplastic large-cell lymphoma
Ethionamide	Drug-susceptible tuberculosis meningitis
Etoposide	Anaplastic large-cell lymphoma
Fluoxetine	Generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive–compulsive disorder
Ifosfamide	Anaplastic large-cell lymphoma
Immunoglobulin	Langerhans cell histiocytosis
Mercaptopurine	Langerhans cell histiocytosis
Methotrexate	Anaplastic large-cell lymphoma, Langerhans cell histiocytosis, psoriasis
Mifepristone – misoprostol	Intrauterine fetal demise
Prednisolone	Anaplastic large-cell lymphoma, Langerhans cell histiocytosis
Rituximab	Multiple sclerosis, Burkitt lymphoma
Vinblastine	Anaplastic large-cell lymphoma, Langerhans cell histiocytosis
Vincristine	Langerhans cell histiocytosis
EML – New formulation/strength	
Medicine	**Formulation/strength**
Arsenic trioxide	Concentrate for solution for infusion: 2 mg/mL
Calcium folinate	Injection: 7.5 mg/mL in 2 mL ampoule, 10 mg/mL in 5 mL ampoule
Carbamazepine	Tablet (scored): 400 mg
Cefotaxime	Powder for injection: 500 mg, 1 g, 2 g (as sodium) in vial
Ceftriaxone	Powder for injection: 500 mg (as sodium) in vial

Table 1 *continued*

EML – New formulation/strength	
Medicine	**Formulation/strength**
Cytarabine	Injection: 100 mg/mL
Dacarbazine	Powder for injection: 200 mg in vial
Daunorubicin	Injection: 2 mg/mL, 5 mg/mL in vial Powder for injection: 20 mg in vial
Doxorubicin	Injection: 2 mg/mL (hydrochloride) in 5 mL, 25 mL vial
Enalapril	Tablet: 10 mg (as hydrogen maleate)
Etoposide	Powder for injection: 100 mg (as phosphate) in vial
Ferrous salt + folic acid	Tablet: equivalent to 60 mg elemental iron + 2.8 mg folic acid
Fluoride	Gel: containing 2500 to 12 500 ppm fluoride (any type) Mouth rinse: containing 230 to 900 ppm fluoride (any type) Varnish: containing 22 500 ppm fluoride (any type)
Furosemide	Injection: 10 mg/mL in 5 mL ampoule Tablet: 20 mg
Insulin injection (soluble)	Injection: 100 IU/mL in 3 mL cartridge or prefilled pen
Intermediate-acting insulin	Injection: 100 IU/mL in 3 mL cartridge or prefilled pen
Methotrexate	Injection: 50 mg/2 mL (Section 8.2.1) Concentrated injection: 1000 mg/10 mL (Section 8.2.1)
Nicotine replacement therapy	Lozenge: 2 mg, 4 mg Oral spray: 1 mg per actuation
p-aminosalicylate sodium	Powder for oral solution: 5.52 g in sachet (equivalent to 4 g p-aminosalicylic acid)
Pegaspargase	Powder for injection: 3750 units in vial
Pentamidine	Powder for injection: 300 mg (as isethionate) in vial
Valproic acid (sodium valproate)	Injection: 100 mg/mL in 3 mL ampoule

Table 1 *continued*

EML – Medicines/formulations deleted	
Medicine	**Formulation/strength**
Amikacin	Capsule 250 mg Oral liquid: 150 mg/5 mL (as palmitate)
Chloramphenicol	Injection: 7.5 mg/mL in 2 mL ampoule, 10 mg/mL in 5 mL ampoule
Chlorpromazine	Injection: 25 mg/mL (hydrochloride) in 2 mL ampoule Oral liquid: 25 mg/5 mL (hydrochloride)[a] Tablet: 10 mg, 25 mg, 50 mg, 100 mg (hydrochloride)[a] [a] Oral formulations of chlorpromazine are now included as therapeutic alternatives under the square box listing for oral haloperidol (Section 24.1)
Dasabuvir	Tablet: 250 mg
Ethionamide	Tablet: 125 mg
Hydroxycarbamide	Solid oral dosage form: 250 mg
Linezolid	Powder for oral liquid: 100 mg/5 mL (Section 6.2.5) Tablet: 400 mg (Section 6.2.3)
Nifurtimox	Tablet: 250 mg
Nystatin	Tablet: 100 000 IU
Ombitasvir + paritaprevir + ritonavir	Tablet: 12.5 mg + 75 mg + 50 mg
p-aminosalicylic acid	Granules: 4 g in sachet
Paracetamol	Tablet: 100 mg
Pegylated interferon alfa (2a or 2b)	Vial or prefilled syringe: 180 micrograms (peginterferon alfa 2a); 80 micrograms, 100 micrograms (peginterferon alfa 2b)
Pentamidine	Powder for injection: 200 mg (as isethionate) in vial
Phenytoin	Oral liquid: 25 mg/5 mL (phenytoin)
Pyrantel	Oral liquid: 50 mg/mL (as embonate or pamoate)

Table 2
Recommended changes on the 2023 EMLc

EMLc – New medicines added	
Medicine	**Indication**
Ansuvimab	Ebola virus disease
Atoltivimab + maftivimab + odesivimab	Ebola virus disease
Ceftolozane + tazobactam	Multidrug-resistant bacterial infections
Cryoprecipitate, pathogen-reduced	Bleeding disorders
Deferasirox	Iron overload
Levetiracetam	Partial- and generalized-onset seizures, status epilepticus
Pegfilgrastim	Febrile neutropenia prophylaxis
Pegylated liposomal doxorubicin	Kaposi sarcoma
Ready-to-use therapeutic food	Severe acute malnutrition
Resin-based composites	Dental caries
Selenium sulfide	Seborrhoeic dermatitis, pityriasis versicolor
Sevoflurane	General anaesthesia
Triamcinolone hexacetonide	Juvenile idiopathic arthritis
EMLc – New indications	
Medicine	**Indication**
Cyclophosphamide	Anaplastic large-cell lymphoma
Cytarabine	Anaplastic large-cell lymphoma, Langerhans cell histiocytosis
Dexamethasone	Anaplastic large-cell lymphoma
Doxorubicin	Anaplastic large-cell lymphoma
Ethionamide	Drug-susceptible tuberculosis meningitis
Etoposide	Anaplastic large-cell lymphoma
Ifosfamide	Anaplastic large-cell lymphoma
Immunoglobulin	Langerhans cell histiocytosis
Mercaptopurine	Langerhans cell histiocytosis
Methotrexate	Anaplastic large-cell lymphoma, Langerhans cell histiocytosis, psoriasis

Table 2 *continued*

EMLc – New indications	
Medicine	**Indication**
Prednisolone	Anaplastic large-cell lymphoma, Langerhans cell histiocytosis
Rituximab	Burkitt lymphoma
Vinblastine	Anaplastic large-cell lymphoma, Langerhans cell histiocytosis
Vincristine	Langerhans cell histiocytosis
EMLc – New formulation/strength	
Medicine	**Formulation/strength**
Adalimumab	Injection: 10 mg/0.2 mL, 20 mg/0.4 mL
Albendazole	Tablet (chewable): 200 mg (Section 6.1.4)
Amikacin	Injection: 50 mg/mL (as sulfate) in 2 mL vial (Section 6.2.1)
Amoxicillin	Tablet (dispersible, scored): 250 mg, 500 mg (as trihydrate)
Amoxicillin + clavulanic acid	Tablet (dispersible): 200 mg (as trihydrate + 28.5 mg (as potassium salt), 250 mg (as trihydrate) + 62.5 mg (as potassium salt)
Arsenic trioxide	Concentrate for solution for infusion: 2 mg/mL
Azathioprine	Oral liquid: 10 mg/mL Powder for injection: 50 mg (as sodium salt) in vial Tablet: 25 mg
Azithromycin	Powder for oral liquid: 200 mg/5 mL (anhydrous)
Calcium folinate	Injection: 7.5 mg/mL in 2 mL ampoule, 10 mg/mL in 5 mL ampoule
Carbamazepine	Tablet (scored): 400 mg
Cefalexin	Tablet (dispersible): 125 mg, 250 mg
Cefotaxime	Powder for injection: 500 mg, 1 g, 2 g (as sodium) in vial
Ceftriaxone	Powder for injection: 500 mg (as sodium) in vial
Ciclosporin	Oral solution: 100 mg/mL

Table 2 *continued*

EMLc – New formulation/strength	
Medicine	**Formulation/strength**
Ciprofloxacin	Solid oral dosage form: 100 mg (as hydrochloride)
Clarithromycin	Solid oral dosage form: 250 mg
Clindamycin	Powder for oral liquid: 75 mg/5 mL (as palmitate hydrochloride)
Cloxacillin	Capsule: 250 mg Powder for injection: 250 mg (as sodium) in vial Powder for oral liquid: 250 mg/5 mL (as sodium)
Cytarabine	Injection: 100 mg/mL
Dacarbazine	Powder for injection: 200 mg in vial
Daunorubicin	Injection: 2 mg/mL, 5 mg/mL in vial Powder for injection: 20 mg in vial
Digoxin	Injection: 100 micrograms/mL in 1 mL ampoule Tablet: 125 micrograms
Doxorubicin	Injection: 2 mg/mL (hydrochloride) in 5 mL, 25 mL vial
Doxycycline	Powder for oral liquid: 25 mg/5 mL (monohydrate) Oral liquid: 50 mg/5 mL (calcium) Tablet (dispersible): 100 mg (as monohydrate)
Enalapril	Oral solution: 1 mg/mL (as hydrogen maleate) Tablet: 10 mg (as hydrogen maleate)
Etoposide	Powder for injection: 100 mg (as phosphate) in vial
Fluconazole	Powder for oral liquid: 50 mg/5 mL
Fluoride	Gel: containing 2500 to 12 500 ppm fluoride (any type) Mouth rinse: containing 230 to 900 ppm fluoride (any type) Varnish: containing 22 500 ppm fluoride (any type)
Furosemide	Injection: 10 mg/mL in 5 mL ampoule Oral liquid: 50 mg/5 mL Tablet: 20 mg

Table 2 *continued*

EMLc – New formulation/strength	
Medicine	**Formulation/strength**
Hydroxycarbamide	Solid oral dosage form: 100 mg
Ibuprofen	Oral liquid: 100 mg/5 mL
Insulin injection (soluble)	Injection: 100 IU/mL in 3 mL cartridge or prefilled pen
Intermediate-acting insulin	Injection: 100 IU/mL in 3 mL cartridge or prefilled pen
Linezolid	Tablet (dispersible): 150 mg (Section 6.2.3)
Mebendazole	Tablet (chewable): 100 mg (Section 6.1.4)
Mercaptopurine	Oral liquid: 20 mg/mL
Methotrexate	Injection: 50 mg/2 mL (Section 8.2.1) Concentrated injection: 1000 mg/10 mL (Section 8.2.1)
Nifurtimox	Tablet (scored): 30 mg (Section 6.5.5.1)
Nitrofurantoin	Solid oral dosage form: 50 mg
p-aminosalicylate sodium	Powder for oral solution: 5.52 g in sachet (equivalent to 4 g p-aminosalicylic acid)
Paracetamol	Oral liquid: 250 mg/5 mL Suppository: 250 mg Tablet (dispersible): 100 mg, 250 mg
Pegaspargase	Powder for injection: 3750 units in vial
Pentamidine	Powder for injection: 300 mg (as isethionate) in vial
Phenobarbital	Injection: 30 mg/mL, or 60 mg/mL (sodium)
Praziquantel	Tablet: 150 mg (Sections 6.1.3 & 6.1.4) Tablet: 500 mg (Sections 6.1.1 & 6.1.3)
Rifampicin	Oral liquid: 20 mg/mL (Section 6.2.4)
Sulfamethoxazole + trimethoprim	Tablet (dispersible): 100 mg + 20 mg (Sections 6.2.1 & 6.5.4)
Valproic acid (sodium valproate)	Injection: 100 mg/mL in 3 mL ampoule
Vancomycin (intravenous)	Powder for injection: 500 mg, 1 g (as hydrochloride) in vial

Table 2 *continued*

EMLc – Medicines/formulations deleted	
Medicine	**Formulation/strength**
Amikacin	Injection: 100 mg/2 mL (as sulfate) in 2 mL vial (Section 6.2.5)
Azithromycin	Oral liquid: 200 mg/5 mL
Chloramphenicol	Capsule 250 mg Oral liquid: 150 mg/5 mL (as palmitate)
Chlorpromazine	Injection: 25 mg/mL (hydrochloride) in 2 mL ampoule Oral liquid: 25 mg/5 mL (hydrochloride) Tablet: 10 mg, 25 mg, 50 mg, 100 mg (hydrochloride)
Clarithromycin	Solid oral dosage form: 500 mg
Clindamycin	Oral liquid: 75 mg/5 mL (as palmitate)
Dasatinib	Tablet: 100 mg, 140 mg
Doxycycline	Oral liquid: 25 mg/5 mL (anhydrous)
Ethambutol	Oral liquid: 25 mg/mL
Ethionamide	Tablet: 125 mg
Haloperidol	Injection: 5 mg in 1 mL ampoule Oral liquid: 2 mg/mL Solid oral dosage form: 0.5 mg, 2 mg, 5 mg
Fluoxetine	Solid oral dosage form: 20 mg (as hydrochloride) (Sections 2.3 & 24.2.1)
Furosemide	Tablet: 10 mg
Hydroxycarbamide	Solid oral dosage form: 250 mg
Isoniazid	Oral liquid: 50 mg/5 mL
Levamisole	Tablet: 150 mg (as hydrochloride)
Linezolid	Powder for oral liquid: 100 mg/5 mL (Section 6.2.5) Tablet: 400 mg; 600 mg (Section 6.2.3)
Nifurtimox	Tablet: 250 mg
Nystatin	Oral liquid: 50 mg/5 mL Tablet: 100 000 IU
p-aminosalicylic acid	Granules: 4 g in sachet

Table 2 *continued*

EMLc – Medicines/formulations deleted	
Medicine	**Formulation/strength**
Paracetamol	Tablet: 100 mg
Pentamidine	Powder for injection: 200 mg (as isethionate) in vial
Phenytoin	Oral liquid: 25 mg/5 mL (phenytoin)
Pyrantel	Oral liquid: 50 mg/mL (as embonate or pamoate)
Pyrazinamide	Oral liquid: 30 mg/mL
Vinorelbine	Capsule: 80 mg

Table 3
Other changes to the 2023 EML and EMLc

Other changes to listings – EML and/or EMLc		
Albendazole	Add "(scored)" to listings for albendazole 400 mg chewable tablets	EML & EMLc
Amitriptyline	Remove square box	EML
Amphotericin B	Add note stating "Liposomal amphotericin B has a better safety profile than the deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost"	EML & EMLc
Azithromycin	Replace "capsule" with "solid oral dosage form"	EML & EMLc
Bedaquiline	Remove age restriction	EML & EMLc
Benznidazole	Add "(scored)" to listings of benznidazole 50 mg and 100 mg tablets	EML & EMLc
Bleomycin	Modify strength description from 15 mg to 15 000 IU	EML & EMLc
Calcium folinate	Include the alternative medicine name "leucovorin calcium" in the listing	EML & EMLc
Clofazimine	Replace "capsule" with "solid oral dosage form"	EML & EMLc
Colistin	Add equivalent strength in colistin base activity	EML & EMLc
Cyclophosphamide	Replace "tablet" with "solid oral dosage form"	EML & EMLc
Deferoxamine	Remove square box	EML & EMLc
Delamanid	Remove age restriction	EML & EMLc
Diazepam	Modify listing for rectal formulations for use in status epilepticus to better describe available dosage forms (Section 2.3 & Section 5.1)	EML & EMLc
Diazepam	Specify lorazepam as therapeutic alternative and add note stating "For short-term emergency management of acute and severe anxiety symptoms only" (Section 24.3)	EML
Digoxin	Transfer listing from the core to the complementary list	EMLc
Eflornithine	Amend bottle size from 100 mL to 50 mL	EML & EMLc
Fluorouracil	Remove specification of vial size	EML & EMLc

Table 3 *continued*

Other changes to listings – EML and/or EMLc		
Fluphenazine	Specify haloperidol decanoate and zuclopenthixol decanoate as therapeutic alternatives	EML
Haloperidol	Specify chlorpromazine (oral formulations only) as therapeutic alternative	EML
Hydroxycarbamide	Include the alternative medicine name "hydroxyurea" in the listing	EML & EMLc
Ivermectin	Remove "(scored)" from listings for ivermectin 3 mg tablets	EML & EMLc
Linezolid	Add square box specifying tedizolid phosphate as a therapeutic alternative for infections caused by multidrug-resistant organisms (Section 6.2.3)	EML
Metronidazole	Replace tablet formulation strength range with specific strengths	EML & EMLc
Midazolam	Modify listings for use in status epilepticus to better describe available dosage forms	EML & EMLc
Nifurtimox	Add "(scored)" to listings of nifurtimox 30 mg and 120 mg tablets	EML & EMLc
Nitrofurantoin	Replace "tablet" with "solid oral dosage form"	EML & EMLc
Nystatin	Replace "tablet" with "solid oral dosage form"	EML & EMLc
Paracetamol	Include the alternative medicine name "acetaminophen" in the listing Replace tablet formulation strength range with specific strengths Add note stating "The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided"	EML & EMLc
Phenoxymethylpenicillin	Replace "tablet" with "solid oral dosage form"	EML & EMLc
Phenytoin	Specify salt or free acid form for all formulations; remove reference to vial size for 50 mg/mL injection formulation	EML & EMLc
Polymyxin B	Include equivalent strength in mg of polymyxin B base	EML & EMLc
Praziquantel	Add "(scored)" to listings for praziquantel 600 mg tablets	EML & EMLc

Table 3 *continued*

Other changes to listings – EML and/or EMLc		
Risperidone	Add square box specifying aripiprazole, olanzapine, paliperidone and quetiapine as therapeutic alternatives for schizophrenia and related psychoses	EML
Sodium stibogluconate or meglumine antimoniate	List each medicine separately	EML & EMLc
Triclabendazole	Add "(scored)" to listings for triclabendazole 250 mg tablets	EML & EMLc
Vancomycin (oral)	Add note stating "vancomycin powder for injection may also be used for oral administration"	EML & EMLc
Vecuronium	Include atracurium as a therapeutic alternative under the square box listing of vecuronium	EMLc
Vinorelbine	Modify listing to read 10 mg/mL in 1 mL or 5 mL vial	EML & EMLc

Changes to sections and sub-sections		
	2021	**2023**
Section 5	Anticonvulsants/antiepileptics	Medicines for diseases of the nervous system
Section 5.1	N/A	Antiseizure medicines
Section 5.2	N/A	Medicines for multiple sclerosis
Section 5.3	N/A	Medicines for parkinsonism
Section 6.7	N/A	Medicines for Ebola virus disease
Section 6.8	N/A	Medicines for COVID-19
Section 9	Antiparkinsonism medicines	Therapeutic foods
Section 12.7	N/A	Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease
Section 18.8	N/A	Medicines for disorders of the pituitary hormone system
Section 24.5.1	N/A	Medicines for alcohol use disorders

Table 3 *continued*

Changes to sections and sub-sections		
	2021	**2023**
Section 24.5.2	N/A	Medicines for nicotine use disorders
Section 24.5.3	N/A	Medicines for opioid use disorders
Section 30	Dental preparations	Dental medicines and preparations

N/A: not applicable.

Table 4
Applications not recommended

New medicines	
Addition of alfacalcidol and calcitriol for treatment of disorders of bone and calcium metabolism	EML & EMLc
Addition of anakinra for treatment of systemic-onset juvenile idiopathic arthritis with macrophage activation syndrome	EML & EMLc
Addition of CD-19-directed antigen receptor (CAR) T cells (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel) for treatment of relapsed or refractory large B-cell lymphoma	EML
Addition of cladribine for treatment of refractory Langerhans cell histiocytosis	EML & EMLc
Addition of crizotinib for treatment of relapsed/refractory anaplastic large-cell lymphoma	EML & EMLc
Addition of cyclin-dependent kinase 4/6 inhibitors (abemaciclib, palbociclib, ribociclib) for treatment of hormone receptor positive/human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer	EML
Addition of donepezil for treatment of Alzheimer disease dementia	EML
Addition of estradiol for induction of puberty	EML
Addition of flomoxef sodium for empiric treatment of community acquired mild/moderate intraabdominal and upper urinary tract infections	EML & EMLc
Addition of glucagon-like peptide-1 receptor antagonists for treatment of obesity	EML
Addition of hypromellose for treatment of dry eye disease	EML & EMLc
Addition of imipenem + cilastatin + relebactam for treatment of bacterial infections due to multidrug-resistant organisms	EML & EMLc
Addition of ketoconazole for treatment of Cushing syndrome	EML
Addition of ocrelizumab for treatment of multiple sclerosis	EML
Addition of osimertinib for treatment of epidermal growth factor receptor (EGFR)-mutation positive advanced or metastatic non-small-cell lung cancer	EML
Addition of PD-1/PD-L1 immune checkpoint inhibitors (pembrolizumab, atezolizumab, cemiplimab, durvalumab) for non-oncogene-addicted locally advanced or metastatic non-small-cell lung cancer	EML
Addition of phenelzine for treatment of treatment-resistant depression	EML
Addition of phosphorus for treatment of hypophosphataemic rickets	EMLc

Table 4 *continued*

New medicines	
Addition of recombinant coagulation factors or bypassing agents as therapeutic alternatives to plasma-derived coagulation factors	EML & EMLc
Addition of risdiplam for treatment of spinal muscular atrophy	EML & EMLc
Addition of somatropin for management of hypoglycaemia secondary to growth hormone deficiency	EMLc
Addition of sunscreen for prevention of skin cancer in people with albinism or xeroderma pigmentosum	EML & EMLc
Addition of ticagrelor for prevention of atherothrombotic events	EML
Addition of tislelizumab for treatment of non-oncogene-addicted locally advanced and metastatic non-small-cell lung cancer	EML
Addition of tocilizumab for treatment of systemic-onset juvenile idiopathic arthritis	EML & EMLc
Addition of toripalimab for treatment of locally advanced or metastatic nasopharyngeal and oesophageal cancers	EML
Addition of ustekinumab for treatment of severe psoriasis	EML
Addition of zanubrutinib for treatment of chronic lymphocytic leukaemia/ small lymphocytic lymphoma	EML
New formulations/strengths	
Oral transmucosal formulations of fentanyl citrate for treatment of breakthrough cancer pain	EML
Methotrexate subcutaneous injection for severe inflammatory conditions	EML & EMLc
Paliperidone palmitate 3-month long-acting injection for maintenance treatment of schizophrenia	EML
New indications	
Zoledronic acid for treatment of osteogenesis imperfecta	EML & EMLc

List of participants

Expert Committee Members

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Declaration of interests

To be effective, the work of WHO and the contributions of its experts must be, and must be perceived to be, objective and independent. In this regard, to ensure the highest integrity and public confidence in its activities, WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential or reasonably perceived conflict of interest related to the subject of the activity in which they will be involved. Declarations of interest and management of any disclosures is an important process governed by the WHO Guidelines for Declaration of Interests (WHO Experts). More information regarding WHO's policy on declarations of interest is available on the WHO website[2].

Prior to being invited to participate in the 24th meeting of the WHO Expert Committee on Selection and Use of Essential Medicines, all experts submitted written declarations of interest. In reviewing and assessing the declarations of interest, the WHO Essential Medicines List Secretariat sought the advice of the Office of Compliance, Risk Management and Ethics.

The declaration of interest process resulted in the participation of the Expert Committee Members and Temporary Advisers, as reported in the list of participants.

Experts who declared having no conflicts of interest were Elie Akl, Zeba Aziz, Francesco Ceppi, Abdol Majid Cheraghali, Pem Chuki, Patrick Okwen, Ilisabeta Pesamino, Gabriela Prutsky-Lopez, Sangeeta Sharma, Fatima Suleman and Indah Widyahening.

The following experts disclosed interests, which were assessed by the Secretariat for actual or potential conflicts and management strategies (if required):

Loice Achieng Ombajo disclosed receiving honoraria from GSK to serve on a scientific advisory board for the Africa Open Lab research programme, from ViiV Healthcare to serve on a scientific advisory board on HIV and Aging, and from Astra Zeneca to serve on a COVID-19 advisory board. She also disclosed having received honoraria from Astra Zeneca, Merck Sharp and Dohme and Mylan Laboratories for speaker engagements and conference travel on topics not related to medicines under evaluation at this meeting. All payments were below the threshold of significant financial interest. Dr Achieng Ombajo also disclosed funding to her institution (University of Nairobi) from ViiV Healthcare and Gilead Sciences for investigator-initiated clinical trials on medicines for HIV (not under evaluation at this meeting), for which she is the principal investigator. Dr Ombajo is the clinical lead of two country grant programmes, the first to improve surveillance of *Candida auris* in Kenya (funded by the Centers for Diseases Control and Prevention) and the second to improve antimicrobial surveillance (funded by the Fleming Fund). These disclosures were considered minor, unrelated to the subject matter of the Expert Committee meeting and did not require further management.

Rita Banzi disclosed research funding to her research unit and institution (Mario Negri Institute for Pharmaceutical Research) below the threshold of significant financial interest from Janssen

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2   https://www.who.int/about/ethics/declarations-of-interest

Pharmaceuticals to support an educational programme for systematic review methodology. She also disclosed funding to her research unit and institution from AC.TA .s.r.l. to support a series of ongoing investigator-initiated clinical trials on the use of hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of different cancers. No personal salary support was received. These disclosures were considered minor, unrelated to the subject matter of the Expert Committee meeting and did not require further management.

Carlos Alberto Cuello Garcia disclosed an appointment as senior research officer by the Canadian Agency for Drugs and Technology in Health (CADTH). In this capacity, Dr Cuello prepares evaluations of medicines that are presented to Agency's policy-makers to make reimbursement decisions. This disclosure was considered not to represent a conflict and did not require further management.

Elisabeth de Vries disclosed that she serves as an expert in data safety monitoring committees for an ongoing trial investigating atezolizumab in adjuvant breast cancer sponsored by a non-profit research programme (National Surgical Adjuvant Breast and Colon Project) and for a completed trial investigating trastuzumab deruxtecan in advanced breast cancer sponsored by a for-profit company (Daiichi Sankyo). Dr de Vries also disclosed that she provides advice to Crescendo Biologics on improving the quality of the design and conduct of preclinical and phase I clinical studies exploring biological activity of bispecific molecules for the treatment of cancers. Sponsors provide funding to Dr de Vries' institution (University Medical Center Groningen) to cover her time commitment.

She also disclosed that her institution is involved in early phase clinical trials to explore the therapeutic and diagnostic/prognostic roles of cancer medicines and biomarkers. Her institution receives institutional funding from Amgen, Bayer, CytomX, Crescendo Biologics, Genetech, G1 Therapeutics, Regeneron, Roche, Servier and Synthon. No personal salary support was received. The trials concerned were not considered to be directly related to medicines under evaluation at the Expert Committee meeting.

She disclosed that she is a current member of the European Society for Medical Oncology Magnitude of Clinical Benefit Scale Working Group, having served as its Chair from 2013 to 2019, and is a current member of the Response Evaluation Criteria in Solid Tumours Working Group, having been its co-chair from 2009 to 2022. She has served as the Chair of the EML Cancer Medicines Working Group since 2020 and was involved in the Working Group's evaluation of cancer medicine applications under consideration at the Expert Committee meeting. All these positions are unpaid.

These disclosures were considered to be unrelated, or not directly related, to the subject matter of the Expert Committee meeting and did not require further management.

Wei Hao disclosed that he was the principal investigator of a phase II clinical trial evaluating a long-acting naltrexone implant to treat opioid dependence sponsored by Shenzhen Sciencare Medical Industries. He disclosed having received honoraria in relation to the conduct of the trial, below the threshold for significant financial interest. The sponsors provided funding to Dr Hao's institution (Second Xiangya Hospital, Central South University) to cover trial costs. Naltrexone (oral formulation and extended-release injection) is a medicine under evaluation at the Expert Committee meeting for treatment of alcohol use disorders. This disclosure was considered to

represent an ostensible conflict of interest. A determination was made that he should be excluded from the deliberation and recommendation for the application for naltrexone. He recused himself from the meeting while the application for naltrexone was being discussed.

Claudia Garcia Serpa Osorio de Castro disclosed that she has received grant funding for consultancy work from Oswaldo Cruz Foundation Funding Agency to support a project on litigation for access to high-cost medicines sponsored by the Brazilian Ministry of Health, and research grant funding from the National Council for Scientific and Technological Development, a foundation linked to the Brazilian Ministry of Science and Technology, to support masters and PhD students involved in comparative effectiveness research. These disclosures were considered not to represent a conflict and did not require further management.

Mike Sharland disclosed that his institution (St George's University of London) has received research funding from the Global Antibiotic Research and Development Partnership (GARDP) to support the development of academic activities, including observational cohort studies, and monitoring antibiotic use in children. GARDP is funded exclusively from independent, non-commercial sources. He also disclosed that he is the Vice Chair and Board Member of the Penta Foundation, an Italian Charitable Foundation that globally supports trials to advance treatments for paediatric infectious diseases. Penta collaborates with multiple drug companies on the optimal design and conduct of observational and interventional trials of medicines. He has served as the Chair of the EML Antimicrobials Working Group since 2017 and was involved in the Working Group's evaluation of antibiotic applications under consideration at the Expert Committee meeting. Both positions are unpaid. These disclosures were considered not to represent a conflict and did not require further management.

He also disclosed that he is the chief investigator of the ongoing PediCAP trial, a European Union-funded study comparing amoxicillin to amoxicillin + clavulanic acid in children admitted to hospital with severe pneumonia in Africa. Sandoz is donating amoxicillin + clavulanic dispersible tablets for the trial. He also disclosed that he is the chief investigator of the NeoSEP1 trial, funded by GARDP and the European & Developing Countries Clinical Trials Partnership, which compares novel combinations of generic antibiotics to treat neonatal sepsis. The antibiotics under study include fosfomycin, provided by InfectoPharm, and flomoxef, provided by Shionogi & Co. Both positions are unpaid. Applications for amoxicillin + clavulanic acid dispersible tablets (submitted by Sandoz) and flomoxef (submitted by GARDP) were under evaluation at the Expert Committee meeting. These disclosures were considered to represent an ostensible conflict of interest. A determination was made that he should be excluded from the deliberation and recommendation on the applications for amoxicillin + clavulanic acid dispersible tablets and flomoxef. He recused himself from the meeting while these applications were being discussed.

Zoubida Tazi Mezalek disclosed financial support below the threshold for significant financial interest from pharmaceutical companies (Hikma, Janssen, AfricPhar and Health Innovation) for reimbursement of travel and accommodation expenses for attendance at conferences. She also disclosed that she served as an investigator in an observational study sponsored by Servier and a phase IV study sponsored by Roche. These disclosures were considered minor, unrelated to the subject matter of the Expert Committee meeting and did not require further management.

1. Introduction

The meeting of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines took place at WHO headquarters in Geneva, Switzerland, from 24 April to 28 April 2023. The aim of the meeting was to review and update the 22nd WHO Model List of Essential Medicines (EML) and the 8th WHO Model List of Essential Medicines for Children (EMLc), the "Model Lists". The meeting agenda included 85 applications covering more than 100 medicines across multiple medicine classes and formulations for addition, deletion, amendment and review.

The meeting was opened by Dr Clive Ondari, Director, Health Products Policy and Standards Department, on behalf of WHO Director-General, Dr Tedros Adhanom Ghebreyesus. Dr Ondari welcomed Committee members and temporary advisers, representatives from WHO regional offices and other UN agencies.

In his opening remarks, Dr Ondari highlighted that in 2023 WHO was celebrating its 75th anniversary and that the WHO Essential Medicines List was approaching 50 years since it was first released. He noted that the Director-General of WHO in 1975, Dr Halfdan Mahler, warned at the World Health Assembly in that year of the "urgent need to ensure that most essential drugs are available at a reasonable price", which led the publication of the first EML 2 years later. He noted that since the first EML, WHO had endeavoured both internally and in partnership with external stakeholders to improve global access to essential medicines for those who need them. This period has seen several important success stories such as widespread access to affordable medicines for HIV, hepatitis C and tuberculosis. However, access to numerous other essential medicines, from 100-year-old insulin to new, sophisticated, targeted treatments for certain cancers, is still limited in many settings and efforts to improve access must continue.

Dr Ondari further elaborated that the central role of the WHO EML to facilitate global access to medicines raised the question of how essential medicines are selected from the thousands available worldwide, with several dozen new ones becoming available each year. Since the beginning of the millennium, decisions on essential medicines have not only increased in number, but they have also become increasingly complex because some new medicines require advanced technological underlying infrastructure for everything from diagnosis to administration to the management of side-effects. Innovative new treatment methods, such as gene and CAR T-cell therapies, are increasingly being studied and have the potential to change the treatment paradigm for many diseases while also being associated with a whole new set of challenges. Dr Ondari noted that at its current meeting the Expert Committee would be reviewing several applications that have been developed following recent updates to WHO guidelines, including for mental health and coronavirus disease 2019 (COVID-19). He observed that

when the first EML was published in 1977, the concept of evidence-based medicine had not yet been established but that since then, evidence-based and transparent decision-making had become the cornerstone of WHO recommendations in the EML and in WHO guidelines. He noted that essential medicines should not just be available and affordable for patients, but they must also be used appropriately. This is where the strong relationship between the EML and WHO guidelines comes into play as transparent and evidence-based recommendations from WHO serve to justify and maintain the trust that countries, health care professionals and patients place in the Model List and WHO guidelines.

Dr Ondari also noted that the 2023 Expert Committee would also consider applications for medicines for rare diseases and that there was sometimes the misconception that medicines for rare diseases could not qualify as essential because of the low prevalence of the diseases. While disease prevalence was one of the factors looked at when selecting essential medicines, low disease prevalence did not necessarily prevent a medicine from being considered essential if the clinical benefits for patients were highly relevant. Furthermore, a disease may be deemed rare in one geographical location and yet be highly prevalent in another. He elaborated that with the increasing availability of targeted treatments and precision medicines, even so-called common diseases were increasingly stratified into "rarer" subcategories for treatment purposes. The EML was an important tool for improving access to essential medicines, but the EML listing was just one step in the process that must be accompanied by other measures to ensure access at the country level. As an example, long-acting insulin analogues, following the recommendation to include them on the EML in 2021, were also included in a call for expression of interest for WHO prequalification. He was happy to report that WHO prequalified the first human insulin in 2022, but acknowledged that it was too early to evaluate the effect of these actions on global insulin prices and access. Nevertheless, a recent publication in the New England Journal of Medicine reported that the prices for long-acting insulins in the United States had fallen by over 70% since 2021.

Dr Ondari further remarked that the mandate of the Medicine Patent Pool, which had long contributed to improving access to essential medicines for infectious diseases in low- and middle-income countries by negotiating voluntary licensing agreements, had been broadened beyond infectious diseases in October 2022. Following this move, the Medicine Patent Pool signed a voluntary licensing agreement with Novartis AG to increase access to nilotinib – an essential medicine for the treatment of chronic myeloid leukaemia. He stressed that WHO strongly encouraged licence holders of other essential medicines for noncommunicable diseases, to engage with the Medicine Patent Pool to make these medicines accessible for patients globally. WHO recognized the importance of medical innovation and novel medicines to advance global health and well-being, but numerous older medicines were available that had not been sufficiently studied

for the benefits they may offer in indications for which they were not originally approved. This was particularly true for antibiotics, where it has proven difficult to develop entirely new medicines, especially for the treatment of multidrug-resistant pathogens. He emphasized the role of the Global Antibiotic Research & Development Partnership (GARDP) in improving the evidence base for new and old antibiotics for difficult-to-treat infections and in making the most effective treatments accessible for patients who need them.

Finally, Dr Ondari reminded Committee members and temporary advisers of their obligations to provide advice to WHO in their individual capacities as experts, and not as representatives of their governments, institutions or organizations. He acknowledged the considerable work that had already been undertaken in preparation for the meeting and thanked the experts for dedicating their time and expertise to support and contribute to WHO's work on essential medicines.

Dr Hanan Balkhy, Assistant Director-General a.i. of the Access to Medicines and Health Products Division and Assistant Director-General of the Antimicrobial Resistance Division, also addressed the Committee. She noted that the concept of essential medicines remains highly relevant after nearly 50 years and that it will need the combined efforts of all stakeholders to adapt the WHO Model Lists to face the challenges of the next 75 years. In her role as assistant Director-General of the Antimicrobial Resistance Division, she took the opportunity to comment on the role of antibiotics on the EML. She reminded the audience that antibiotics have occupied a large section on the EML ever since its first edition in 1977 and that in 2017 the AWaRe framework revolutionized the listing of antibiotics on the EML by classifying them into three categories (Access, Watch, Reserve). She noted that the AWaRe framework had been adopted by many countries to monitor antibiotic use and guide antibiotic stewardship activities. She recalled that WHO had adopted a target that at least 60% of antibiotic use should be from the Access category, a target endorsed most recently by the Muscat ministerial manifesto. She highlighted that WHO now has a companion publication available in multiple formats, the WHO AWaRe antibiotic book, which will help countries achieve this goal by providing up-to-date, evidence-based guidance on the management of over 30 infectious syndromes and the use of Reserve antibiotics. She noted that the AWaRe antibiotic book potentiates the impact of the EML and WHO guidelines by providing a key tool to improve antibiotic use and combat antimicrobial resistance worldwide. She also mentioned that the Secretariat was exploring ways that this approach could be applied in different therapeutic areas, building on the success of the AWaRe antibiotic book.

Dr Balkhy concluded that prioritizing those medicines that provide the most benefit, the EML was an important tool to achieve WHO's Triple Billion target and thanked the experts for their enthusiasm, dedication, and commitment as vital contributors to the success of the EML.

2. Open session

The open session of the meeting was held in person and virtually and was chaired by Clive Ondari, Director, Department of Health Product Policy and Standards on behalf of the Director-General. A variety of interested parties attended the session, including representatives of WHO Member States, nongovernmental organizations, academia and civil society.

Updates from the WHO Secretariat were presented by Benedikt Huttner, Essential Medicines Team Lead and Secretary of the Expert Committee, Ana Aceves Capri, Essential Diagnostics List Secretariat, and Martina Penazzato, Global Accelerator for Pediatric Formulations (GAP-f) Secretariat.

Chairs of the EML Working Groups for antimicrobials (Mike Sharland) and cancer medicines (Elisabeth de Vries) presented updates of the work undertaken by these working groups since the last Expert Committee meeting.

Three speakers gave presentations on topics of relevance to the current and ongoing work of WHO on essential medicines. Holger Schunemann, Professor of Medicine and Clinical Epidemiology at McMaster University, Hamilton, Canada presented on integrity and transparency of decisions on essential medicines. Subasree Srinivasan, Medical Director of the Global Antibiotic Research & Development Partnership (GARDP), Geneva, Switzerland presented on bridging antibiotic innovation and access and preserving the power of antibiotics, and Enrico Costa from the WHO Collaborating Centre for Pharmaceutical Policy and Regulation at Utrecht University in the Kingdom of the Netherlands presented an evaluation of rare diseases and the WHO Model Lists.

Additional presentations and/or statements were made by the following participants:

- Wendy Weidner, Alzheimer's Disease International
- Paul Domanico, Clinton Health Access Initiative
- George Pentheroudakis, European Society for Medical Oncology
- James Anderson, International Federation of Pharmaceutical Manufacturers & Associations
- Esin Aysel Kandemir, International Society of Oncology Pharmacy Practitioners
- Thiru Balasubramanian, Knowledge Ecology International
- Daniela Garone, Médecins Sans Frontières
- Giulia Segafredo, Medicines Patent Pool
- Joanna Laurson, Neurology Organizations
- Ian Tannock, Optimal Cancer Care Alliance

- Durhane Wong-Rieger, Rare Diseases International
- Kacper Rucinski, Spinal Muscular Atrophy Organizations

Copies of all presentations and statements are available on the WHO website[3].

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[3] 24th Expert Committee on Selection and Use of Essential Medicines [webpage]. Geneva: World Health Organization; 2023 (https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/24th-eml-expert-committee, accessed 30 August 2023).

3. General items

Procedure for updating the WHO Model Lists

The Expert Committee noted that the procedure for updating the Model Lists has only been updated once since the publication of the first EML in 1977. The Committee also took note of the fact that since the revised procedures were introduced in 2001 (as outlined in Executive Board document EB109/8), the medicine evaluation landscape has become increasingly complex and that some aspects of the procedure may benefit from revision. Issues that were discussed by the Committee and can be considered as part of a broader discussion with Member States are: the actual application process, including how to balance the quality of the applications against the openness of the process that accepts applications without filtering them for quality; issues surrounding effective but highly priced medicines which pose difficulties as feasibility and acceptability could be low; the role of products commonly not classified as medicines on the Model Lists, such as condoms, oxygen and toothpastes; the role of the Model Lists in clinical areas where WHO does not have guidelines; the dissemination of the Model Lists; the role with national lists to facilitate progress towards universal health coverage; and the role of the Model Lists in the context of public health emergencies of international concern. The Committee therefore recommended that WHO consider initiating a process to reassess the procedure for updating WHO's Model Lists of Essential Medicines. This process should be an inclusive collaboration with Member States and other relevant stakeholders, including for example other UN organizations, WHO Collaborating Centres, universities and scientific societies, international procurement agencies, nongovernmental organizations, professional associations, national essential medicines programme representatives, representatives from the pharmaceutical industry and patient organizations.

Off-label use of medicines

The Expert Committee noted the comments received from the International Federation of Pharmaceutical Manufacturers and Associations on off-label use of medicines included on the Model Lists. The Committee reiterated the views expressed by the 2015 Expert Committee regarding consideration of medicines for inclusion on the Model Lists for off-label uses or indications. Namely, that labelling is the responsibility of national regulatory authorities and consequently different labels may exist for the same product in different countries, and that there is thus no global standard for what is considered off-label. Furthermore, market authorization holder(s) may not seek to update approved labels for older products if doing so is not determined to be commercially viable, and there are many examples of older products whose regulatory labels are inconsistent with

current clinical evidence and current clinical practice. Consequently, the Expert Committee reaffirmed that off-label status of a medicine need not be a reason to exclude it from the Model Lists, if it otherwise meets the criteria for inclusion. Because of the intended global audience of the Model Lists and the differences in national regulatory labelling, the Committee recommended that off-label status should not be specifically marked in the Model Lists. The Committee recognized that it is a responsibility of relevant national decision-makers to consider national labelling and legal requirements in the selection and use of medicines at the country level. The Committee considered that the inclusion on the Model Lists of off-label medicines that are associated with relevant clinical benefits and financial advantages can play an important role in informing national selection and facilitating progress towards universal health coverage.

Rare diseases

Medicines to treat rare diseases have been included on the Model Lists since the first EML was published in 1977. The Expert Committee acknowledged that rare diseases include a diverse group of conditions that individually affect a small portion of the population. However, collectively, they can affect millions of people worldwide. There is no universally agreed definition of "rare", with prevalence-based national and regional definitions of rare diseases (often in the context of orphan medicine legislation) varying considerably. Furthermore, a disease may be considered rare in one population or setting, while being highly prevalent in another, as disease prevalence can vary depending on various population-specific, environmental and geographic factors. The Committee also noted that with increasing advances in precision medicine and targeted treatments in some areas (e.g. oncology), small/rare subcategories of otherwise more common diseases are emerging. The Committee noted that many, but not all, medicines for rare diseases are highly priced and may be unaffordable for many patients and health care systems, particularly in resource-constrained settings.

The Expert Committee recognized the role of the Model Lists in providing an evidence-based blueprint to inform decision-making for national essential medicines lists, including selection of medicines for rare diseases. The Committee also recognized the important advocacy role that inclusion on the Model Lists can play in fostering further action that can lead to increased access and affordability of essential medicines for rare diseases. The Committee considered that the low prevalence of a disease should not be a reason to exclude medicines for its treatment from the Model Lists, if they otherwise meet the criteria for inclusion.

Age appropriateness of formulations of essential medicines for children

In consideration of the review of the age appropriateness of formulations of medicines on the EMLc, and the comparison report of the EML versus EMLc, the Expert Committee recommended changes to the EMLc for addition of new, age-appropriate formulations and strengths of existing essential medicines, deletion of unavailable or age-inappropriate formulations and strengths, and other listing modifications as proposed in the application. The Committee also endorsed the proposals for further review of the public health relevance and evidence for specific medicines for use in children for potential future consideration for inclusion on the EMLc. The Committee noted and welcomed the ongoing review being coordinated by the Secretariat for the remaining sections of the EMLc for consideration by the 2025 Expert Committee.

COVID-19 therapeutics

Given the global recognition of the need for effective therapeutics to prevent and treat COVID-19, as well as the need to ensure adequate and affordable access globally to these treatments, the Expert Committee recommended that effective and safe therapeutics for COVID-19 should be considered as essential medicines and should therefore be prioritized by countries for national selection and procurement. However, the Committee also recognized the continued rapid evolution of the evidence base for COVID-19 therapeutics, which contrasts with the biennial timeline of the updates of the Model Lists. Furthermore, the evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), combined with changing population immunity, may influence disease severity and thus affect the relative and absolute benefits associated with COVID-19 therapeutics. The Committee considered that in the context of public health emergencies, there is a risk in listing medicines on the WHO Model Lists that later must be removed because they are no longer relevant for the reasons outlined above, a scenario that should be avoided. The Committee recommended that countries should refer to WHO and national guidelines to determine prioritization of medicines during public health emergencies.

The Expert Committee recommended a new section be added to the EML and EMLc for COVID-19 therapeutics, but that specific, individual medicines should not be listed at this time. Rather, the Committee recommended that this section of the Model Lists should direct national decision-makers to the WHO living guidelines for COVID-19 therapeutics, noting that these are being revised and updated regularly. Importantly, these living guidelines also include recommendations for use of other medicines already included on the Model Lists (e.g. dexamethasone, oxygen), as well as recommendations against the use of medicines that are included on the Model Lists for other indications (e.g. hydroxychloroquine, lopinavir-ritonavir).

4. Summary of recommendations

Changes to sections of the Model Lists

Refer to Table 3 of the Executive Summary for details of changes to sections and subsections of the Model Lists.

Additions to the Model Lists

Section 1.1.1: Sevoflurane was added to the core list of the EML and EMLc as an inhalational anaesthetic.

Section 5.1: Levetiracetam was added to the core list of the EML and EMLc for treatment of focal- and generalized-onset seizures. Levetiracetam injection was added to the complementary list of the EML and EMLc for management of status epilepticus.

Section 5.2: Cladribine and glatiramer acetate were added to the complementary list of the EML for the treatment of multiple sclerosis.

Section 6.2.3: Ceftolozane + tazobactam was added to the complementary list of the EML and EMLc for treatment of infections due to multidrug-resistant organisms. Tedizolid phosphate was added as a therapeutic alternative to linezolid.

Section 6.2.5: Pretomanid was added to the complementary list of the EML for the treatment of multidrug-resistant tuberculosis.

Section 6.4.4.2.1: Ravidasvir was added to the core list of the EML for the treatment of chronic hepatitis C virus infection for use in combination with sofosbuvir.

Section 6.7: Ansuvimab and atoltivimab + maftivimab + odesivimab were added to the core list of the EML and EMLc for treatment of Ebola virus disease in accordance with recommendations in WHO guidelines.

Section 8.2.1: Pegylated liposomal doxorubicin was added to the complementary list of the EML and EMLc for treatment of Kaposi sarcoma.

Section 8.2.2: Pegfilgrastim was added to the complementary list of the EML and EMLc for prophylaxis of febrile neutropenia and to facilitate administration of dose-dense chemotherapy regimens.

Section 9: Ready-to-use therapeutic food was added to the core list of the EMLc for treatment of severe acute malnutrition in children.

Section 10.3: Deferasirox was added to the core list of the EML and EMLc for treatment of transfusional iron overload in patients with thalassaemia syndromes, sickle-cell disease and other chronic anaemias, with a square box listing specifying oral deferiprone as a therapeutic alternative.

Section 11.1: Pathogen-reduced cryoprecipitate was added to the core list of the EML and EMLc for use as a transfusional blood component, with a square box listing specifying non-pathogen-reduced cryoprecipitate as a therapeutic alternative.

Section 12.7: Three fixed-dose combinations of cardiovascular medicines (acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide; acetylsalicylic acid + atorvastatin + ramipril; atorvastatin + perindopril + amlodipine) were added to the core list of the EML for use in primary and secondary prevention of atherosclerotic cardiovascular diseases. Components of the combinations are listed with a square box, indicating other medicines within the respective pharmacological classes as therapeutic alternatives.

Section 13.1: Selenium sulfide was added to the core list of the EMLc for treatment of seborrhoeic dermatitis and pityriasis versicolor in children.

Section 18.8: Cabergoline was added to the core list of the EML for management of hyperprolactinaemia associated with prolactin-secreting pituitary adenomas (prolactinomas), with a square box listing specifying bromocriptine as a therapeutic alternative. Octreotide was added to the complimentary list of the EML for use in the management of gigantism and acromegaly in adults with growth hormone-producing tumours.

Section 22.2: Letrozole was added to the complementary list of the EML for the treatment of anovulatory infertility associated with polycystic ovary syndrome or unexplained infertility, with a square box listing specifying anastrozole as a therapeutic alternative.

Section 24.1: Olanzapine immediate-release injection was added to the core list of the EML for the acute treatment of schizophrenia and related psychoses.

Section 24.2.2: Quetiapine was added to the core list of the EML for the treatment of bipolar disorders, with a square box listing specifying aripiprazole, olanzapine and paliperidone as therapeutic alternatives.

Section 24.5.1: Acamprosate and naltrexone were added to the core list of the EML for treatment of alcohol use disorder.

Section 29.3: Triamcinolone hexacetonide was added to the complementary list of the EML and EMLc for use in the treatment of oligoarticular forms of juvenile idiopathic arthritis.

Section 30: resin-based composites were added to the core list of the EML and EMLc for use as dental sealants (low-viscosity forms) and as filling materials (high-viscosity forms) in the prevention and treatment of dental caries.

Deletions from the Model Lists

The following medicines were deleted from the Model Lists:

- chlorpromazine for the treatment of psychotic disorders in children (EMLc)
- dasabuvir for the treatment of chronic hepatitis C virus infection (EML)
- fluoxetine for the treatment of depression in children (EMLc)
- haloperidol for the treatment of psychotic disorders in children (EMLc)
- ombitasvir + paritaprevir + ritonavir for the treatment of chronic hepatitis C virus infection (EML)
- pegylated interferon alfa (2a or 2b) for the treatment of chronic hepatitis C virus infection (EML).

Refer to Tables 1 and 2 of the Executive Summary for details of the deletion of specific formulations and/or strengths of listed medicines from the EML and EMLc, respectively.

New indications

<u>Section 5.2</u>: New indication of multiple sclerosis for rituximab on the EML.

<u>Section 6.2.5</u>: New indication of drug-susceptible tuberculosis meningitis for ethionamide on the EML and EMLc.

<u>Section 8.2</u>:

- New indication of anaplastic large cell lymphoma for cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, methotrexate, prednisolone and vinblastine on the EML and EMLc.
- New indication of Langerhans cell histiocytosis for cytarabine, immunoglobulin (Section 11.2.1), mercaptopurine, methotrexate, prednisolone, vinblastine and vincristine on the EML and EMLc.
- New indication of Burkitt lymphoma for rituximab on the EML and EMLc.

<u>Section 13.4</u>: New indication of psoriasis for methotrexate tablets on the EML and EMLc.

Section 22.3: New indication of intrauterine fetal demise for mifepristone – misoprostol on the EML.

Section 24: New indications of anxiety disorders and obsessive–compulsive disorder for fluoxetine on the EML.

New formulations/strengths

Section 6.2.1: Inclusion of amoxicillin + clavulanic acid 200 mg + 28.5 mg dispersible tablet on the EMLc.

Section 10.1: Inclusion of ferrous salt + folic acid tablet containing 60 mg elemental iron + 2.8 g folic acid on the EML.

Section 18.5.1: Inclusion of 100 IU/mL cartridge and prefilled pen delivery systems for human insulin on the EML and EMLc.

Section 24.5.2: Inclusion of nicotine replacement therapy lozenges (2 mg and 4 mg) and oral spray (1 mg per actuation) on the EML.

Section 30: Inclusion of fluoride gel, mouth rinse and varnish formulations to the EML and EMLc.

Refer also to Tables 1 and 2 of the Executive Summary for details of the addition of other new formulations/strengths of listed medicines on the EML and EMLc, respectively.

Other changes to listings

Refer to Table 3 of the Executive Summary for details of other changes to the listing of medicines on the Model Lists.

Applications not recommended

Section 2: Inclusion of fast-acting oral transmucosal formulations of fentanyl citrate on the EML for the treatment of breakthrough cancer pain.

Section 5:

- – Inclusion of donepezil on the EML for the treatment of dementia due to Alzheimer disease.
- – Inclusion of risdiplam on the EML and EMLc for the treatment of spinal muscular atrophy.
- – Inclusion of ocrelizumab on the EML for the treatment of multiple sclerosis.

Section 6:

- Inclusion of flomoxef sodium on the EML and EMLc for the treatment of community-acquired mild-to-moderate intraabdominal and upper urinary tract infections.
- Inclusion of imipenem + cilastatin + relebactam on the EML for the treatment of infections due to multidrug-resistant organisms.

Section 8:

- Inclusion of CD-19-directed antigen receptor (CAR) T-cells (axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel) on the EML for the treatment of adults with relapsed or refractory large B-cell lymphoma.
- Inclusion of cladribine on the EML and EMLc for the treatment of Langerhans cell histiocytosis.
- Inclusion of crizotinib on the EML and EMLc for the treatment of relapsed or refractory anaplastic large cell lymphoma.
- Inclusion of cyclin-dependent kinase 4/6 inhibitors (abemaciclib, palbociclib and ribociclib) on the EML for the treatment of hormone receptor positive/HER2-negative advanced breast cancer.
- Inclusion of osimertinib on the EML for the treatment of EGFR-mutated locally advanced or metastatic non-small-cell lung cancer.
- Inclusion of PD-1 and PD-L1 immune checkpoint inhibitors on the EML for first-line treatment of metastatic non-small-cell lung cancer in patients with tumour PD-L1 expression ≥ 50% (pembrolizumab, atezolizumab, cemiplimab), and of locally advanced non-small-cell lung cancer in patients with tumour PD-L1 expression ≥ 1% (durvalumab).
- Inclusion of tislelizumab on the EML for the treatment of locally advanced and metastatic non-small-cell lung cancer without patient preselection based on PD-L1 tumour expression.
- Inclusion of toripalimab on the EML for the treatment of locally advanced and metastatic nasopharyngeal and oesophageal cancers.
- Inclusion of zanubrutinib on the EML for the treatment of chronic lymphocytic leukaemia and small lymphocytic lymphoma.

Section 10: Inclusion of recombinant coagulation factors or bypassing agents on the EML and EMLc as therapeutic alternatives to plasma-derived coagulation factors.

Section 12: Inclusion of ticagrelor on the EML for the prevention of atherothrombotic events.

Section 13:

- Inclusion of sunscreen on the EML and EMLc for the prevention of skin cancer in people with albinism or xeroderma pigmentosum.
- Inclusion of ustekinumab on the EML for the treatment of severe psoriasis.

Section 18:

- Inclusion of alfacalcidol and calcitriol on the EML and EMLc for the treatment of disorders of bone and calcium metabolism.
- Inclusion of 17-β-estradiol on the EML for induction of puberty.
- Inclusion of glucagon-like peptide-1 receptor agonists on the EML for weight loss in obesity.
- Inclusion of ketoconazole on the EML for the treatment of Cushing syndrome.
- Inclusion of phosphorus on the EMLc for the treatment of hypophosphataemic rickets.
- Inclusion of somatropin on the EMLc for the management of hypoglycaemia secondary to growth hormone deficiency.
- Inclusion of zoledronic acid on the EML and EMLc for the treatment of osteogenesis imperfecta.

Section 21: Inclusion of hypromellose on the EML and EMLc for the treatment of dry eye disease.

Section 24:

- Inclusion of paliperidone palmitate 3-month long-acting injection on the EML for maintenance treatment of schizophrenia.
- Inclusion of phenelzine on the EML for the treatment of treatment-resistant depression.

Section 29:

- – Inclusion of anakinra on the EML and EMLc for the treatment of systemic-onset juvenile idiopathic arthritis with macrophage activation syndrome.
- – Inclusion of tocilizumab on the EML and EMLc for the treatment of systemic-onset juvenile idiopathic arthritis.

5. Applications for the 23rd Model List of Essential Medicines and the 9th Model List of Essential Medicines for Children

Section 1: Anaesthetics, preoperative medicines and medical gases

1.1 General anaesthetics and oxygen

1.1.1 Inhalational medicines

Sevoflurane – addition – EML & EMLc

Sevoflurane	ATC code: N01AB08

Proposal

Addition of sevoflurane to the core list of the EML and EMLc as an inhalational gas for general anaesthesia.

Applicant

AbbVie Biopharmaceuticals GmbH, Chicago, IL, United States of America

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

1.1.1 Inhalational medicines

Dose form(s) & strengths(s)

Inhalation

Core/complementary

Core

Individual/square box listing

Individual

Background

The Model Lists currently include halothane, isoflurane and nitrous oxide as inhalational gases for general anaesthesia.

A review of the evidence on inhalational anaesthetics was considered by the Expert Committee in 2011. At that time, the Model List included only halothane (with a square box) and nitrous oxide. The Committee noted that halothane was widely used in both induction and maintenance in adults and children but had been gradually replaced in high-income countries by isoflurane, enflurane, desflurane, and sevoflurane for safety reasons. Furthermore, it was noted that ensuring the availability of halothane was increasingly problematic in many settings. The Committee considered that none of these medicines was best in all situations, with choice determined by the availability of the medicines and specific vaporizers. While isoflurane causes less hepatic failure than halothane and has advantages for maintenance, it is unsuitable for induction. Enflurane also has a lower rate of hepatic failure and less cardiovascular toxicity than halothane but increases the risk of seizure and has to be avoided in patients with epilepsy. Isoflurane and enflurane have more rapid onset and recovery times than halothane. Sevoflurane and desflurane have the most rapid onset and offset of action and few adverse effects, such as airway irritation (desflurane), agitation in more than 20% of children during recovery, and convulsions (sevoflurane). Both sevoflurane and desflurane were noted to be more expensive than halothane, isoflurane or enflurane. The Committee recommended the inclusion of isoflurane but not enflurane (due to the risks of convulsions) or sevoflurane (due to cost). The Committee recommended that halothane remain listed, but the square box be removed. The Committee concluded that where available, halothane provides an affordable option for induction and maintenance of anaesthesia. However, where availability is a problem, isoflurane would provide an acceptable option for maintenance. The Committee noted that nitrous oxide can be used as a single agent where general anaesthesia is not required, or in combination with inhalational anaesthetics. Use in combination reduces the dose, toxicity and costs of inhalational drugs. The Committee therefore recommended nitrous oxide remain listed (*1*).

Public health relevance

According to estimates from 2016, about 6% of the world's population requires surgery each year and about 92% of the surgeries will require anaesthesia (*2*). The overarching goal of anaesthesia is to block sensation to a specific area or the whole body. In general anaesthesia, the patient is kept in a safe and controlled state of unconsciousness by a mixture of medicines and sensation is blocked to the entire body. In 2008, it was estimated that about 234 million major surgical procedures are performed worldwide every year (*3*). Inhalational anaesthetics, including sevoflurane, are not only used in major surgeries, but may also be used in outpatient surgeries and dental procedures.

The most commonly used inhalational anaesthetics are halothane, sevoflurane, desflurane, isoflurane and nitrous oxide (*4*). Of these, sevoflurane is

the most used because of its low blood–gas solubility allowing for rapid induction and quick recovery time, less irritation to the airway passages, lower pungency and acceptable cardiovascular side-effects (*5*–*7*).

Summary of evidence: benefits

The application presented summaries of the findings of multiple meta-analyses and clinical trials comparing sevoflurane and other EML-listed inhalational anaesthetics for various outcomes. A summary from the United States Food and Drug Administration (FDA)-approved product information for the AbbVie brand of sevoflurane was also presented (*8*).

Meta-analyses

A meta-analysis of 56 studies in adults and children found that sevoflurane reduced mean extubation time after surgery by 13% (95% confidence interval (CI) 1.4% to 23%) compared with isoflurane. Sevoflurane was also associated with reduced incidence of prolonged extubation (51%, 95% CI 49% to 54%) and reduced mean time to following commands (27%, 95% CI 18% to 36%) compared with isoflurane (*9*).

A meta-analysis of nine studies (1562 participants) found that sevoflurane was associated with statistically significant shorter recovery times (in minutes) than isoflurane for time of emergence (mean difference (MD) –2.9, 95% CI –3.1 to –2.7), extubation (MD –1.6, 95% CI –1.9 to –1.3), response to commands (MD –3.0, 95% CI –3.3 to –2.7), orientation (MD –4.5, 95% CI –4.8 to –4.2) and first post-operative analgesic (MD –8.9, 95% CI –10.8 to –7.0). There was no significant difference between the anaesthetics for time to discharge from recovery room (MD 0.7 minutes, 95% CI –2.7 to 4.1 minutes) (*10*).

A meta-analysis of six studies (634 participants) compared the recovery profile after ambulatory anaesthesia for isoflurane and sevoflurane (*11*). Statistically significant differences were reported between isoflurane and sevoflurane, favouring sevoflurane, for time to opening eyes (2.4 minutes; 95% CI 1.8 to 2.9 minutes), time to obeying commands (2.4 minutes, 95% CI 1.8 to 2.9 minutes), time to transfer from phase I to phase II recovery (8.2 minutes, 95% CI 5.7 to 10.6 minutes), time to home readiness (5.1 minutes, 95% CI 2.8 to 7.4 minutes) and time to home discharge (25 minutes, 95% CI 0.4 to 50.0 minutes). In addition, sevoflurane patients showed significantly less postoperative drowsiness. There were no significant differences between treatments for postoperative nausea, vomiting or dizziness.

A network meta-analysis of 38 randomized controlled trials (3996 participants) evaluated survival in patients undergoing cardiac surgery receiving inhalational or intravenous (IV) anaesthesia (*12*). Sevoflurane and desflurane were each associated with significantly reduced mortality compared with total IV

anaesthesia. The posterior mean of odds ratios (OR) and 95% credible intervals (CrI) were OR 0.31 (95% CrI 0.14 to 0.64) for sevoflurane and OR 0.43 (95% CrI 0.21 to 0.82) for desflurane.

A meta-analysis of 16 randomized controlled trials (961 participants) compared sevoflurane with isoflurane on postoperative outcomes of cardiac surgery (*13*). There were no significant differences between anaesthetics for length of time in the intensive care unit, length of hospital stay, time to extubation or levels of S100β (a marker of cerebral ischaemia) and troponin after surgery. Levels of creatinine kinase (CK)-MB 24 hours after surgery were significantly higher with isoflurane than with sevoflurane. The authors concluded that the choice of anaesthetic does not have a significant impact on postoperative outcomes.

Another systematic review and meta-analysis of 68 randomized controlled trials (7104 participants) evaluated the effects of inhalational anaesthetics on mortality and postoperative pulmonary and other complications following cardiac and non-cardiac surgery (*14*). Overall, inhalational anaesthetics were associated with significantly reduced mortality, and fewer pulmonary and other complications compared with total IV anaesthesia. In non-cardiac surgery, inhalational anaesthetics were not associated with reduced mortality or complications. Compared with isoflurane in cardiac surgery, sevoflurane showed reduced mortality and fewer pulmonary and other complications but the differences were not statistically significant. In non-cardiac surgery, sevoflurane showed reduced mortality and fewer other complications than isoflurane, while isoflurane was associated with fewer pulmonary complications than sevoflurane. All differences were not statistically significant.

A meta-analysis of six randomized controlled trials (873 participants) evaluated the effect on kidney function of sevoflurane and isoflurane 24 and 72 hours after anaesthesia (*15*). There were no statistically significant differences between the groups at either time point for serum/plasma creatinine, blood urea nitrogen, urinary protein or glucose excretion. Another meta-analysis of 41 randomized controlled trials also reported on the effect of sevoflurane versus other anaesthetics (inhaled and total IV anaesthesia) on renal function (*16*). No difference was found between the groups for serum creatinine, creatinine clearance or blood urea nitrogen at 24 hours.

A meta-analysis of 23 randomized controlled trials (2363 participants) evaluated the incidence of emergence agitation in children younger than 12 years anaesthetized with sevoflurane versus halothane (*17*). Emergence agitation was significantly more common with sevoflurane in pooled meta-analyses of all studies (OR 2.21, 95% CI 1.77 to 2.77) and only high-quality studies (OR 1.82, 95% CI 1.37 to 2.41).

Other studies

A retrospective study and a prospective trial of adult patients undergoing non-cardiac surgery compared length of hospital stay for inhalational anaesthetics (*18*). In the retrospective analysis, the adjusted geometric mean for length of hospital stay was significantly longer for isoflurane (2.85 days) than sevoflurane (2.55 days) and desflurane (2.64 days). There was no difference between isoflurane and sevoflurane on the secondary outcome of mean 72-hour verbal response scale pain scores. In the prospective trial, no significant differences were found between sevoflurane and isoflurane for length of hospital stay.

A randomized study compared the induction characteristics of maximum initial inspired concentrations of 8% sevoflurane and 5% halothane in 51 children aged 3 months to 3 years (*19*). There was no significant difference between treatments in the mean time to loss of consciousness, although the time was shorter with sevoflurane than halothane (72 seconds versus 76 seconds). Similarly, mean time to acceptance of the face mask and mean time taken to reach complete induction were shorter with sevoflurane but neither difference was statistically significant. Ten (of 25) and 17 (of 26) patients in the sevoflurane and halothane groups, respectively, had severe struggling. Another study compared 2% sevoflurane with 0.75% halothane, supplementing 66% nitrous oxide in oxygen for induction, maintenance and recovery in 63 children aged 5–12 years undergoing outpatient dental extractions (*20*). The mean time to loss of eyelash reflex was significantly shorter with sevoflurane than halothane (89 seconds versus 127 seconds). Mean time to eye opening after anaesthesia was significantly longer with sevoflurane than halothane (167 seconds versus 102 seconds). Times to walking and standing and discharge were not significantly different between the treatment groups. Complications did not differ significantly between treatment groups during recovery, but nausea was significantly lower in sevoflurane patients than halothane patients after discharge from the hospital. A third study compared sevoflurane and halothane during induction, surgery and recovery in 100 patients aged 2–12 years undergoing outpatient dental anaesthesia (*21*). Mean time to loss of eyelash reflex was significantly shorter with sevoflurane than halothane (1.5 minutes versus 1.9 minutes). Mean time to insertion of mouth prop was significantly longer with sevoflurane than halothane (3.9 minutes versus 3.5 minutes). Times to eye opening and discharge were shorter for sevoflurane than halothane but the differences were not statistically significant. The incidence of arrhythmias was significantly greater for halothane than sevoflurane (62% versus 28%).

A randomized trial compared recovery times with isoflurane and sevoflurane in 80 children undergoing spinal surgery (*22*). Sevoflurane patients had significantly shorter mean extubation times compared to isoflurane patients (6.4 minutes versus 10.7 minutes). Compared with isoflurane, sevoflurane was

associated with significantly shorter mean emergence time (7.8 minutes versus 12.8 minutes) and time to full modified Aldrete score (13.9 minutes versus 20.3 minutes). Meeting the discharge criteria and postoperative events were similar for both treatment groups. Another study compared recovery times with isoflurane and sevoflurane in 84 children aged 2–24 months following cleft lip surgery (*23*). Sevoflurane patients had significantly shorter mean extubation times than isoflurane patients (320 seconds versus 583 seconds). The sevoflurane group also had significantly shorter mean times for spontaneous respiration, hip flexion and eye opening. A third study assessed recovery times with sevoflurane, isoflurane and desflurane in 60 children aged 7–18 years undergoing craniotomy for supratentorial tumour excision (*24*). Compared with isoflurane, sevoflurane patients had significantly shorter mean extubation times (14.0 minutes versus 21.3 minutes), mean emergence times (11.7 minutes versus 15.5 minutes) and mean times to reach Aldrete score ≥9 (29.3 minutes versus 35.6 minutes). The desflurane group also had significantly shorter times on all three measures versus the isoflurane group. No significant differences were seen between the sevoflurane and desflurane groups.

A prospective randomized trial compared sevoflurane and isoflurane for maintenance of and recovery from anaesthesia in 104 elderly patients (*25*). Sevoflurane patients had significantly shorter median extubation time than isoflurane patients (8 minutes versus 11 minutes). The sevoflurane group also had significantly shorter time to eye opening (8.5 minutes versus 12.5 minutes) and time to discharge from the post-anaesthesia care unit (21 minutes versus 27.5 minutes) compared with the isoflurane group.

Summary of evidence: harms

The application stated that most adverse events with sevoflurane were mild or moderate in severity and transient in duration. Nausea and vomiting were observed in the postoperative period, which are common sequelae of surgery and general anaesthesia and may be due to inhalational anaesthetic, other agents administered intra-operatively or postoperatively and the patient's response to the surgical procedure. As with all potent inhaled anaesthetics, sevoflurane may cause dose–dependent cardiorespiratory depression.

The most commonly reported adverse reactions with sevoflurane described were:

- adults – hypotension, nausea and vomiting;
- elderly people – bradycardia, hypotension and nausea; and
- children – agitation, cough, vomiting and nausea.

A summary of the most frequent adverse drug reactions in sevoflurane clinical trials is shown in Table 5.

Table 5

Most frequent adverse drug reactions in sevoflurane clinical trials

System organ class	Adverse reactions	Frequency
Psychiatric disorders	Agitation	Very common
Nervous system disorders	Somnolence, dizziness, headache	Common
Cardiac disorders	Bradycardia Tachycardia Atrioventricular block complete QT prolongation associated with torsade de pointes	Very common Common Uncommon Unknown
Vascular disorders	Hypotension Hypertension	Very common Common
Respiratory, thoracic and mediastinal disorders	Cough Respiratory disorder, laryngospasm	Very common Common
Gastrointestinal disorders	Nausea, vomiting Salivary hypersecretion	Very common Common
General disorders and administration site conditions	Chills, pyrexia	Common
Investigations	Blood glucose abnormal, liver function test abnormal[a], white blood cell count abnormal, fluoride increased[b]	Common
Injury, poisoning and procedural complications	Hypothermia	Common

[a] Occasional cases of transient changes in hepatic function tests were reported with sevoflurane and reference agents.
[b] Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anaesthesia. Concentrations of inorganic fluoride generally peak within 2 hours of the end of sevoflurane anaesthesia and return within 48 hours to pre-operative levels. In clinical trials, elevated fluoride concentrations were not associated with impairment of renal function.

Source: Sevoflurane company core data sheet

Important risks for sevoflurane include:

- cardiovascular changes, including cardiac arrhythmias/cardiac events in children,
- hepatic disorders,

- malignant hyperthermia,
- perioperative hyperkalaemia,
- convulsions,
- history of Pompe disease,
- mitochondrial disorders, and
- hypothermia.

Systematic standardized surveillance for reports associated with these risks are conducted by AbbVie. Reports of these risks are reviewed as cases are received, and reviews of aggregate reports are performed on a quarterly basis. The application reported that no new safety signals had been detected through these surveillance activities coincident with sevoflurane therapy during the current reporting interval.

Common adverse effects of halothane include hypotension, bradycardia, arrhythmias (particularly in neonates and children) and mild liver dysfunction. Halothane has also been associated with hepatotoxicity that in some cases can lead to liver failure, so-called halothane hepatitis, which has a high mortality rate. Halothane-related hepatotoxicity has been the main reason for the declining use of this medicine in many settings (*26*).

WHO guidelines

WHO guidelines for surgical anaesthesia are not currently available.

Costs/cost–effectiveness

Anaesthetics generally contribute to less than 5% of a hospital pharmacy budget and account for about 3–4% of the cost of a surgical procedure (*27*). The cost of anaesthesia is driven by the choice of volatile agent and depends on several other factors, including patient populations, duration of anaesthesia, length of surgical unit stay, and cost of the anaesthesia delivery system.

Specific information on the cost of sevoflurane marketed by AbbVie was not provided in the application. Rather, the application described studies in which factors including reduced mean extubation time (*9*) and reduced length of hospital stay (*18*) associated with sevoflurane use were proposed as potentially resulting in reduced overall costs.

The cost–effectiveness of general anaesthetic agents in adult and child day surgery patients was evaluated in a 2003 study in the United Kingdom (*28*). Total costs were calculated for individual patient resource use up to 7 days after discharge. Incremental cost–effectiveness ratios were expressed as cost per episode of postoperative nausea and vomiting avoided. In both adults and children, induction and maintenance anaesthesia with sevoflurane had higher costs and a higher incidence of postoperative nausea and vomiting and was dominated by

the alternative regimens (total intravenous anaesthesia (propofol) or intravenous induction with propofol or inhalational maintenance with halothane, isoflurane or sevoflurane).

In most settings, the direct costs of sevoflurane are higher than for halothane and isoflurane. A full evaluation of the comparative cost–effectiveness needs to take into account many other associated costs (e.g. delivery systems, carrier gases and disposables) (*29*).

Availability

Sevoflurane, in innovator and generic brands, has wide global marketing approval.

Other considerations

Global warming potential of inhaled anaesthetics

The global warming potential of desflurane, isoflurane and sevoflurane have been evaluated to determine their impact on climate change (*30*). Various techniques were used to estimate the potential for each gas. The 20-year global warming potential values (a higher number indicates a greater impact) for sevoflurane, isoflurane and desflurane were 440, 1800 and 6810, respectively (global warming potential for carbon dioxide being 1; a ton of sevoflurane in the atmosphere thus corresponds to an emission of 440 tons of CO_2). The gases atmospheric lifetimes were estimated to be 1.1, 3.2 and 14.0 years for sevoflurane, isoflurane, desflurane, respectively.

Committee recommendations

The Expert Committee noted that the use of anaesthetics has steadily increased globally over the past few years, with the expansion of health care services. The Committee recognized that volatile anaesthetics are greenhouse gases, with detrimental environmental impact due to their contribution to global warming if leaked into the atmosphere.

The Committee noted that among the volatile anaesthetic gases, sevoflurane has a lower global warming potential than the alternatives, primarily desflurane, which is not currently included on the Model Lists, but also halothane and isoflurane, which are included.

The Committee noted that the clinical efficacy and safety of sevoflurane appears to be similar to isoflurane, with consistent findings across type of surgery and setting. Sevoflurane is indicated for induction and maintenance of general anaesthesia in adult and paediatric patients for inpatient and outpatient surgery. The Committee also noted that vaporizers are essential components of anaesthesia equipment with inhaled anaesthetics. As with other inhalational anaesthetics, degradation and production of degradation products can occur when sevoflurane is exposed to desiccated absorbents. Since the level of anaesthesia may be altered

rapidly, only vaporizers producing predictable concentrations of sevoflurane should be used.

In consideration of the volatile anaesthetics already included on the Model Lists, the Committee noted that halothane is no longer used in many countries because of its harm profile. The Committee also noted that the price difference between halothane, isoflurane and sevoflurane had decreased since sevoflurane was previously considered for inclusion in the Model Lists in 2011.

Therefore, the Committee recommended the inclusion of sevoflurane on the core list of the EML and EMLc as an inhalational anaesthetic based on evidence of similar efficacy and safety to isoflurane, and a lower global warming potential than the currently listed alternatives. The Committee considered that more efficient use of sevoflurane in preference to halothane and isoflurane can contribute to reducing greenhouse gas emissions. In addition, given the limited role of halothane among anaesthetic gases, the Committee recommended that halothane be flagged for deletion from the Model Lists without further discussion in 2025, unless an application is received in support of its retention.

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Section 2: Medicines for pain and palliative care
2.2 Opioid analgesics

Fentanyl – new formulation – EML

Fentanyl	**ATC code: N02AB03**

Proposal

Addition of oral transmucosal formulations of fentanyl citrate on the complementary list of the EML for use in the treatment of breakthrough pain in adult patients with cancer already receiving opioid analgesics to manage cancer pain.

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Noncommunicable Diseases

EML/EMLc

EML

Section

2.2 Opioid analgesics

Dose form(s) & strengths(s)

Buccal film: 200 micrograms, 400 micrograms, 600 micrograms, 800 micrograms, 1.2 mg (as citrate)

Lozenge: 200 micrograms, 400 micrograms, 600 micrograms, 800 micrograms, 1.2 mg, 1.6 mg (as citrate)

Tablet (sublingual): 100 micrograms, 200 micrograms, 300 micrograms, 400 micrograms, 600 micrograms, 800 micrograms (as citrate)

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Oral transmucosal formulations of fentanyl have not previously been considered for inclusion in the EML. In 2017, fentanyl transdermal patches were included on the EML for the management of chronic cancer pain.

While intravenous morphine was included on the first list in 1977, immediate-release formulations of oral morphine have been included on the EML (tablets and oral liquid) since 1984. Hydromorphone and oxycodone are included as alternatives to morphine under a square box listing.

Public health relevance

Cancer is a major public health problem worldwide and is the second leading cause of death, accounting for an estimated 9.9 million deaths and more than 19 million new cases in 2020 (*1*). The cancer burden continues to grow globally, with an estimated doubling of the yearly incidence by 2040, and places tremendous physical, emotional and financial strain on individuals, families, communities and health systems (*2,3*). Despite this growth in incidence, the number of deaths from cancer is decreasing annually because more patients are benefiting from early detection and new improved treatments (*4*).

More than 80% of patients with cancer develop pain before death, and pain is one of the most feared consequences of cancer for both patients and families (*5*). Moderate-to-severe pain has been reported in 38% of the cases (*6*). This pain is often assessed at 7 or higher in the numeric rating scale (with 0 being no pain and 10 the worst pain imaginable) (*7*). Breakthrough cancer pain is a transient exacerbation of pain in the context of otherwise adequately controlled background pain.

An accurate estimate of the prevalence of breakthrough cancer pain is not available. A systematic review and meta-analysis of 19 observational studies (6065 participants) reported a pooled prevalence rate of breakthrough cancer pain of 59.2% (95% confidence interval (CI) 58.0% to 60.4%, high heterogeneity). Subgroup analysis found that the lowest and highest pooled prevalence rates were reported in studies conducted in the outpatient setting (39.9%, 95% CI 35.8% to 44.0%) and hospice setting (80.5%, 95% CI 77.9% to 83.1%) (*8*).

Breakthrough cancer pain can occur as a direct consequence of the tumour (70–80% of cases), as a result of cancer therapy (10–20% of cases) or be unrelated to the tumour or treatment (< 10% cases) (*9*).

Breakthrough pain has a significant impact on the quality of life of patients, being associated with more severe pain-related functional impairment and psychological distress (*10,11*). It is also associated with high use of health care resources, mainly related to a higher number of hospital admissions and drug costs (*12,13*).

Summary of evidence: benefits

A 2013 Cochrane systematic review of 15 randomized trials (1699 participants) evaluated the efficacy of opioid analgesics compared with placebo or active comparator for management of breakthrough cancer pain (*14*). The studies included reported on seven different transmucosal fentanyl formulations – five administered orally and two administered nasally. Eight studies compared the transmucosal fentanyl formulations with placebo, four studies compared them with another opioid, one study was a comparison of different doses of the same formulation and two were randomized titration studies. For the comparison of transmucosal fentanyl versus placebo, transmucosal fentanyl was significantly superior to placebo for pain intensity difference at 10 minutes (mean difference (MD) 0.39, 95% CI 0.27 to 0.52; six studies, 988 participants), and at 15 minutes (MD 0.49, 95% CI 0.35 to 0.62; seven studies, 538 participants). No significant difference was observed at 30 minutes (MD 0.92, 95% CI 0.75 to 1.09; seven studies, 538 participants). For the comparison of transmucosal fentanyl versus oral morphine, the point estimate in the mean pain intensity difference at 15 minutes favoured fentanyl, but this was not statistically significant (MD 0.37, 95% CI 0.00 to 0.73; two studies, 308 participants). Similarly, for the comparison of oral transmucosal fentanyl citrate versus intravenous morphine, the point estimate for mean pain intensity difference at 15 minutes favoured fentanyl, but was not statistically significant (MD 0.80, 95% CI 0.00 to 1.60; one study, 50 participants). Results for other time points for comparisons with oral and intravenous morphine were not reported.

Brief summaries of the results of eight trials from the 2013 Cochrane review, considered by the applicants to be relevant to the application, are presented below.

A randomized, placebo-controlled, double-blind study evaluated oral transmucosal fentanyl citrate for treatment of breakthrough pain in 93 adult patients with cancer (*15*). After titration to an effective fentanyl dose, participants were given 10 randomly ordered treatment units (seven fentanyl, three placebo). Of 804 breakthrough pain episodes treated, 247 were with placebo and 557 were with fentanyl. Episodes of breakthrough pain treated with fentanyl had significantly larger changes in pain intensity and better pain relief at all time points (15, 30, 45 and 60 minutes) than episodes treated with placebo. Episodes of breakthrough pain treated with placebo required the use of rescue medication significantly more often than episodes treated with fentanyl (34% versus 15%; relative risk (RR) 2.27, 95% CI 1.51 to 3.26).

Two randomized trials compared fentanyl buccal tablet with placebo in patients with breakthrough cancer pain (*16,17*). In the first study, after an open-label titration phase to determine effective dose, 77 patients were randomly assigned to receive a prespecified dose sequence of 10 tablets (seven fentanyl,

three placebo). Of 701 breakthrough pain episodes treated, 208 were with placebo and 493 were with fentanyl. The primary outcome measure was the summed pain intensity difference at 30 minutes. Mean summed pain intensity difference at 30 minutes (standard error (SE)) was significantly greater for buccal fentanyl (3.0 (SE 0.12)) than for placebo (1.8 (SE 0.18)). For other outcome measures including pain relief, pain intensity difference, summed pain intensity differences and summed total pain relief and patient ratings of global performance, results all significantly favoured buccal fentanyl (16). The second study, of similar design, included 87 patients in the double-blind phase. The primary outcome measure was summed pain intensity difference at 60 minutes, which significantly favoured buccal fentanyl compared to placebo – 9.7 (SE 0.63) versus 4.9 (SE 0.50). Pain intensity differences and pain relief also significantly favoured buccal fentanyl at all time points (17).

A randomized phase II study evaluated efficacy and tolerability of sublingual fentanyl tablets in 27 patients with breakthrough cancer pain (18). Participants received placebo, fentanyl 100 micrograms, 200 micrograms and 400 micrograms in random order at four breakthrough pain episodes. The primary efficacy measure was pain intensity difference; overall, the difference was significantly larger with 400 micrograms of fentanyl compared with placebo, and improved pain relief was reported for 100 micrograms and 200 micrograms of fentanyl, although this was not statistically significant. The 400 microgram strength was also associated with significantly reduced use of rescue medication and improved global assessment of treatment.

A randomized placebo-controlled, phase III study evaluated efficacy and tolerability of sublingual fentanyl orally disintegrating tablet for breakthrough cancer pain, with 61 patients included in the primary efficacy analysis (19). Following a 2-week open-label titration phase, participants received fentanyl or placebo in random order. For the primary efficacy measure of summed pain intensity difference at 30 minutes, there was a significant improvement for fentanyl compared with placebo (49.5 versus 36.6, $P = 0.0004$). Treatment was also associated with significant improvements in pain intensity difference and pain relief at time points from 10 minutes after dose administration. A similar study evaluated the efficacy and tolerability of fentanyl buccal soluble film formulation in 80 adults with breakthrough cancer pain (20). Mean summed pain intensity difference at 30 minutes was significantly greater for episodes treated with fentanyl compared with placebo, with significant differences maintained to the last assessed time point of 60 minutes. Pain relief values for fentanyl were significantly better than placebo at 30 minutes after dose administration, and the percentage of pain episodes with a 33% or 50% decrease in pain was also significantly greater with fentanyl than placebo.

A randomized, double-blind, double-dummy, multiple crossover trial compared oral transmucosal fentanyl and immediate-release morphine sulfate in

93 adults with breakthrough cancer pain (*21*). After an open-label dose titration phase, participants received 10 prenumbered sets of randomized capsules and oral transmucosal units (5 x successful fentanyl dose + 5 x placebo, 5 x successful morphine dose + 5 x placebo). Oral transmucosal fentanyl performed significantly better than immediate-release morphine for efficacy measures including pain intensity, pain intensity difference and pain relief at all time points. Global performance rating scores also significantly favoured fentanyl. Significantly more pain episodes treated with oral transmucosal fentanyl had a greater than 33% change in pain intensity score at 15 minutes than episodes treated with immediate-release morphine (42.3% versus 31.8%, *P* < 0.001).

A randomized, double-blind dose titration study in ambulatory cancer patients evaluated safety and efficacy of increasing doses of oral transmucosal fentanyl for treatment of breakthrough cancer pain (*22*). This study was not designed to compare fentanyl with usual opioid rescue medicines, however exploratory analyses were performed. These analyses showed that fentanyl treatment was associated with significantly greater analgesic effects at time points up to 60 minutes, and a more rapid onset of effect than usual rescue opioids. Participants rated the global satisfaction of oral transmucosal fentanyl citrate significantly higher than global performance of their usual opioid rescue medicine (2.74 versus 2.09, *P* = 0.0002).

The following studies were not included in the 2013 Cochrane review.

A mixed-treatment meta-analysis of five randomized trials indirectly compared fentanyl preparations, morphine and placebo for the treatment of breakthrough cancer pain to determine the relative contributions to pain relief from oral morphine and the fentanyl preparations using placebo as the common comparator (*23*). The overall probability of superior pain relief, as measured by differences in pain intensity difference scores, compared with placebo was calculated for 15- to 60-minute intervals after dosing. For the first 30 minutes after dosing, the probabilities of superiority over placebo were 56%, 83%, 66% and 73% for immediate-release morphine, fentanyl buccal tablet, fentanyl orally disintegrating tablet and fentanyl lozenge, respectively. Comparing fentanyl preparations with immediate-release morphine over the first 30 minutes after dosing, the probabilities of superiority over morphine were estimated to be 58% for buccal tablet, 56% for orally disintegrating tablet and 62% for lozenge.

The long-term effectiveness of fentanyl orally disintegrating tablets for treatment of breakthrough cancer pain was assessed in a non-randomized, open-label, phase III study (139 participants) (*24*). Effectiveness was evaluated at screening for participation and at each monthly visit using patients' global evaluation of medication, the brief pain inventory and the depression, anxiety and positive outlook scale. Evaluation of patient satisfaction using the patients' global evaluation of medication measure showed an increase in satisfaction ("very satisfied" or "satisfied")

with study pain medication at the end of the study (12 months) versus time at study enrolment (77% versus 54%). For quality-of-life measures, the brief pain inventory evaluation of pain severity indicated that mean levels of pain generally remained stable throughout the study, except for current pain, which was significantly lower at the 6-month visit, compared with at screening. Mean brief pain inventory scores for pain relief improved significantly at both the 6-month and end-of-study visits, compared with at screening. Brief pain inventory scores for interference of pain with daily functioning decreased over the study period, suggesting improvement. The scores on the depression, anxiety and positive outlook scale showed numerical trends towards improvement in all three quality-of-life domains (depression, anxiety and well-being) at the end of the study, compared with at screening. Improvement in depression scores at 6 months was statistically significant.

Subgroup analyses from a multicentre, prospective, observational, open-label study assessed the effect of fentanyl sublingual tablets in the management of breakthrough pain in patients with cancer according to age (< 65 and ≥ 65 years), measuring pain intensity, onset of pain relief, frequency and duration of breakthrough pain episodes, and adverse events at 3, 7, 15 and 30 days. Health-status tools used were the Short Form 12, version 2 questionnaire, and the Hospital Anxiety and Depression Scale (25). Self-reported levels of pain intensity improved significantly compared with baseline for all assessment points and both subgroups. For each assessment point, reduction in pain intensity was greater in the younger age group (67.3% reduction versus 56.3% reduction).

A randomized, open-label study compared the efficacy and safety of oral transmucosal fentanyl and oral morphine in Indian patients (186 participants) (26). Primary efficacy endpoints were reduction in pain determined by numerical rating scale at 5, 15, 30 and 60 minutes, and percentage of breakthrough pain episodes showing at least 33% reduction in pain intensity at 15 minutes. Patients treated with fentanyl experienced significantly greater reduction in pain intensity of breakthrough episodes compared with those treated with oral morphine at all time points assessed. The percentage of breakthrough pain episodes with more than 33% reduction in pain intensity at 15 minutes was significantly greater in patients treated with fentanyl compared with patients treated with morphine (56% versus 39%).

Efficacy and safety studies of oral transmucosal fentanyl versus placebo conducted in the Japanese population also showed positive results (27,28).

Summary of evidence: harms

The adverse effects of fentanyl citrate are generally consistent with the known adverse effects of potent opioid analgesics (14). The most commonly reported adverse effects associated with fentanyl formulations in the treatment of breakthrough cancer pain reported across various studies include asthenia, constipation, dizziness, headache, nausea, pruritus, somnolence and vomiting (15–19,21,22).

Studies with transmucosal fentanyl citrate have shown no differences in pharmacokinetic parameters between younger and older people, and so dose modification is not considered necessary for elderly patients (*29*).

An alert published in 2018 by the Spanish Medicines Agency reported that almost 60% of the cases of abuse and/or dependence reported to the Spanish Pharmacovigilance System involved patients in whom immediate-release fentanyl was used for off-label indications. A systematic review of the literature found an overall incidence of addiction of up to 50% in non-oncology patients, while in oncology patients it was up to 7.7%. In the context of trials evaluating new presentations of rapid-acting fentanyl, 11% of patients were found to have aberrant behaviour associated with its use, of whom < 1% were found to be addicted (*30*).

WHO guidelines

The 2018 WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents includes the best practice statement, "breakthrough pain should be treated with a rescue medicine, which should be an opioid such as morphine in its immediate-release formulation" (*31*).

The WHO Guideline Development Group considered a single small randomized controlled trial (68 participants) which compared analgesics specifically for management of breakthrough pain in an older population with multiple cancer types. The trial provided low strength of evidence that the choice between sustained-release and immediate-release morphine may make no difference in preventing breakthrough pain or reducing pain. The trial did not report on pain relief speed, pain relief maintenance, quality of life, functional outcomes or respiratory depression. The Guideline Development Group agreed that they could not justify making a recommendation on the basis of only one eligible low-quality trial that looked at too few of the options that were clinically available. However, given the urgent need for guidance to manage breakthrough pain for both patients and clinicians, the Guideline Development Group decided to make a best practice statement that breakthrough pain should always be relieved with rescue medicine based on clinical experience and patient need.

The Guideline Development Group highlighted that the cost of certain formulations, such as transmucosal fentanyl, was likely to be prohibitively expensive for some low- and middle-income settings, and that cheaper medicines, such as immediate-release oral morphine, should be made available as a priority if they were not already available (*31*).

Costs/cost–effectiveness

Breakthrough cancer pain imposes a significant financial burden on patients and health systems through increased hospitalization and health care utilization (*12,32*).

An economic analysis of oral fentanyl formulations for treatment of breakthrough cancer pain was conducted from the Italian national health services perspective (*33*). The base-case analysis found that compared with placebo, all formulations assessed (sublingual fentanyl citrate, fentanyl sublingual tablets, fentanyl buccal soluble film, fentanyl buccal tablet and oral transmucosal fentanyl citrate) were associated with incremental costs per quality-adjusted life year gained lower than €50 000–60 000, the incremental cost–effectiveness ratio threshold generally used in Italy. Among formulations, sublingual fentanyl citrate dominated all others (lower cost, greater effectiveness).

An economic analysis from Sweden evaluated the cost–effectiveness of intranasal fentanyl spray compared with oral transmucosal fentanyl citrate and fentanyl buccal tablet for the treatment of breakthrough cancer pain (*34*). The base-case analysis found that compared with placebo, all formulations assessed were associated with incremental costs per quality-adjusted life year gained lower than the willingness-to-pay threshold in Sweden of €45 000.

The application presented estimates of annual treatment costs of transmucosal fentanyl by country and region. Average national treatment costs per patient per year calculated in the application based on the defined daily dose for sublingual fentanyl of 600 micrograms ranged from US$ 189.70 in Egypt to US$ 48 386.40 in Lebanon. Average treatment costs per patient per year by region based on the defined daily dose of 600 micrograms were reported in the application as US$ 4695.60 in Africa, US$ 6455.50 in Asia and the South Pacific, US$ 5673.10 in Europe, US$ 28 534.30 in North America and US$ 3214.60 in South America.

Availability

The application reported that 24 brands (innovator and generic) of transmucosal fentanyl formulations were variously available in 47 countries globally. Availability in low- and middle-income countries appears limited.

Other considerations

The Expert Committee noted the comments received during the public consultation period in relation to the application from the International Association for Hospice and Palliative Care, the Worldwide Hospice Palliative Care Alliance, the Groupe de Recherche et d'Actions Sociales in Burkina Faso and the WHO Collaborating Centre for Training and Policy on Access to Pain Relief. These stakeholders all expressed their opposition to the proposed inclusion of oral transmucosal fentanyl on the Model List, citing the following reasons.

- Patients must remain on around-the-clock opioids while taking oral transmucosal fentanyl citrate. Given the limited availability of opioids for pain and palliative care in resource-constrained settings, it would be challenging to meet these requirements in low- and middle-income countries.

- Morphine (with oxycodone and hydromorphone as alternatives) is already included in the EML. The inclusion of both immediate-release and sustained-release oral preparations enables morphine to be successfully used in both acute and chronic cancer pain, and breakthrough pain. Morphine is the strong opioid of choice for treatment of moderate-to-severe pain. No evidence exists to support the need for, or the addition of, another pure agonist to treat breakthrough pain.

- Data are lacking on dose-equivalence for transmucosal fentanyl compared with other opioids and oral, modified-release formulation of fentanyl. This means that using transmucosal fentanyl to commence or titrate opioids to effect is less safe than the usual, recommended practice of immediate- and modified-release morphine (or equivalent opioids).

- Because of its rapid onset and lipophilic characteristics with selective activity for μ-receptors expressed in the brain, spinal cord and other tissues, fentanyl citrate has a higher risk of non-medical use compared with the other pure agonists included in the WHO EML. Its short time to onset should be considered of equal importance to its short duration of action. In many cases, patients using fentanyl citrate for breakthrough pain often consume more opioid in total over a 24-hour period than if they had been prescribed their usual regimen of immediate-release with or without modified release morphine (or equivalent longer-acting opioids) for breakthrough pain.

- Oral transmucosal fentanyl citrate is available in only a few, mostly high-income, countries. Appropriate use of oral transmucosal fentanyl may not be feasible in low-income settings, where health care workers may not receive training in the administration and pharmacokinetics of fentanyl, which could lead to serious adverse events and potential fatalities.

- The cost–effectiveness of oral transmucosal fentanyl versus immediate-release morphine is not known. Inclusion of oral transmucosal fentanyl on the EML may result in the allocation of public funds for the procurement of an expensive formulation in lieu of more cost-effective formulations already included in the list.

- Breakthrough pain is not homogenous and whilst transmucosal fentanyl has a place in treating some types of breakthrough pain and for some patients, it does not and must not replace immediate-release morphine.

Committee recommendations

The Expert Committee acknowledged that most cancer patients with active cancer develop pain during the course of the disease, and that pain is one of the most feared consequences of cancer for both patients and their families. The Committee noted that the EML currently includes immediate-release formulations of oral morphine, which is recognized as the strong opioid of choice for breakthrough cancer pain. The Committee also acknowledged the serious problems with access to morphine in many parts of the world.

The Committee acknowledged that the evidence presented in the application shows oral transmucosal fentanyl (on a background of regular opioid dosing) to be an effective option for the treatment of breakthrough cancer pain. When compared with immediate-release morphine, oral transmucosal fentanyl might provide some advantage in terms of lower pain intensity and better pain relief scores. However, the Committee noted that most studies compared oral transmucosal fentanyl to placebo and therefore these data did not provide compelling evidence of the superiority of transmucosal fentanyl compared with other fast-acting opioids, including immediate-release oral morphine which is already included on the Model List.

The Committee considered that any advantages of oral transmucosal fentanyl are easily off-set by several safety concerns. Fentanyl has an estimated 50 to 100 times greater potency than morphine, has more complex pharmacokinetics and is associated with greater potential for drug–drug interactions – factors that necessitate specialist training for its safe and appropriate use, which may not be widely available in low- and middle-income settings. The Committee also recognized that access to immediate-release oral morphine in many settings is limited, meaning that the necessary background opioid treatment required for appropriate use of oral transmucosal fentanyl may not be available, further compromising its safe and appropriate use. Furthermore, while opioid misuse is reported to be uncommon in patients with cancer, fentanyl has a higher addictive potential than other opioids and has been associated with increased trends in opioid overdose deaths in non-medical users of opioids in several countries.

The Committee noted a lack of cost–effectiveness data comparing oral transmucosal fentanyl with immediate-release morphine, but considered that oral transmucosal fentanyl is more costly than oral morphine, which is not matched by commensurate therapeutic benefits.

Therefore, the Expert Committee did not recommend the addition of oral transmucosal fentanyl to the EML for use in the treatment of breakthrough cancer pain in adults based on the lack of evidence of superiority over already listed immediate-release morphine, safety concerns and lack of compelling cost–effectiveness data.

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Section 5: Medicine for diseases of the nervous system
Donepezil – addition – EML

Donepezil	ATC code: N06DA02

Proposal

Addition of donepezil to the complementary list of the EML for the management of Alzheimer disease dementia.

Applicant

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EML/EMLc

EML

Section

5 Medicines for diseases of the nervous system

Dose form(s) & strengths(s)

Tablet: 5 mg, 10 mg
Tablet (orodispersible): 5 mg, 10 mg
Oral solution: 1 mg/mL

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Medicines for Alzheimer disease dementia have not previously been evaluated for inclusion in the EML.

Public health relevance

In 2019, it was estimated that there were over 55 million people with dementia worldwide, 61% of whom lived in low- and middle-income countries. Due to rapidly ageing populations, this number is set to increase to 78 million by 2030 and to at least 139 million by 2050. Dementia causes disability and care dependency in older age and ranks as the 25th leading cause of disability-adjusted life years. Alzheimer disease and other dementias were the seventh leading cause of death globally in 2019 (*1*).

Summary of evidence: benefits

Consensus is lacking on what represents clinically important effect sizes for outcome measures for patients with Alzheimer disease dementia, their families or care-givers or their doctors (*2–4*).

The application identified national health technology appraisals undertaken to inform dementia clinical guideline development, and additional systematic reviews and randomized trials.

The application presented a brief summary of findings of the 2018 United Kingdom National Institute for Health and Care Excellence (NICE) dementia care health technology appraisal of cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine for treatment of Alzheimer disease (*5*). This appraisal updated the 2016 NICE clinical guidelines and included data from 19 randomized trials comparing donepezil with placebo in adults with a diagnosis of mild to moderately severe Alzheimer disease (*6*).

Pooled cognitive outcomes showed a statistically significant difference in favour of donepezil measured using cognitive assessment scale scores:

- Mini Mental State Examination score: weighted mean difference (WMD) 1.17 points (95% confidence interval (CI) 0.88 to 1.45) at 12 weeks and 1.21 points (95% CI 0.84 to 1.57) at 24 weeks;
- Alzheimer Disease Assessment Scale–Cognitive Subscale score: WMD −1.97 (95% CI −3.38 to −0.56) at 12 weeks and −2.90 (95% CI −3.61 to −2.18) at 24 weeks.

A 2018 systematic review and network meta-analysis of 142 studies (110 randomized controlled trials, 21 non-randomized controlled trials and 11 cohort studies) evaluated the comparative effectiveness and safety of cholinesterase inhibitors or memantine for Alzheimer disease (*7*). The network meta-analyses of cognitive outcomes measured using Mini Mental State Examination scale (56 randomized controlled trials, eight treatments, 10 446 participants) found the following interventions to be superior to placebo:

- donepezil (mean difference (MD) 1.39, 95% credible interval (CrI) 0.53 to 2.24),
- donepezil + memantine (MD 2.59, 95% CrI 0.12 to 4.98),
- transdermal rivastigmine (MD 2.02, 95% CrI 0.02 to 4.08).

Network meta-analyses of cognitive outcomes measured using the Alzheimer Disease Assessment Scale–Cognitive Subscale (53 randomized controlled trials, six treatments, 11 348 participants) found the following interventions to be superior to placebo:

- donepezil (MD –3.29, 95% CrI –4.57 to –1.99),
- galantamine (MD –2.13, 95% CrI –3.91 to –0.27).

A subsequent systematic review and individual patient data network meta-analysis of 80 randomized controlled trials (21 138 participants) including 12 randomized controlled trials with individual patient data (6906 participants) evaluated the comparative efficacy and safety of cholinesterase inhibitors or memantine by patient characteristics for managing Alzheimer dementia (*8*). Significant improvements in Mini Mental State Examination scores were seen for donepezil (MD 1.41, 95% CI 0.51 to 2.32) and donepezil + memantine (MD 2.57, 95% CI 0.07 to 5.07) compared with placebo. Transdermal rivastigmine and the combinations of donepezil + memantine, galantamine + memantine, and transdermal rivastigmine + memantine showed MDs greater than 1.40, however associated 95% CIs were wide and included zero. Donepezil, memantine and their combination showed a larger improvement in cognitive performance in patients with moderate-to-severe cognitive impairment. Donepezil and transdermal rivastigmine showed the greatest improvement in cognitive performance in patients with mild-to-moderate disease.

A 2019 meta-analysis of 36 randomized trials (6611 participants) evaluated the efficacy and safety of cholinesterase inhibitors and memantine for the treatment of Alzheimer disease (*9*). From studies of donepezil versus placebo, there were significant differences favouring donepezil in cognition as measured using the Alzheimer Disease Assessment Scale–Cognitive Subscale, functional outcomes measured using the AD Cooperative Study Activities of Daily Living subscale and global assessment of change measured using Clinician's Interview-Based Impression of Change Plus Caregiver Input scale. No effect of donepezil was observed for behavioural outcomes measured using the Neuropsychiatric Inventory scale.

Summary of evidence: harms

The application described donepezil as being generally safe and well tolerated, with minor side-effects including nausea, vomiting, diarrhoea, loss of appetite, weight loss, muscle cramps and urinary difficulties. QTc interval prolongation and

torsade de pointes have been reported in postmarketing studies and routine pulse checks are recommended at baseline, monthly intervals during dose titration, and 6-monthly intervals thereafter (*10*). Rhabdomyolysis and neuroleptic malignant syndrome have been reported rarely in association with donepezil.

Safety outcomes from the systematic reviews and meta-analyses described above were not reported in the application but are summarized below.

The 2018 systematic review reported no increased risk of adverse events, falls or bradycardia with any of the medicines evaluated. Increased risks of diarrhoea, nausea and vomiting were reported for donepezil (*7*).

In the systematic review and individual patient data network meta-analysis, a network meta-analysis of studies with individual patient data and aggregate data, compared all available treatments for adverse events (*8*). According to *P*-scores (a statistical score used to rank treatments in meta-analyses), oral rivastigmine and donepezil had the least favourable safety profiles. Estimated treatment effects were imprecise compared with placebo.

The 2019 meta-analysis noted that high drop-out rates and adverse effects associated drop-outs were observed in randomized controlled trials of cholinesterase inhibitors and memantine. The meta-analysis reported discontinuation due to adverse events and drop-outs due to any reason. Compared with placebo, donepezil was significantly associated with increased discontinuation due to adverse events (odds ratio (OR) 1.24, 95% CI 1.04 to 1.19). There was no significant difference between donepezil and placebo for drop-outs due to any reason (OR 1.12, 95% CI 0.91 to 1.37) (*9*). Adverse effects observed were gastrointestinal and nervous system effects including nausea, vomiting, diarrhoea, anorexia, dizziness, depression and headache; however, the incidence of these effects was not compared.

Additional evidence

A Cochrane systematic review of 30 randomized controlled trials (8257 participants) identified during the application review process assessed the efficacy and safety of donepezil in people with Alzheimer disease of all severities, and also compared efficacy and safety of different doses of donepezil (*11*). Most of the included studies were of 6 months' duration or shorter. One study (286 participants) had a duration of 52 weeks. The studies tested mainly donepezil capsules at a dose of 5 mg/day or 10 mg/day. Two studies tested a slow-release oral formulation that delivered 23 mg/day. Most of the included studies (n=21) included participants with mild-to-moderate disease. The primary analysis compared the efficacy and safety of donepezil 10 mg/day versus placebo at 24 to 26 weeks of treatment (13 randomized controlled trials, 3396 participants). Seventeen studies were industry funded or sponsored, four studies were funded independently of industry and for nine studies no information was given on

the funding source. Donepezil was associated with improved outcomes after 26 weeks for cognitive function measured with the Alzheimer Disease Assessment Scale–Cognitive Subscale (MD –2.67, 95% CI –3.31 to –2.02), Mini Mental State Examination score (MD 1.05, 95% CI 0.73 to 1.37) and the Severe Impairment Battery (MD 5.92, 95% CI 4.53 to 7.31). Donepezil was also associated with improved functioning measured with the Alzheimer Disease Cooperative Study activities of daily living score for severe Alzheimer disease (MD 1.03, 95% CI 0.21 to 1.85). A higher proportion of participants treated with donepezil experienced improvement on the Clinician-rated Global Impression of Change scale (OR 1.92, 95% CI 1.54 to 2.39). No difference was observed between treatment groups for behavioural symptoms measured by the Neuropsychiatric Inventory (MD –1.62, 95% CI –3.43 to 0.19) or by the Behavioural Pathology in Alzheimer Disease scale (MD 0.4, 95% CI –1.28 to 2.08). No difference was observed between treatment groups for quality of life (MD –2.79, 95% CI –8.15 to 2.56). Participants treated with donepezil were more likely to withdraw from the studies before the end of treatment (24% versus 20%; OR 1.25, 95% CI 1.05 to 1.50) or to experience an adverse event during the studies (72% versus 65%; OR 1.59, 95% 1.31 to 1.95).

WHO guidelines

The 2015 WHO Mental Health Gap Action Programme (mhGAP) guidelines make the following recommendations on cholinesterase inhibitors and memantine for the treatment of dementia in non-specialist health settings (*12*).

"Cholinesterase inhibitors and memantine may be offered to people with dementia in non-specialist health settings. Non-specialists need to be trained and supervised to ensure competence in diagnosis and monitoring. The use of cholinesterase inhibitors should be focused upon those with mild to moderate Alzheimer's disease, where the majority of evidence is available. Memantine may be considered for those with moderate to severe Alzheimer's disease and vascular dementia. Memantine should not be prescribed for Lewy Body dementia." (quality of evidence: very low, strength of recommendation: conditional).

"Rationale: Cholinesterase inhibitors and memantine offer symptomatic benefits in cognitive, functional, global and behavioural outcomes, although the size of this benefit is uncertain and the quality of the evidence very low. Adverse effects and safety in the long-term may represent serious concerns. Dementia diagnosis and subtype definition and management with the above medications require training, supervision, and support. Moreover, these medications are associated with high acquisition costs. Remarks: Consideration should be given to adherence and monitoring of adverse effects."

The 2016 WHO mhGAP Intervention Guide includes the following recommendations for the use of cholinesterase inhibitors or memantine in dementia (*13*).

"For dementia without behavioural and/or psychological symptoms, do not consider cholinesterase inhibitors (like donepezil, galantamine and rivastigmine) or memantine routinely for all cases of dementia. Consider medications only in settings where specific diagnosis of Alzheimer disease can be made AND where adequate support and supervision by specialists and monitoring (for side-effects and response) from carers is available. If appropriate: For dementia with suspected Alzheimer disease, and with close monitoring, consider cholinesterase inhibitors (e.g. donepezil, galantamine, rivastigmine) OR memantine. For dementia with associated vascular disease, consider memantine."

Costs/cost–effectiveness

The application presented the findings of multiple systematic reviews, health technology assessments and other studies that evaluated the cost–effectiveness of treatments for Alzheimer disease, including donepezil. Most were conducted more than 15 years ago, before the introduction of generic donepezil, and may be of limited applicability today because of changes in acquisition costs.

The most recent systematic review of seven cost–effectiveness analyses was published in 2012 (*14*). Analyses for patients treated in trials of donepezil versus placebo showed incremental cost–effectiveness ratios ranging from dominance (clinically superior and cost saving) up to €20 867 per quality-adjusted life year (QALY), suggesting that donepezil was a cost-effective or even a cost-saving strategy at common willingness to pay thresholds in high-income countries.

A 2020 analysis of the cost–effectiveness of treatments for Alzheimer disease using real-world evidence from Thailand utilized a simulation model to compare the costs and cost–effectiveness of donepezil, galantamine, rivastigmine, memantine and no treatment (*15*). Effectiveness was measured as QALYs, and costs included direct medical expenditures (outpatient, inpatient and emergency visits; medications), out-of-pocket payments, costs of transportation and formal caregiving services, and the indirect costs of unpaid informal caregiving time. From a societal perspective, the mean incremental cost–effectiveness ratio for donepezil treatment was US$ 4062 per QALY, and thus cost-effective at the willingness-to-pay threshold of 160 000 Thai bahts/QALY gained (US$ 4994/QALY gained) applied in Thailand. The incremental cost–effectiveness ratio decreased with early introduction of treatment.

Multiple other (older) economic evaluation studies, primarily conducted in high-income settings, have found donepezil to be a cost-effective intervention compared with placebo (*16–28*).

A global survey conducted by the applicants collected information on the price of a 5 mg tablet of donepezil. Reported prices ranged from US$ 0.13 to US$ 6.60 per tablet.

Availability

Donepezil is available in innovator and generic brands.

Medicines to treat dementia are approved in fewer low- and middle-income countries compared with high-income countries (78% and 97%, respectively). Generics are reported to be available in 59% of low- and middle-income countries compared with 85% of high-income countries. Full reimbursement of such medicines has been reported in 26% of low- and middle-income compared to 76% of high-income countries (*1*).

Committee recommendations

The Expert Committee recognized that Alzheimer disease is a leading cause of disability and dependency worldwide, with high disease burden and associated costs. It also recognized that there is a substantial demand and need for effective treatments for dementia due to Alzheimer disease. The Committee noted that medicines such as donepezil and other cholinesterase inhibitors have been available in several regions of the world for symptomatic management of dementia due to Alzheimer disease for a long time but they had not previously been evaluated for inclusion on the EML.

The Committed acknowledged that moderate-certainty evidence suggested donepezil may be associated with a statistically significant effect on cognitive outcome scores compared with placebo. However, most of the Committee members considered that these improvements were unlikely to be clinically meaningful. Committee members held different views about the interpretation of the clinical importance of possible benefits associated with donepezil. Most of them considered the benefits of donepezil at the population level to be minimal or nil. A few members considered the benefits to be small but would consider offering donepezil to people with dementia due to Alzheimer disease in the absence of other effective treatments. All experts agreed that there was no clear evidence of prolonged benefits over time.

The Committee noted from the evidence that the effect of donepezil on activities of daily living was limited, while no difference on behavioural symptoms and quality of life was found. The limited duration of studies was also considered by the Committee to be inadequate to assess the longer-term clinical benefit of a treatment for a chronic degenerative disorder such as Alzheimer disease. There is no evidence that donepezil or other cholinesterase inhibitors can reverse or slow the progression of Alzheimer disease.

The Committee accepted that the adverse effects of donepezil are generally mild and that donepezil is well tolerated in most patients. However, the Committee noted that the risk of adverse effects increases with higher doses, and there is potential for numerous drug–drug and drug–disease interactions, especially considering that polypharmacy is common in older people.

The Committee considered that patients included in dementia trials are generally younger and characterized by a better performance status compared with patients seen in routine dementia health care facilities, which affects generalizability of trial results to the population with Alzheimer dementia encountered in routine clinical care.

Overall, it was the view of most of the Committee members that the overall benefit-to-harm profile of donepezil was unfavourable.

The Committee noted evidence from studies conducted primarily in high-income countries that determined donepezil to be cost-effective compared with placebo when added to standard of care for patients with dementia. However, given the Committee's views about the benefit-to-harm profile, this evidence was not considered compelling and did not influence the recommendation.

The Committee noted that diagnosis of Alzheimer disease dementia in later stages is potentially feasible even in the context of resource-constrained settings, as it is mostly based on clinical symptoms, which become clearer as the disease progresses. However, diagnosis in early stages is more challenging, and it is usually managed by specialized health care professionals experienced in the use of validated memory or cognitive function tests. The Committee expressed concerns about the feasibility and availability of specialized diagnostic services for Alzheimer disease, especially in resource-constrained settings. While the 2015 WHO guidelines state that donepezil may be offered in non-specialist settings, clinicians must be adequately trained to ensure safe and effective treatment, which may be an important barrier to diagnosis and feasibility of appropriate use.

The Committee noted that donepezil is already included in some national essential medicines and reimbursement lists. The Committee also noted however that debate over the overall clinical benefit at the population level in recent years has resulted in reconsideration of continued reimbursement for donepezil in some countries, notably France. Other countries have introduced prescribing limitations or shared-care protocols and monitoring in specialist settings.

Therefore, based on these considerations, the Expert Committee did not recommend inclusion of donepezil on the EML for the treatment of dementia due to Alzheimer disease.

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Risdiplam – addition – EML and EMLc

Risdiplam	ATC code: M09AX10

Proposal

Addition of risdiplam to the core list of the EML and EMLc for treatment of spinal muscular atrophy (SMA) in paediatric and adult patients.

Applicant

Knowledge Ecology International

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

5 Medicines for diseases of the nervous system

Dose form(s) & strengths(s)

Powder for oral liquid: 0.75 mg/mL

Core/complementary

Core

Individual/square box listing

Individual

Background

Risdiplam has not previously been considered for inclusion on the Model Lists. There are currently no treatments for SMA included on the EML or EMLc.

Public health relevance

SMA is a hereditary genetic disease caused by a mutation in the survival motor neuron (*SMN1*) gene resulting in insufficient levels of survival motor neuron protein. Signs of SMA include muscle weakness and hypotonia, motor difficulties, loss of motor skills, proximal muscle weakness, hyporeflexia, tongue fasciculations and signs of low motor neuron disease (*1*). Estimates of the incidence of SMA vary from 1 in 6000 to 1 in 12 000 live births (*2*, *3*). The data and research on the incidence of SMA is predominately from Europe and North America. However,

the few studies conducted in low- and middle-income countries have reported similar birth incidence with fewer cases surviving the first year of life (*4*).

Five types of SMA exist, which are classified by age at onset of symptoms. Type 0 is usually identified in utero because of a decrease or loss of fetal movement and infants born with SMA type 0 have survival of under 6 months. Type 1 develops in babies younger than 6 months, and this type is the leading genetic cause of death in early infancy (*5*). Type 2 clinically manifests between 7 months and 18 months, type 3 develops after 18 months, and type 4 develops in adulthood and usually causes mild problems (*1*).

Patients diagnosed with SMA exhibit a wide range of motor function, from extremely weak infants unable to sit to adults who can play sport (*3*). Clinically meaningful treatment outcomes for infants and children are achieving motor milestones, improvement or stabilization of motor and respiratory function, ventilation-free survival and overall survival. For adults, stabilization of motor function and respiratory function, maintaining independence, fewer hospital visits and health-related quality of life are meaningful treatment outcomes (*6*).

Risdiplam is the first oral treatment for SMA. There are currently two other disease-modifying therapies to treat SMA. Nusinersen is an *SMN2* targeting antisense oligonucleotide administered by intrathecal injection. Onasemnogene abeparvovec is a gene therapy using a recombinant adeno-associated viral vector containing DNA encoding the normal *SMN1* gene administered through a one-time intravenous infusion. Unlike the alternatives, risdiplam treatment does not require hospitalization for administration.

Summary of evidence: benefits

No systematic reviews or meta-analyses involving risdiplam have been done nor any direct head-to-head studies comparing risdiplam with the two other treatments for SMA. As such, the only studies comparing risdiplam with nusinersen and/or onasemnogene abeparvovec are indirect treatment comparisons. The main clinical trials and indirect comparisons are summarized below.

Risdiplam has been evaluated in three clinical trials. FIREFISH examined risdiplam for type 1 SMA in infants (28 days to 7 months), SUNFISH examined risdiplam for type 2/3 non-ambulant SMA in children and young adults (2 to 25 years) and RAINBOWFISH evaluated risdiplam in genetically diagnosed, presymptomatic infants (birth to 6 weeks). FIREFISH and SUNFISH each had two parts: a dose-finding exploratory phase II trial, and a phase III trial testing efficacy and safety.

In FIREFISH part 1, 21 patients were enrolled. Their baseline characteristics were consistent with symptomatic patients with type 1 SMA. The median age at enrolment was 6.7 months (range: 3.3–6.9 months) and the median time between onset of symptoms and the first dose was 4.0 months

(range: 2.0–5.8 months). A total of 17 patients received the therapeutic dose of risdiplam (the dose selected for part 2). After 12 months of treatment, 41% (7/17) of these patients were able to sit independently for at least 5 seconds. After 24 months of treatment, three more patients receiving the therapeutic dose were able to sit independently for at least 5 seconds, leading to a total of 59% (10/17) achieving this motor milestone (*7*).

In FIREFISH part 2, 41 patients with type 1 SMA were enrolled. The median age at onset of clinical signs and symptoms of type 1 SMA was 1.5 months (range: 1.0–3.0 months), 54% were females, 54% were described as Caucasian and 34% as Asian. The median age at enrolment was 5.3 months (range: 2.2–6.9 months) and the median time between onset of symptoms and the first dose was 3.4 months (range: 1.0–6.0 months). At baseline, the median score on the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) was 22.0 points (range: 8.0–37.0 – possible scores ranged from 0 to 64 with lower scores indicating more severe disease) and the median Hammersmith Infant Neurological Examination Module 2 (HINE-2) score was 1.0 (range: 0.0–5.0 – possible scores ranged from 0 to 26 with lower scores indicating more severe disease). At month 24, 44% (18/41) (90% confidence interval (CI) 31% to 58%) of patients achieved sitting without support for 30 seconds. Patients continued to achieve additional motor milestones as measured by the Bayley Scales of Infant and Toddler Development–third edition (BSID-III): 85% (35/41) were able to roll (*8*). In a pooled efficacy analysis of FIREFISH part 1 and part 2 outcomes based on the patients treated with the recommended dose, 28% (16/58) of patients achieved the ability to stand as measured by HINE-2. Despite the progress described, no infants achieved independent standing or walking, as assessed by the BSID-III gross motor subscale (*9*).

RAINBOWFISH was an open-label, single-arm, multicentre clinical study to investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of risdiplam in infants up to 6 weeks of age who had been genetically diagnosed with SMA but had not presented any symptoms (*10*). The primary analysis was conducted at 12 months in six infants with two or three *SMN2* copies. The primary endpoint was the proportion of infants sitting without support for 5 or more seconds. Efficacy data from the study indicated that the infants reached a sufficient CHOP-INTEND score: six (100%) infants were able to sit without support, four (67%) were able to stand and three (50%) were able to walk independently. In addition, the infants maintained their swallowing and feeding abilities. Thus far, the study has shown that, after 12 months of treatment with risdiplam, most presymptomatic infants met key milestones.

SUNFISH was conducted in non-ambulant patients with types 2 and 3 SMA aged from 2 to 25 years. Part 1 of SUNFISH was dose-finding and exploratory. Part 2 was a multicentre trial to investigate the efficacy, safety, pharmacokinetics

and pharmacodynamics of risdiplam. In SUNFISH Part 1, 51 patients were enrolled. Exploratory efficacy analyses showed improvements in motor function scores after 24 months of treatment with mean increases from baseline in the 32-item Motor Function Measure (MFM32) total score (2.7 points, 95% CI 1.2 to 4.2, n = 44), Revised Upper Limb Module total score (2.5 points, 95% CI 1.5 to 3.4, n = 51) and Hammersmith Functional Motor Scale–Expanded total score (0.6 points, 95% CI –0.6 to 1.8, n = 51). Younger patients (2–11 years) achieved greater improvements in motor function than older patients (12–25 years) (*11*).

SUNFISH part 2 is a randomized, placebo-controlled, double-blind study of 180 non-ambulant patients with type 2 (128 patients, 71%) or type 3 (52 patients, 29%) SMA (*12*). Patients were randomized 2:1 to receive either a therapeutic dose of risdiplam or placebo. Randomization was stratified by age group. The primary endpoint was change from baseline in the 32-item MFM-32 score at month 12. MFM-32 has a possible range of scores from 0 (severe functional impairment) to 100 (no functional impairment). Patients in SUNFISH part 2 had a mean baseline MFM-32 score of 46.1. The baseline demographic characteristics were balanced between risdiplam and placebo arms except for scoliosis (63% of patients in the risdiplam arm and 73% of patients in the placebo control). At 12 months, the least squares mean change from baseline in MFM-32 scores in the risdiplam and placebo groups were 1.36 (95% CI 0.61 to 2.11) and –0.19 (95% CI –1.22 to 0.84), respectively, and a treatment difference of 1.55 points (95% CI 0.30 to 2.81, P = 0·016) favouring risdiplam. This difference is encouraging, particularly if progress is going to be maintained over time.

Indirect comparisons

Risdiplam and nusinersen

Three studies explored indirect comparisons with nusinersen. The first qualitative comparison of treatment between risdiplam and nusinersen concluded that both medicines have had a substantial positive impact on the quality of life of patients with SMA (*13*). The second study, (funded by the manufacturer of risdiplam) concluded that risdiplam may be superior to nusinersen with regard to survival and motor function in patients with type 1 SMA. The comparison reported a lower likelihood of serious adverse events with risdiplam compared with intrathecally injected nusinersen. The authors noted that the lower likelihood of serious adverse events may also be associated with better efficacy for risdiplam, as there could be some collinearity between motor function and severe adverse events. Comparing risdiplam with nusinersen in types 2 or 3 SMA was challenging due to the large differences in population. As a result, the study could not draw concrete conclusions from indirect comparisons with types 2 and 3 SMA (*14*). The third indirect comparison was conducted by the German Institute for Quality and Efficiency in Health Care. The agency concluded that there was no evidence of

differences in efficacy between risdiplam and nusinersen, with the exception of long-term ventilation that might be necessary less often with risdiplam (*15*).

Risdiplam and onasemnogene abeparvovec

Two studies indirectly compared risdiplam and onasemnogene abeparvovec and found mixed results. One study found that treatment with onasemnogene abeparvovec compared with risdiplam was associated with greater improvement in CHOP-INTEND scores. However, the study cohorts were not fully matched for their disease severity and age (*16*). The second study was an indirect comparison by the manufacturer of risdiplam which found insufficient evidence to draw conclusions on the relative efficacy of the two treatments because of the substantial differences in study populations (*14*).

Summary of evidence: harms

The safety of risdiplam in treatment of later-onset SMA was evaluated in the SUNFISH part 2 study (*12*). The most common adverse events were fever, diarrhoea and rash, reported in less than 10% of the patients that received risdiplam. Adverse events that occurred in at least 5% of patients treated with risdiplam and at an incidence of ≥ 5 percentage points higher than placebo included fever (22% versus 17%), diarrhoea (17% versus 8%), rash (17% versus 2%), mouth and aphthous ulcers (7% versus 0%), arthralgia (5% versus 0%) and urinary tract infection (5% versus 0%).

The safety of risdiplam in infantile-onset SMA was evaluated in the FIREFISH study (parts 1 and 2) (*7,8*). The most frequent adverse reactions reported were similar to those reported in later-onset SMA patients. In addition, in FIREFISH part 2, 54% of infants experienced upper respiratory tract infections. Serious adverse events were reported in 68% of patients, with the most frequently reported serious adverse event being pneumonia, a frequent complication due to the SMA itself (e.g. because of bronchoaspiration) which might lead to death.

The safety of risdiplam in presymptomatic infants with genetically diagnosed SMA was evaluated in the RAINBOWFISH study (*10*). No treatment-related serious adverse events were reported in infants treated for ≤ 22.8 months.

WHO guidelines

WHO guidelines for treatment of SMA are not available.

Costs/cost–effectiveness

All three available treatments for SMA are currently very costly.

The application described health technology assessments and reimbursement considerations of risdiplam made by health technology assessment agencies in Canada (*6,17*), Ireland (*18*), the Kingdom of the Netherlands (*19*)

and the United Kingdom (*20*). Overall, health technology assessment agencies found cost–effectiveness analyses difficult to conduct due to the limited number of studies comparing the efficacy of risdiplam with nusinersen or onasemnogene abeparvovec. In some settings, risdiplam was recommended for reimbursement subject to conditions such as price reductions or managed entry arrangements. In others, risdiplam was not recommended for reimbursement until the cost–effectiveness relative to the alternative treatments was improved.

A cost–effectiveness study comparing risdiplam and nusinersen for the treatment of SMA type 1 patients in China reported risdiplam to be dominant over nusinersen, with increased quality-adjusted life years and lower costs (*21*).

Table 6 reports a cost comparison of risdiplam, nusinersen and onasemnogene abeparvovec provided in the application.

Table 6

Cost comparison of current SMA treatments

Medicine	Price, in US$ per patient
Risdiplam	Up to 340 000 a year
Onasemnogene abeparvovec	2 125 000 (single injection)
Nusinersen	750 000 for the first year; 375 000 a year for subsequent years

The application highlights that the most important component of the manufacturing cost of the medicine is the cost of the active pharmaceutical ingredient. The prices of the active pharmaceutical ingredient depend upon manufacturing methods, the scale of production and the extent of competition among suppliers. The current price of risdiplam per unit of active pharmaceutical ingredient in high-income countries ranges from US$ 118 to US$ 209 million per kg. According to the applicant, in a competitive market, manufacturing costs for risdiplam active pharmaceutical ingredient per kg could be as low as US$ 4000 to US$ 40 000, depending on the production scale.

Availability

As of December 2022, risdiplam was approved in 81 countries. Marketing authorization has been filed in several additional countries. Currently, there are no generic manufacturers, nor existing or planned licensing agreements between the patent holder (Roche) and generic manufacturers. A request by Knowledge Ecology International for a voluntary licence to manufacture and sell a generic version of risdiplam was not granted by Roche. Roche has offered access programmes in some lower-income countries to make risdiplam more affordable.

Other considerations

In about 10 high-income countries, universal newborn screening programmes now include screening for SMA to identify infants with possible mutations of the *SMN1* gene, allowing presymptomatic infants to be treated before the loss of motor neurons, with the goal of achieving improved clinical outcomes (*22*). This number is likely to increase over the next few years.

Committee recommendations

The Expert Committee acknowledged that SMA, a hereditary genetic disease caused by a defect or mutation in the *SMN1* gene is associated with considerable morbidity and mortality in affected children and adults. While it has a relatively low incidence in the general population, disease clusters are possible, particularly in families with increased prevalence of consanguinity. The Committee reaffirmed that low incidence of a disease is not a factor on its own that precludes the inclusion of medicines in the Model Lists. Indeed, essential medicines for rare diseases have been included since the first Model List was published (e.g. blood coagulation factors, antirabies hyperimmune serum (later equine rabies immunoglobulin)).

The Committee noted the current availability of three different treatments for SMA: one small molecule (risdiplam); one antisense oligonucleotide (nusinersen); and one gene therapy (onasemnogene abeparvovec). These treatments share some characteristics: they are associated with potentially important clinical benefits which appear to be greatest with early introduction of treatment in presymptomatic infants who carry the gene mutation and in symptomatic patients with recent onset of symptoms; and they are all highly priced. Between risdiplam and nusinersen, the Committee noted the feasibility advantages of risdiplam over nusinersen. The latter requires an intrathecal injection every 4 months which must be done in hospital by trained health professionals and has adverse effects such as headaches, vomiting, back pain and risk of infections, while risdiplam is given orally at home.

The Committee noted that the body of evidence for efficacy and safety of risdiplam in SMA was still limited, with only a small number of patients exposed to long-term treatment. The Committee noted that most patients had a disease duration of at least 3 months when they were enrolled in the clinical trials. About 50% of children treated with risdiplam showed improvement in motor function (e.g. sitting without support for 5 or more seconds) at 24 months, and more children achieved motor milestones with prolonged treatment. While risdiplam is likely associated with longer survival without requirement for permanent mechanical ventilation, based on the available data so far, no participants could stand or walk alone when risdiplam has been given after disease onset. The Committee noted that based on the available evidence in patients with symptomatic disease,

improvements in motor function were observed in younger children (younger than 5 years) but that these improvements became increasingly less noticeable in older children, adolescents and adults. Treatment-related adverse effects were generally mild. Overall, the Committee considered that the magnitude and long-term duration of benefits and potential harms of risdiplam were still uncertain.

The Committee noted that newborn screening for SMA has been introduced into routine screening panels in some high-income countries in recent years. However, the effectiveness of such screening programmes in identifying potential patients in a presymptomatic stage of the disease has not yet been assessed. The Committee also noted the preliminary results of ongoing clinical trials of risdiplam in presymptomatic infants up to 6 weeks of age. As risdiplam is likely to be associated with larger benefits when treatment is started before symptom onset, the Committee considered that it would be important to study its long-term effectiveness in those settings where routine newborn screening programmes for SMA are implemented.

The Committee advised that data on SMA screening programmes and use of risdiplam in presymptomatic infants should be reviewed as they become available, as well as longer term trial clinical outcomes for use of risdiplam in older, less severely affected, symptomatic patients.

The Committee noted the current high price of risdiplam and that reimbursement decisions in some high-income countries have been made subject to managed entry arrangements or price reductions. Generic versions of risdiplam are not currently available. The Committee also noted that a request made by Knowledge Ecology International for a voluntary licence to manufacture and sell a generic version of risdiplam had not been granted by the patent holder. Nevertheless, the Committee considered that risdiplam could be flagged to the Medicines Patent Pool as a potential candidate for negotiating public health-oriented licences, to facilitate affordable access in low- and middle-income countries.

Based on these considerations, the Expert Committee did not recommend inclusion of risdiplam on the core list of the EML and EMLc for treatment of spinal muscular atrophy.

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5.1 Antiseizure medicines

Levetiracetam – addition – EML and EMLc

Levetiracetam	ATC code: N03AX14

Proposal

Addition of levetiracetam to the core list of the EML and EMLc for treatment of focal-onset and generalized-onset epilepsy and benzodiazepine-refractory status epilepticus in adults and children.

Applicant

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EML/EMLc

EML and EMLc

Section

5.1 Antiseizure medicines

Dose form(s) & strengths(s)

Oral solution: 100 mg/mL

Tablet: 250 mg, 500 mg, 750 mg, 1000 mg

Concentrate solution for infusion: 500 mg/5 mL in 5 mL vial

Solution for infusion: 5 mg/mL, 10 mg/mL, 15 mg/mL in 100 mL bag

Core/complementary

Core

Individual/square box listing

Individual

Background

Levetiracetam has not previously been evaluated for inclusion on the Model Lists.

The EML currently lists 10 antiseizure medicines: carbamazepine, diazepam, ethosuximide, lamotrigine, lorazepam, magnesium sulfate, midazolam, phenobarbital, phenytoin, and valproic acid. With the exception of magnesium sulfate (which is listed for use only in eclampsia and severe pre-eclampsia), the same medicines are also included on the EMLc. These medicines are intended to treat generalized and partial epilepsy, mostly as first-line therapies.

Public health relevance

The public health relevance of effective and safe treatments for epilepsy is well established. Epilepsy, a disorder characterized by spontaneous unprovoked seizures, is one of the most common serious neurological conditions and affects more than 50 million people worldwide (*1*). Seizures may start in one part of the brain (focal epilepsy) or in both hemispheres simultaneously (*2*). Both types of epilepsy are associated with risk of injury, head injury and death. About 70% of people can achieve freedom from seizures with appropriately selected antiseizure medicines (*3*).

While older antiseizure medicines can be effective in controlling seizures, they can be associated with long-term side-effects (phenobarbital, carbamazepine, valproic acid, phenytoin) and slow cognition (phenobarbital), can have complex drug–drug interactions (phenobarbital, carbamazepine, phenytoin) and can be teratogenic (valproic acid). Lamotrigine, a newer antiseizure medicine, can cause skin rash in 1 in 30 people, may have its metabolism affected by estrogen-containing oral contraceptives/hormone replacement therapies, and is not a medicine that can be used in emergency settings.

Treatment strategies for epilepsy should be individualized according to the seizure type, coprescribed medications and comorbidities, the person's lifestyle, and the preferences of the person and their family and/or caregivers.

Levetiracetam is a well established medicine in the pharmacological armamentarium for epilepsy treatment, and offers the following benefits:

- effective in both focal-onset and generalized-onset epilepsies;
- no adverse effects on cognition;
- no known long-term side-effects;
- minimal drug–drug interactions; no interaction with contraception or hormone replacement therapy;
- effective in all ages;
- can be used intravenously in the emergency treatment of generalized tonic-clonic status epilepticus (prolonged convulsive seizures associated with significant risk);
- parenteral preparation available that can be used in people with symptomatic seizures, people with comorbid liver/cardiac conditions and people with epilepsy who are unable to take oral preparations;

- effective in older people with lower risk of adverse events;
- safe in pregnancy with no increased risk above the background risk of teratogenicity in the general population.

Levetiracetam is particularly beneficial for more vulnerable groups such as older people with seizures and women/girls of childbearing potential who have epilepsy.

Summary of evidence: benefits

The applicants conducted and presented the findings of a systematic literature review and network meta-analysis which summarized the evidence from recent meta-analyses comparing the effectiveness and safety of antiseizure medications in adults and children with epilepsy.

The evidence synthesis included one Cochrane systematic review and network meta-analysis of individual patient data of the efficacy and tolerability of antiseizure medications in children and adults with focal or generalized epilepsy (*4*). Carbamazepine, phenytoin, valproic acid, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide, eslicarbazepine acetate and lacosamide were compared for time to seizure remission (efficacy) when used as monotherapy in children and adults with focal-onset seizures (simple focal, complex focal or secondary generalized) or generalized tonic-clonic seizures with or without other generalized seizure types. The analysis included 14 789 records from 39 randomized trials, with certainty of evidence profiles elaborated according to the confidence in network meta-analysis (CiNeMA) approach. For focal-onset seizures, carbamazepine and lamotrigine were taken as comparators, while for generalized-onset seizures valproic acid was used as the comparator, as these medicines are considered first-choice in the treatment of the respective epilepsy types.

The network meta-analysis (*4*) showed high-certainty evidence that for focal-onset seizures, levetiracetam was as effective as lamotrigine (hazard ratio (HR) 1.01, 95% confidence interval (CI) 0.87 to 1.18; two randomized controlled trials, 902 participants) and carbamazepine (HR 1.08, 95% CI 0.94 to 1.24; three studies, 1567 participants).

The network meta-analysis also showed high-certainty evidence that for generalized-onset seizures, levetiracetam was as effective as valproic acid (HR 0.99, 95% CI 0.82 to 1.20; two randomized controlled trials, 1032 participants).

The network meta-analysis reported sensitivity analysis results adjusted for age, which showed similar estimates to those in the main results. Overall, the age range for the network meta-analysis was 1 to 95 years, with 4/39 studies providing individual patient data for people 15 years or younger, and 35/39 studies including people older than 15 years (*4*).

An update was reported in 2018 of American Academy of Neurology/ American Epilepsy Society guidelines on treatment of adults with new-onset epilepsy (*5*). The authors systematically searched records up to November 2015 to update the previous guidelines, dating back to 2004. Several second-generation antiseizure medications were considered to be effective for new-onset focal epilepsy. The authors highlighted that lamotrigine, levetiracetam and zonisamide were the preferred antiseizure medications to decrease seizure frequency in adults with new-onset focal epilepsy.

Another study reported on the indications to start an antiseizure medication treatment after a first seizure, but the efficacy and safety of levetiracetam were not investigated (*6*).

A narrative review in 2022 covered optimal antiseizure medication choices in adults with epilepsy (*7*). Among 26 medications for epilepsy approved by the US Food and Drug Administration, 24 were considered to have similar antiseizure efficacy for focal epilepsy and nine had similar efficacy for generalized epilepsy. The authors stressed that the choice of antiseizure medication must be based on the seizure and epilepsy types, the epilepsy syndrome, and the adverse effects associated with the drug. Levetiracetam, together with lamotrigine, was suggested as a first-line option for both focal-onset and generalized-onset seizures, particularly for women and girls of childbearing potential given the low teratogenic risk.

The SANAD II study was a randomized, open-label, non-inferiority, phase IV trial which compared levetiracetam to valproic acid for treatment of generalized and unclassified epilepsy (*8*). Although levetiracetam did not reach the non-inferiority margins defined versus valproic acid, it was associated with a similar probability of 12-month remission compared with valproic acid in the long-term and is considered non-inferior to valproic acid for generalized epilepsy.

Summary of evidence: harms

The Cochrane systematic review and network meta-analysis provided data on both acceptability of treatments (i.e. all-cause treatment discontinuation, generally considered a pragmatic proxy of the balance between desirable and undesirable effects) and tolerability (i.e. adverse events) (*4*).

The network meta-analysis showed high-certainty evidence that:

- for focal-onset seizures, levetiracetam had better acceptability (HR 0.80, 95% CI 0.69 to 0.93) and tolerability (HR 0.65, 95% CI 0.47 to 0.90) compared with carbamazepine (three studies, 1567 participants).
- for focal-onset seizures, levetiracetam had similar acceptability (HR 1.01, 95% CI 0.86 to 1.20) and tolerability (HR 1.16, 95% CI 0.81 to 1.66) compared with lamotrigine (two studies, 902 participants).

- for generalized-onset seizures, levetiracetam had similar acceptability (HR 1.13, 95% CI 0.89 to 1.42) and tolerability (HR 1.21, 95% CI 0.66 to 2.21) compared with valproic acid (two studies, 1032 participants).

The most commonly reported adverse events across all antiseizure medicines were drowsiness/fatigue, headache or migraine, gastrointestinal disturbances, dizziness/faintness, and rash or skin disorders.

A systematic review and meta-analysis of 96 studies (58 461 participants) evaluated the risk of congenital malformations and prenatal outcomes of antiseizure medications in infants and children exposed to antiseizure medications in utero (9). Levetiracetam and lamotrigine emerged as the only antiseizure medications with risks similar to placebo, suggesting the preferred use of lamotrigine and levetiracetam for women and girls of childbearing potential.

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders (10) includes the following recommendations.

- Monotherapy with lamotrigine or levetiracetam, or valproic acid (sodium valproate), should be offered as first-line treatment for generalized-onset seizures in men/boys and women/girls who are not of childbearing potential (strong recommendation, high certainty of evidence).
- In women and girls of childbearing potential with generalized-onset seizures, lamotrigine or levetiracetam should be offered as first-line monotherapy (strong recommendation, high certainty of evidence).
- Monotherapy with lamotrigine or levetiracetam should be offered as first-line treatment for focal onset seizures in children and adults with epilepsy. If neither lamotrigine nor levetiracetam are available, then carbamazepine should be used as an alternate first-line treatment for focal onset seizures in children and adults with epilepsy (strong recommendation, high certainty of evidence).
- In adults with established status epilepticus (i.e. seizures persisting after two doses of benzodiazepines), either intravenous postherniation, intravenous phenytoin, intravenous levetiracetam, intravenous phenobarbital or intravenous valproic acid (sodium valproate) should be considered with appropriate monitoring (conditional recommendation, low certainty of evidence).

> - In children with established status epilepticus (i.e. seizures persisting after two doses of benzodiazepines), intravenous fosphenytoin, intravenous phenytoin, intravenous levetiracetam, intravenous phenobarbital or intravenous valproic acid (sodium valproate), should be considered with appropriate monitoring (conditional recommendation, moderate certainty of evidence).

Costs/cost–effectiveness

The SANAD-II trial provided an economic evaluation alongside a randomized trial including 990 people comparing antiseizure medicines for people with newly diagnosed focal epilepsy in the United Kingdom (*8*). The study reported quality-adjusted life years (QALYs) calculated from participant-completed EuroQol-5 Dimension (EQ-5D) questionnaires scored using the United Kingdom tariff. The study took a National Health Services payer perspective and a personal social services perspective, which includes services provided by local communities. Lamotrigine was shown to be cost-saving and health-improving in the base case, dominating the other options. At a £20 000 per QALY threshold, lamotrigine had a greater than 99.9% probability of being the preferred option. This was the case in the adult subgroup analysis but not for people younger than 16 years, where levetiracetam was cost saving and health improving when compared to lamotrigine. From the sensitivity analyses, lamotrigine remained dominant apart from when QALYs were valued using the epilepsy specific NEWQOL-6D (levetiracetam becomes the preferred option at a £20 000 per QALY threshold).

The application presented a summary comparison of costs in the fully government-funded National Health Service in the United Kingdom of starting doses of levetiracetam and other EML-listed antiseizure medicines (Table 7).

Table 7
National Health Service indicative price of antiseizure medicines, United Kingdom

Medicine	Dose, in mg	Number of doses	Indicative price, in £
Carbamazepine	200	84	3.83
Lamotrigine (originator)	25	56	23.53
Lamotrigine (generic)	25	56	2.64
Levetiracetam (originator)	250	60	28.01
Levetiracetam (generic)	250	60	2.51
Phenytoin	300	28	9.11
Phenobarbital	30	28	0.63–0.94

Availability

Levetiracetam is available globally in originator and generic brands.

Levetiracetam is already listed on the country-specific EMLs in Albania, Algeria, Bahrain, Bhutan, Bulgaria, Czechia, Estonia, Iran (Islamic Republic of), Iraq, Jordan, Latvia, Lithuania, Maldives, Mexico, Montenegro, North Macedonia, Oman, Poland, Portugal, Romania, Russian Federation, Rwanda, Serbia, Seychelles, Slovakia, Sweden, Syrian Arab Republic, Thailand, Timor Leste and Viet Nam (*11*).

Other considerations

Women and girls of childbearing potential

Very specific risks arise in females with epilepsy that need to be considered across the lifespan (*12*). It is important that antiseizure medicines have limited interactions with contraception or hormone replacement therapy and that medications with limited teratogenic risk are available (*9*). Enzyme-inducing medications such as carbamazepine, phenytoin and phenobarbital can interfere with the oral contraceptive and render it less effective. Oestrogen-containing oral contraceptives can lower lamotrigine levels. Levetiracetam does not interact with oral contraceptives thereby making it preferred for women taking these products.

Levetiracetam is also the antiseizure medicine with the best overall safety in pregnancy (*12*, *13*). Levetiracetam is not thought to substantially increase teratogenic risk above that seen in the general population. By contrast, valproic acid increases the risk of structural anomalies (e.g. spina bifida, cleft lip, cleft palate, cardiac anomalies) up to around 10% and women taking valproic acid through pregnancy have a 30–40% risk that their offspring will have neurodevelopmental anomalies (autism, learning disabilities) (*13*).

Older people

Levetiracetam has previously been reported as effective in reducing seizure frequency in older adults aged > 65 years (*14*). In that study, 76.9% of patients had at least a 50% reduction in seizure frequency, with only 19.2% experiencing an adverse event leading to discontinuation.

Levetiracetam is not an enzyme-inducing antiseizure medicine. The reduced drug–drug interactions are particularly important in older people who may be on polytherapy. Levetiracetam also does not have an adverse effect on bone health, giving it additional advantages over carbamazepine, phenytoin, phenobarbital and valproic acid.

Specific ethnic populations

Many antiseizure medicines can cause skin rashes, including carbamazepine, lamotrigine and phenytoin. However, the HLA-B*1502 allele, which is more

common in people of Han Chinese origin, is associated with a marked increase in the risk of severe skin rashes with carbamazepine and phenytoin (*15*). Levetiracetam is substantially less likely to be associated with rash, even in people who have experienced dermatological reactions with one of the other antiseizure medicines.

Status epilepticus

Status epilepticus is defined as a convulsive seizure lasting more than 5 minutes. It is associated with a significant risk of morbidity and mortality and expedient management is essential. Benzodiazepines (diazepam, lorazepam) are established as first-line treatment, but the choice of second-line treatment if benzodiazepines are ineffective is uncertain. Two recent studies have evaluated different antiseizure medicines for use in status epilepticus. The Established Status Epilepticus Treatment Trial (ESETT) randomized 384 adult participants to receive levetiracetam, fosphenytoin or valproic acid. Efficacy and incidence of adverse events were similar for all agents (*16*). The EcLiPSE trial randomly assigned 1432 children aged 6 months to 18 years to receive phenytoin or levetiracetam for benzodiazepine-refractory status epilepticus (*17*). Levetiracetam was not significantly superior to phenytoin for status epilepticus, which concurs with another study (ConSEPT) (*18*). However, the EcLiPSE study investigators concluded that the ease of administration of levetiracetam meant that it could be an appropriate treatment for benzodiazepine-refractory status epilepticus.

Although levetiracetam is not necessarily more effective than either phenytoin or valproic acid in treating established status epilepticus, there may be some specific advantages in resource-constrained settings of having levetiracetam available to treat status epilepticus.

Committee recommendations

The Expert Committee recognized that epilepsy is a common, serious neurological condition with a significant disease burden, affecting millions of people around the world. The Committee acknowledged that treatment strategies for people with epilepsy need to be individualized considering multiple factors including, but not limited to, seizure type, comorbidities, adverse event profile, concomitant medication use, pregnancy and patient preferences. The Committee also noted that three quarters of people living with epilepsy in low-income countries do not get the treatment they need, increasing their risk of dying prematurely and condemning many to a life of stigma.

The Committee noted the high-certainty evidence presented in the application that levetiracetam was as effective as alternative EML-listed antiseizure medicines for focal-onset seizures and generalized-onset seizures. The Committee also noted that levetiracetam is an effective treatment option for

use in adults and children in the treatment of status epilepticus that does not respond to treatment with benzodiazepines.

The Committee also noted the high-certainty evidence presented for safety, which indicates that levetiracetam has similar or greater acceptability and tolerability than alternative antiseizure medicines. Importantly, the Committee noted that the risks of congenital malformation and neurodevelopmental disorders in infants and children exposed to levetiracetam (and lamotrigine) in utero are similar to those of placebo, while other antiseizure medicines currently included on the Model Lists have a significant risk of inducing congenital malformations and neurodevelopmental disorders. Carbamazepine, phenobarbital and valproic acid are associated with chronic and severe teratogenic effects, the most common of which are congenital heart disease, cleft lip/palate, and urogenital and neural tube defects. Therefore, levetiracetam and lamotrigine are preferred antiseizure medications for use in women and girls of childbearing potential. The Committee noted that levetiracetam (and lamotrigine) will be recommended in the updated WHO mhGAP guidelines as first-line treatment options for women and girls of childbearing potential with generalized-onset seizures.

Based on these considerations, the Expert Committee recommended the inclusion of oral levetiracetam on the core list of the EML and EMLc for the treatment of focal- and generalized- onset seizures in adults and children. The Committee also recommended the inclusion of intravenous levetiracetam on the complementary list of the EML and EMLc for the treatment of benzodiazepine-refractory status epilepticus in adults and children.

Additionally, the Committee recommended that the section title in the Model Lists be updated from "anticonvulsants/antiepileptics" to "antiseizure medicines".

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5.2 Medicines for multiple sclerosis

Cladribine, glatiramer and rituximab – addition – EML

Cladribine	**ATC code: L04AA40**
Glatiramer acetate	**ATC code: L03AX13**
Rituximab	**ATC code: L01FA01**

Proposal

Addition of cladribine, glatiramer acetate and rituximab (with a square box specifying ocrelizumab as a therapeutic alternative) to the complementary list of the EML for the treatment of adults with multiple sclerosis (MS).

Applicant

Multiple Sclerosis International Federation

WHO Collaborating Centre in Evidence Based Research Synthesis and Guideline Development, Direzione Generale Cura della Persona Salute e Welfare, Regione Emilia-Romagna, Bologna, Italy

WHO technical department

The Department of Mental Health and Substance Use provided comments on two applications submitted for Expert Committee consideration for disease-modifying therapies for MS – this application and an application for ocrelizumab submitted by the patent holder, Roche.

The technical department supported the inclusion of disease-modifying therapies for MS on the EML, highlighting that the proposals were well aligned with the mandate of the intersectoral global action plan on epilepsy and other neurological disorders (*1*), which includes a strategic objective to "provide effective, timely and responsive diagnosis, treatment, and care" for people with neurological disorders such as MS.

EML/EMLc

EML

Section

5.2 Medicines for multiple sclerosis

Dose form(s) & strengths(s)

Cladribine – Tablet: 10 mg

Glatiramer acetate – Injection: 20 mg/mL, 40 mg/mL

Rituximab – Injection: 500 mg/50 mL in 50 mL vial

Core/complementary

Complementary

Individual/square box listing

Individual listings for cladribine and glatiramer acetate. Square box listing for rituximab, specifying ocrelizumab as a therapeutic alternative.

Individual listing for ocrelizumab was also requested in a separate application submitted by F. Hoffmann-La Roche Ltd and considered by the Expert Committee at this meeting.

Background

In 2019, the Expert Committee reviewed an application from the Multiple Sclerosis International Federation requesting the addition of glatiramer acetate, fingolimod and ocrelizumab on the Model Lists for use in the treatment of MS. The Committee acknowledged the important public health burden of MS and the need for effective and affordable treatments. However, the Committee noted that the superiority of the proposed medicines over other therapeutic options in terms of benefits, harms and affordability did not clearly emerge from the application. The Committee noted that some commonly used treatments were not included in the application (e.g. azathioprine, natalizumab, dimethyl fumarate, cladribine), or were not given full consideration (e.g. rituximab), with reasons for their exclusion being unclear. In particular, the Committee noted the evidence presented in the application in relation to rituximab and considered that rituximab could have a relevant clinical role in the treatment of MS and recommended that any future application include evidence for rituximab versus active comparators, not just placebo. The Committee therefore did not recommend listing of glatiramer acetate, fingolimod or ocrelizumab at the time, and requested a revised application which comprehensively reviewed the relative roles of relevant available medicines for MS (*2*).

Public health relevance

MS is a chronic autoimmune disease characterized by inflammation of the central nervous system that leads to demyelination, axonal loss and progressive neuronal degeneration, resulting in irreversible disability and cognitive impairment (*3*, *4*). Common symptoms include pain, fatigue, mood and cognitive changes, mobility and sensory impairment, visual disturbances, and elimination dysfunction. Symptoms can vary in severity and can result in significant disability, and reduction in quality and length of life.

Data on the global prevalence of MS vary. The Global Burden of Disease study reported that globally, about 1.8 million people (23 per 100 000) had MS in

2019. Age-standardized prevalence per 100 000 population shows large variability across WHO regions, ranging from 4 cases per 100 000 in the Western Pacific Region to 60 per 100 000 in the European Region (*5*). The atlas of MS estimated that globally, about 2.8 million people (36 per 100 000) had MS in 2020 (*6*). The number of people with MS per 100 000 population also showed large variability across WHO regions, ranging from 5 per 100 000 in the African and Western Pacific regions to 133 per 100 000 in the European Region (*6*).

MS is most often diagnosed between the ages of 20 and 50 years, but the disease may also first manifest in older adults and children. Women are affected 2–3 times more than men (*7, 8*).

MS is broadly divided into relapsing and progressive forms, classified in three different clinical phenotypic patterns based on the presence of transient attacks of neurological symptoms and/or a progressive worsening of the neurological function: relapsing-remitting MS, secondary progressive MS and primary progressive MS (*9*). Relapsing-remitting MS is characterized by relapses and remissions of neurological symptoms, with relapses associated with new areas of inflammation in the central nervous system. Over time, most people with relapsing-remitting MS will transition to secondary progressive MS, marked by gradual worsening of neurological function with or without additional inflammatory events. Primary progressive MS is characterized by the absence of clearly defined relapses (*9, 10*).

The course of MS is highly variable and unpredictable, and patients may have a broad range of neurological symptoms or signs, depending on the location and degree of central nervous system inflammation. Life expectancy for patients with MS is 5–10 years shorter than for the general population (*3, 11, 12*). Exposure to any disease-modifying therapy for MS is associated with a lower risk of death compared with no exposure (*13*).

MS has a substantial negative impact on health-related quality of life (*14–16*). People with MS have significantly lower health-related quality of life scores than people who have other chronic diseases, such as chronic ischaemic heart disease, gastro-oesophageal reflux disease, non-insulin-dependent diabetes mellitus, or inflammatory bowel disease (*17*). People with MS are less likely to be employed, more likely to take time off work when they are employed, and more likely to retire early than the general population (*18–20*).

Globally, an estimated 1 million people (unpaid spouses, partners, children, family members or friends) are involved in the overall care of people living with MS (*21*). Caregivers often stop working to care for the person with MS, further increasing the societal burden of the disease (*22*). Caregivers of people with MS also experience high levels of distress and reduced quality of life (*23, 24*).

Summary of evidence: benefits

The application described the detailed process undertaken by the applicants to prioritize the medicines being proposed for EML listing from among 30 medicines used in the treatment of MS. The EML application was planned as part of a comprehensive guideline coordinated by the Multiple Sclerosis International Federation. The evidence synthesis informing the guideline process was supported by a Cochrane network meta-analysis on treatments for both progressive (*25*) and relapsing/remitting MS (*26*). The network meta-analyses were conducted with placebo as the common comparator. The network meta-analyses are in later stages of preparation for publication in the Cochrane Library. The guideline followed the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) method. The guideline panel and the supporting methodological team first generated all questions following the patient, intervention, comparison and outcome (PICO) framework and prioritized outcomes using a structured approach which included health outcome descriptors and definitions, establishing *a priori* all important and critical outcomes. Absolute effects were estimated across all outcomes. A summary table demonstrating the desirable and undesirable effects, net balance of effects and certainty of the evidence was created. The medicines evaluated in the network meta-analyses were ranked based on a numeric coefficient summing the values calculated for the desirable and undesirable effects. Based on the relevance of the outcomes and associated net benefit, the guideline panel was then requested to prioritize the 10 medicines with the largest net benefit, and then prioritize among these medicines those that would offer the greatest benefits taking into account the needs of special populations, such as adolescents, and pregnant or breastfeeding women. Short-listed medicines were cladribine, rituximab/ocrelizumab, dimethyl fumarate, fingolimod, interferon beta 1b/1a and glatiramer acetate. Four medicines were ultimately proposed for addition to the EML by the guideline panel. The justification for the selection of rituximab (with ocrelizumab as a therapeutic alternative), cladribine and glatiramer acetate, and summaries of evidence for benefit for each medicine are described below.

Rituximab/ocrelizumab

Rituximab (with ocrelizumab as a square box alternative) was considered a feasible and acceptable option in resource-constrained settings due to balance of effects, mode of administration (6-monthly infusions), and low requirements for screening and monitoring. These medicines have a low risk of rebound effect if treatment is discontinued and low discontinuation rates by people with MS. They require infusion facilities and cold storage at the health care facility. Rituximab and ocrelizumab, while contraindicated during pregnancy, may be used in pregnant women with careful timing of treatment. Rituximab and ocrelizumab have

been extensively used off-label in paediatric MS. Clinical trials of ocrelizumab in children and adolescents with relapsing-remitting MS are ongoing. On-label ocrelizumab is more costly than off-label rituximab, but off-label prescribing is limited in some settings, making ocrelizumab potentially more acceptable and/or feasible in these settings. Rituximab is already listed on the WHO EML for other indications, is off-patent with many authorized biosimilar products, and is part of the WHO prequalification programme. For these reasons, rituximab was proposed as the representative of the square box grouping.

Rituximab

A randomized controlled trial compared rituximab with placebo in patients with relapsing-remitting MS switching from a previous disease-modifying therapy (*27*). There was low-certainty evidence of an appreciable benefit in the number of patients presenting with relapses at 48 weeks: absolute difference 198 fewer per 1000 (95% confidence interval (CI) 304 fewer to 17 fewer), and very low-certainty evidence of benefit in terms of the number of patients with new gadolinium-enhancing positive T1 lesions seen on magnetic resonance imaging (MRI): absolute difference 307 fewer per 1000 (95% CI 394 to 141 fewer).

A non-randomized study compared rituximab with other disease modifying therapies (interferon beta or glatiramer acetate, dimethyl fumarate, fingolimod, natalizumab) as initial treatment in patients with relapsing-remitting MS, assessing relapse and new gadolinium-enhancing positive T1 lesions seen on MRI as desirable effects (*28*). There was low-certainty evidence of a large effect in relapse risk over 24 months for rituximab compared with interferon beta or glatiramer acetate: absolute difference 227 fewer per 1000 (95% CI 254 to 154 fewer). There was low-certainty evidence that rituximab may result in an appreciable reduction in relapses when compared with natalizumab (absolute difference 148 fewer per 1000, 95% CI 187 to 0 fewer) and dimethyl fumarate (absolute difference 84 fewer per 1000, 95% CI 110 to 0 fewer).

Efficacy data on rituximab versus other disease-modifying therapies in patients with relapsing-remitting MS switching from a previous disease-modifying therapy were evaluated in three Swedish cohort register-based studies (*29–31*). There was moderate-certainty evidence that rituximab showed the highest appreciable benefit in terms of risk of relapse versus interferon beta or glatiramer acetate (absolute risk difference 215 fewer patients with relapse per 1000, 95% CI 248 to 127 fewer) over a median follow-up of 24 and 18 months. There was also very low-certainty evidence of benefit for rituximab in terms of new or enlarging T2 weighted lesions seen on MRI versus fingolimod (absolute risk difference 286 fewer per 1000, 95% CI 290 to 266 fewer), over median follow up of 24 and 18 months, respectively. Other desirable effects for which rituximab showed appreciable benefit versus fingolimod were: fewer new gadolinium-

enhancing positive T1 weighted lesions seen on MRI (172 fewer per 1000, 95% CI 186 to 126 fewer, very low-certainty evidence); fewer relapses (161 fewer per 1000, 95% CI 172 to 116 fewer; moderate-certainty evidence) with median follow up of 18 months; and disability versus interferon or glatiramer acetate (12 fewer per 1000, 95% CI 42 fewer to 35 more; very low-certainty evidence), with median follow up of 24 months.

A randomized controlled trial conducted in the United States and Canada assessed the efficacy and safety of rituximab versus placebo as initial treatment in patients with primary progressive MS over 24 months' follow-up (*32*). Both disability and frequency of relapse were reduced in patients treated with rituximab (absolute risk reduction: 75 fewer per 1000 (95% CI 158 fewer to 24 more; moderate-certainty evidence) and 13 fewer per 1000 (95% CI 28 fewer to 31 more; low-certainty evidence), respectively.

Rituximab in patients with secondary progressive MS switching from a previous disease modifying therapy was assessed in two small randomized controlled trials in the Islamic Republic of Iran (*33*, *34*), and one small case–control study in Switzerland and the Kingdom of the the Netherlands (*35*). One of the trials comparing rituximab with cyclophosphamide did not report any prioritized benefit outcome (*34*). The other trial compared rituximab with glatiramer acetate and showed a benefit on new gadolinium-enhancing positive T1 weighted MRI lesions in favour of rituximab (absolute risk difference: 28 fewer lesions per 1000, 95% CI 82 fewer to 166 more; very low-certainty evidence) over a median follow-up of 12 months (*33*). The non-randomized study showed a benefit on disability in patients treated with rituximab versus those treated with other disease modifying therapies (absolute risk difference 164 fewer per 1000, 95% CI 250 to 20 fewer; very low-certainty evidence) (*35*).

Ocrelizumab

No direct evidence of ocrelizumab versus placebo in patients with relapsing forms of MS was available. Two pivotal randomized controlled trials (OPERA I and OPERA II) assessed the efficacy and safety of ocrelizumab versus interferon beta 1a in this patient population (*36*). The OPERA studies used the calculated annualized relapse rate as the outcome measure of relapse reduction. These results were not included in the network meta-analysis performed by the applicants, which instead used as the outcome measure, the proportion of people who had or did not have a relapse within defined time periods. Refer to the ocrelizumab summary for details of the evidence from the OPERA I and OPERA II studies.

One randomized controlled trial (ORATORIO) assessed the efficacy and safety of ocrelizumab versus placebo in patients with primary progressive MS (*37*). Ocrelizumab was associated with a benefit on disability (absolute risk difference 61 fewer per 1000, 95% CI 160 fewer to 89 more; very low-certainty

evidence) and on quality of life measured using the SF-36 (physical) scale (standardized mean difference 0.04 higher; 95% CI 0.12 lower to 0.19 higher; moderate-certainty evidence) at 36 months' follow-up.

Cladribine

Cladribine, fingolimod and dimethyl fumarate were all considered to be feasible and acceptable options in resource-constrained settings due to the balance of effects, mode of administration (oral) and easy storage. Fingolimod requires more maintenance for screening and monitoring and has a risk of rebound of MS disease activity if access to treatment is discontinued suddenly, for example, due to unreliable supply of medicine, and it can diminish response to vaccines. Dimethyl fumarate has low requirements for screening and monitoring but has a higher discontinuation rate compared with other oral treatments. Cladribine has a short treatment period of four short courses over 2 years (although subsequent treatment may be required in some people), which is an advantage for settings where drug supply irregularities are common. Further advantages of cladribine include its allowance of family planning (because of its treatment period of four short courses over 2 years), a low risk of rebound, low requirements for screening and monitoring, a low discontinuation rate, and potentially favourable cost–effectiveness. Cladribine, while contraindicated in pregnancy, may be used in women of childbearing age with careful timing of treatment.

A randomized controlled trial (CLARITY) assessed the efficacy and safety of cladribine versus placebo in patients with relapsing-remitting MS (*38*). Cladribine produced appreciable benefit on disability (absolute risk difference 53 fewer people developing disability per 1000, 95% CI 83 to 17 fewer; low-certainty evidence), on relapse (240 fewer per 1000, 95% CI 285 to 183 fewer; high-certainty evidence), quality of life assessed using the EQ-5D VAS (standardized mean difference (SMD) 0.19 higher, 95% CI 0.06 to 0.32 higher; moderate-certainty evidence) and the EQ-5D index (SMD 0.24 higher, 95% CI 0.11 to 0.37 higher; moderate-certainty evidence) at 24 months' follow-up.

No evidence from randomized controlled trials was identified for cladribine in progressive MS.

Glatiramer acetate

Glatiramer acetate was considered an important treatment option mainly for special populations, as it is safe for use in pregnancy and during breastfeeding, and is used in paediatric MS. The most appropriate medicines during pregnancy are glatiramer acetate and interferon, both of which are also safe to use during breastfeeding. Glatiramer acetate was judged to have a better safety profile than interferon, and is generally more tolerated than interferons, which may cause flu-like adverse effects. Both medicines have the disadvantage of the need for frequent injections as their mode of administration and require refrigeration.

While both have few screening and monitoring requirements, glatiramer acetate has the fewest requirements. Glatiramer acetate also has the advantage of no known drug interactions. Generic forms are available.

Three randomized controlled trials provided direct evidence of glatiramer acetate versus placebo in patients with relapsing-remitting MS (*39–41*). Treatment with glatiramer acetate reduced: disability at 24 months (absolute risk difference 49 fewer per 1000, 95% CI 73 to 21 fewer; very low-certainty evidence); relapse at 24 months (82 fewer per 1000, 95% CI 122 to 36 fewer; very low-certainty evidence); and new MRI gadolinium-enhancing positive T1 lesions at 24 months (135 fewer per 1000, 95% CI 191 to 53 fewer; very low-certainty evidence).

Two randomized controlled trials provided direct evidence of glatiramer acetate versus placebo in patients with primary progressive MS (*42, 43*). Treatment with glatiramer acetate reduced disability at 24 months (absolute risk difference 68 fewer per 1000, 95% CI 174 fewer to 85 more; very low-certainty evidence).

Summary of evidence: harms

Rituximab

Two randomized controlled trials assessed the safety of rituximab in patients switching from a previous disease modifying therapy in relapsing-remitting MS (*27*) and primary progressive MS (*32*) and showed a higher frequency of serious adverse events versus placebo (pooled absolute risk difference 21 more adverse events per 1000, 95% CI 36 fewer to 100 more), including common infections (19 more per 1000, 95% CI 67 fewer to 96 more) and infusion reactions within 24 hours of the first infusion (435 more per 1000, 95 % CI 344 more to 513 more). Conversely, death, cancer and infusion reaction after the second infusion were less frequent in patients treated with rituximab – absolute differences: six fewer deaths per 1000, 95% CI 10 fewer to 24 more); three fewer cancers per 1000, 95% CI 10 fewer to 28 more); and 28 fewer infusion reactions per 1000, 95% CI 151 fewer to 266 more).

A Swedish non-randomized study compared rituximab with other disease modifying therapies (interferon or glatiramer acetate, dimethyl fumarate, fingolimod, natalizumab) in treatment-naive patients with relapsing-remitting MS (*28*). Rituximab versus interferon or glatiramer acetate produced fewer serious adverse effects (grade 3 or 4): four fewer serious adverse effects per 1000, 95% CI 27 fewer to 68 more; very low-certainty evidence. It also produced fewer serious adverse effects than natalizumab (46 fewer per 1000, 95% CI 71 fewer to 45 more; very low-certainty evidence). In comparison with dimethyl fumarate, more patients treated with rituximab experienced serious adverse effects (22 more per 1000, 95% CI 8 fewer to 227 more). No absolute difference in estimates on serious adverse effects could be drawn with fingolimod, given the extremely wide 95% CI of the odds ratio (0.07 to 26.21). For opportunistic infections, the

point estimate versus natalizumab favoured rituximab (17 fewer infections per 1000, 95% CI 20 fewer to 45 more; very low-certainty evidence).

Six retrospective non-randomized studies reported undesirable effects of rituximab versus other disease-modifying therapies in patients with relapsing-remitting MS switching treatment (*29–31,44–46*). Rituximab a lower frequency of serious adverse effects when compared with fingolimod and natalizumab (17 fewer per 1000; 95% CI 24 fewer to 27 more, and 29 fewer per 1000; 95% CI 38 fewer to 111 more, respectively, very low certainty evidence). Similarly, the frequency of common infections was lower among patients treated with rituximab compared to those on ocrelizumab (61 fewer per 1000; 95% CI 62 fewer to 36 fewer; very low-certainty evidence) and higher than interferon or glatiramer acetate, fingolimod or natalizumab: 24 more per 1000, 95% CI 4 to 53 more; 14 more per 1000, 95% CI 5 fewer to 39 more; and 27 more per 1000, 95% CI 4 to 59 more, respectively; very low-certainty evidence in all comparisons. Cancer was less frequent in patients treated with rituximab compared with patients treated with fingolimod and natalizumab: 7 fewer per 1000, 95% CI 11 fewer to 1 more; and 3 fewer per 1000, 95% CI 6 fewer to 3 more, respectively; very low-certainty evidence in both comparisons. Infusion reactions within 24 hours of the first infusion were less common with rituximab than ocrelizumab (6 fewer per 1000, 95% CI 12 fewer to 35 more; very low-certainty evidence). Relative estimates on mortality were too imprecise (few events, very wide CIs) to allow reporting absolute differences.

Two small randomized controlled trials assessed safety of rituximab compared with glatiramer acetate (*33*) and cyclophosphamide (*34*) in patients with progressive MS switching from a previous disease-modifying therapy. Their results were not pooled with those of the non-randomized studies. Common infections were more frequent in patients treated with rituximab than those on glatiramer acetate (45 more per 1000, 95% CI 17 fewer to 405 more; very low-certainty evidence) and less frequent than in patients on cyclophosphamide (204 fewer per 1000, 95% CI 337 fewer to 26 more; very low-certainty evidence).

Ocrelizumab

No direct evidence of safety of ocrelizumab versus placebo in patients with relapsing MS was available.

Safety data of ocrelizumab versus placebo in patients with primary progressive MS from the ORATORIO trial (*37*) showed that serious adverse events were more common in patients treated with ocrelizumab (18 more per 1000, 95% CI 99 fewer to 97 more; very low-certainty evidence), as was treatment discontinuation due to adverse events (8 more discontinuations per 1000, 95% CI 15 fewer to 57 more; moderate-certainty evidence) and death (4 more per 1000, 95% CI 3 fewer to 65 more; very low-certainty evidence).

Cladribine

From the CLARITY trial of cladribine versus placebo in patients with relapsing-remitting MS (*38*), mortality was not higher (0 fewer per 1000, 95% CI 2 fewer to 12 more; moderate-certainty evidence), while serious adverse events were more common with cladribine (27 more per 1000, 95% CI 15 fewer to 92 more; very low-certainty evidence). Treatment discontinuation due to adverse events was also higher with cladribine (18 more per 1000, 95% CI 26 fewer to 128 more; low-certainty evidence).

No evidence from randomized controlled trials was identified for cladribine in progressive MS.

Glatiramer acetate

Three randomized controlled trials provided direct evidence of glatiramer acetate versus placebo in patients with relapsing-remitting MS (*39–41*), showing similar mortality (1 fewer per 1000, 95% CI 2 fewer to 4 more; low-certainty evidence) and serious adverse events (4 fewer per 1000, 95% CI 24 fewer to 20 more; low-certainty evidence). More patients on glatiramer acetate discontinued treatment due to adverse events (22 more per 1000, 95% CI 1 to 51 more; moderate-certainty evidence).

One randomized controlled trial compared glatiramer acetate with placebo in patients with progressive MS (*43*). Compared with placebo, serious adverse events were more frequent with glatiramer acetate (9 more per 1000, 95% CI 9 fewer to 55 more; low-certainty evidence), as was treatment discontinuation due to adverse events (36 more per 1000, 95% CI 6 to 108 more; moderate-certainty evidence). Mortality was lower in the glatiramer acetate group (16 fewer per 1000, 95% CI 20 to 0 fewer; moderate-certainty evidence).

WHO guidelines

WHO guidelines for the treatment of MS are not currently available.

Costs/cost–effectiveness

Median prices (cost per patient per year in US$), and price ranges for the proposed medicines based on 18 countries across different income settings were identified in the application (Table 8). Ex-factory price was retrieved whenever available.

Table 8
Median price of medicines for multiple sclerosis, by country income level

Medicine, formulation	Median cost (range) per patient a year, US$[a]		
	High-income countries	Upper middle-income countries	Lower middle-income countries
Cladribine, 10 mg tablet	26 298 (24 684–62 628)	23 834 (9480–31 104)	6602[b]
Glatiramer acetate, 40 mg/mL injection	8511 (6355–12 566)	6618 (1987–11 797)	960[b]
Ocrelizumab, 300 mg/10 mL injection	24 192 (24 090–66 681)	17 928 (6790–25 296)	4600 (1200–22 580)
Rituximab, 500 mg/50 mL injection	4298 (3912–8813)	3089 (2899–4596)	2330 (120–7184)

[a] Currency exchange rates on 6 June 2022.
[b] Only one value available.

The dynamic nature and wide variations observed among countries may depend on context-dependent price components such as the local health system, supply chain, regulatory measures, ability and willingness to negotiate, and non-context-specific factors, such as market fluctuations, availability of alternatives, and available follow-on products (*47*). The information is also unreliable as national drug agency price databases are often unavailable, or their access may be restricted due to pharmaceutical companies requesting non-disclosure agreements. Negotiations between the local ministry of health and drug companies may end in substantial discounts, up to > 70%, and are usually confidential.

Evidence on cost–effectiveness of disease modifying therapies included in the application was retrieved through a systematic search of economic analysis studies on all available disease-modifying therapies, but these data have several limitations when used to inform clinical practice recommendations. Most economic analyses are available on recently marketed drugs and most studies are performed in high-income settings. Therefore, their results may not be transferable to countries with a different income level and willingness-to-pay threshold. Most studies are funded by the company producing the medicine being assessed, thus their results should be interpreted with caution. Moreover, the results of economic analysis studies cannot be quantitatively pooled in a meta-analysis, and their methodological quality is hard to assess due to the lack of established evaluation criteria. In some cases, parameters used by the analysis authors to

assess clinical effectiveness and cost vary, producing inconsistent and sometimes conflicting results. Most of the studies identified focused on specific direct costs (e.g. medicine price) while other direct costs (e.g. for administration, monitoring of MS course and activity, relapse treatment, and adverse event management), as well as indirect costs (e.g. loss of productivity, absenteeism, early retirement, and travel costs to reach health care facilities) are often not considered in economic modelling.

Among the studies identified in the application, several suggested a superiority of cladribine over other disease-modifying therapies for cost–effectiveness, but they were all funded by the company producing the medicine, so their results should be interpreted with caution. Similar considerations can be made for studies of glatiramer acetate and ocrelizumab. An independent cost–effectiveness analysis from the Islamic Republic of Iran found rituximab to be cost-effective when compared with natalizumab in the treatment of relapsing-remitting MS (*48*).

Availability

Cladribine, glatiramer acetate and ocrelizumab are approved by stringent regulatory authorities including in Australia, Canada, European Union, Switzerland, the United Kingdom and the United States for the treatment of relapsing-remitting MS. Only ocrelizumab has regulatory approval for treatment of progressive forms of MS. Rituximab is used off-label for MS but has regulatory approval for other indications.

The availability of the medicines proposed in this application varies between regions and country-income classifications. Survey data on global use of the proposed medicines from the Multiple Sclerosis International Federation Atlas are shown in Table 9 (*49*).

Table 9
Number of countries using the proposed medicines for multiple sclerosis, by income level and WHO region

Medicine	Income level					WHO region					
	HIC	UMIC	LMIC	LIC	Total	Africa	Americas	Eastern Mediterranean	Europe	Western Pacific	South-East Asia
Surveys completed, no.	44	30	23	10	107	15	17	18	42	9	6
Rituximab	33	20	16	1	70	6	13	12	28	5	6
Ocrelizumab	39	19	8	0	66	2	15	12	35	2	0
Cladribine	35	11	6	0	52	1	9	8	29	4	1
Glatiramer acetate	39	17	8	1	65	5	12	7	35	5	1

HIC: high income countries; UMIC: upper middle-income countries; LMIC: lower middle-income countries; LIC: low-income countries.

An evaluation of 137 national essential medicines lists (50) found the following information.

- Rituximab is included in 41 of the national EMLs assessed, however it was not possible to determine if the listing is for the indication of MS.

- Ocrelizumab is not included in any of the national EMLs assessed.

- Cladribine is included in national EMLs of 16/137 countries, however it was not possible to determine whether this is the oral or intravenous formulation, nor if the listing is for the indication of MS.

- Glatiramer acetate is included in 19 of the national EMLs assessed.

Rituximab 500 mg/50 mL injection was produced by three manufacturers (Celltrion Inc., Sandoz GmbH and Roche Products Limited) at the time for the application and has been prequalified by WHO under the pilot programme for prequalification of biotherapeutics. In line with prequalification processes, these products were prequalified for the indications for which rituximab is included on the EML, namely oncology indications.

Other considerations

The product patents on rituximab and glatiramer acetate have expired, and several biosimilar and generic products have been approved and are used in several countries. Secondary patents have been granted in some jurisdictions, but they may not prevent entry of follow-on products.

Cladribine compound patents expired in 2005. Secondary patent applications on the treatment regimen for MS, expected expiry in 2025, were filed in several countries and granted (e.g. in Brazil, China, Russia, South Africa, Ukraine, United States and Europe). In India the equivalent application was abandoned. A secondary patent for oral formulation of cladribine has been granted in several countries including Brazil, China, India, South Africa, United States, and also in Europe. Patents originally expiring in 2024 have been extended by way of Supplementary Protection Certificates in Europe until 2029. A United States patent owned by Merck for treating progressive forms of MS was recently granted with equivalents pending in several countries; the expected expiry is 2041.

Ocrelizumab is protected by a product patent expiring in 2023, sometimes extended by patent term extensions or supplementary protection certificates until 2028 or 2029. It is unlikely follow-on products can enter the market before expiry. Secondary patents have been filed and granted, which are expiring in 2029 or possibly as late as 2036.

Committee recommendations

The Expert Committee noted that MS is the most common non-traumatic cause of neurological disability in young adults. About 2.8 million people are living with MS worldwide, with women affected 2–3 times more than men. The most common form is relapsing-remitting MS, characterized by relapses and remissions of neurological symptoms. Over time, most people with relapsing-remitting MS develop a secondary progressive course of the disease (secondary progressive MS) marked by gradual worsening with or without additional inflammatory events. Currently, there are no medicines specifically for the treatment of MS included on the Model List. However, rituximab is included for other conditions, is widely available and is listed on many national essential medicines lists.

The Committee acknowledged the availability of a large number of disease-modifying medicines for MS (particularly for the treatment of relapsing and remitting forms of the disease) and the need to prioritize the most effective, best tolerated, and most affordable options. In 2019, the Committee considered an application to include glatiramer acetate, fingolimod and ocrelizumab and noted that there was no clear-cut superiority of these drugs over other options in terms of safety, efficacy and affordability. Moreover, commonly used agents (e.g. natalizumab) and off-label medications (e.g. rituximab) were excluded from that application.

The Committee considered that the approach taken in the current application submitted by the Multiple Sclerosis International Federation, based on the work done by two specific initiatives – MSIF Off-Label Treatments (MOLT) and MSIF Essential Medicines (MEMP) guidelines – to identify which medicines to prioritize for EML listing from among the many available was comprehensive, up-to-date, transparent, robust and evidence-based. The Committee recognized the value of involving different organizations and stakeholders at the global level, including consultation with people living with MS. The Committee considered that the application's selection of cladribine, glatiramer acetate and rituximab as priority medicines for EML inclusion was well justified and supported by evidence of clinical benefit and safety across different settings, as well as suitability for use in different patient populations (e.g. pregnant women) and feasibility. The inclusion on the EML of three medicines, with different routes of administration, different prices (including the availability of generic and biosimilar products) and different recommended uses, would provide valuable options for patients and national selection decisions and could facilitate improved access to treatment for people living with MS.

The Committee noted that, in line with the MEMP and MOLT recommendations, rituximab, cladribine and glatiramer acetate emerged as effective, feasible and acceptable options for the treatment of MS. The addition of multiple medicines allows options with different price, routes of administration and potential use in pregnancy. Generics of glatiramer acetate and rituximab biosimilars are available at lower cost than branded products, which could facilitate access to treatment.

The Committee considered that inclusion of a new section for medicines for the treatment of MS in the WHO Model List of Essential Medicines could increase global advocacy efforts to reduce the global burden of MS, especially in low- and middle-income countries where the unmet need for access is greater. This would also raise awareness of the need for specialized care and diagnostics, as well as monitoring of the disease response and progression.

The Committee recognized that rituximab did not have regulatory approval for the indication of MS but is widely used in clinical practice, is supported by evidence of efficacy and safety, and is reimbursed for MS in several countries. The Committee acknowledged the benefits of ocrelizumab in the management of relapsing/remitting and primary progressive forms of MS. However, there was no compelling evidence of its superiority over alternative treatments, specifically rituximab, which has the same molecular target (CD20). The Committee considered the option of listing ocrelizumab as alternative to rituximab, but also recognized the difference in current prices of the two products and the fact that off-label use of medicines is allowed in many countries, when robust evidence exists. The Committee concluded that including ocrelizumab

as a therapeutic alternative to rituximab could result in considerable additional expenditure at the country level for patients and health systems, without offering additional clinical benefit. The Committee considered that inclusion only of the less expensive rituximab on the EML might serve to facilitate its use (albeit off-label) for MS.

The Committee recalled and reiterated the views expressed by the 2015 Expert Committee on consideration of medicines for inclusion on the Model Lists for off-label uses or indications: that is, labelling is the responsibility of national regulatory authorities and there may consequently be different labels for the same product in different countries, and there is thus no global standard for what is considered off-label. Furthermore, updating approved labels for older products may not be pursued by market authorization holder(s) if doing so is not considered commercially viable, and there are many examples of older products whose regulatory labels are inconsistent with current clinical evidence and current clinical practice. Consequently, the Expert Committee reaffirmed that off-label status of a medicine need not be a reason to exclude it from the Model Lists if it otherwise meets the criteria for inclusion. The Committee considered that the Model List can play an important role in identifying those medicines for which off-label use is supported by convincing evidence, complementing the assessment and labelling by jurisdictional authorities.

Therefore, the Committee recommended the inclusion of cladribine, glatiramer acetate and rituximab as individual medicines on the complementary list of the EML in a new section dedicated to medicines for MS. The recommendation was based on the important public health need, and evidence of efficacy, safety and feasibility of use of the medicines proposed. The Committee did not recommend the inclusion of ocrelizumab as an alternative under a square box listing for rituximab for the reasons outlined above.

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Ocrelizumab – addition – EML

Ocrelizumab	ATC code: L04AA36

Proposal

Addition of ocrelizumab to the complementary list of the EML for treatment of adults with relapsing and progressive forms of multiple sclerosis (MS).

Applicant

F. Hoffmann-La Roche Ltd, Basel, Switzerland

WHO technical department

The Department of Mental Health and Substance Use provided comments on two applications submitted for Expert Committee consideration for disease-modifying therapies for MS – this application and an application for inclusion of three disease-modifying therapies for MS submitted by the Multiple Sclerosis International Federation. The technical department supported the inclusion of disease-modifying therapies for MS on the EML, highlighting that the proposals were well aligned with the mandate of the intersectoral global action plan on epilepsy and other neurological disorders (*1*), which includes a strategic objective to "provide effective, timely and responsive diagnosis, treatment, and care" for people with neurological disorders such as MS.

EML/EMLc

EML

Section

5.2 Medicines for multiple sclerosis

Dose form(s) & strengths(s)

Injection: 30 mg/mL in 10 mL vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background

In 2019, the Expert Committee reviewed an application from the Multiple Sclerosis International Federation requesting the addition of glatiramer acetate, fingolimod

and ocrelizumab on the Model Lists for use in the treatment of MS. The Committee acknowledged the important public health burden of MS and the need for effective and affordable treatments. However, the Committee noted that the superiority of the proposed medicines over other therapeutic options in terms of benefits, harms and affordability did not clearly emerge from the application. The Committee noted that some commonly used treatments were not included in the application (e.g. azathioprine, natalizumab, dimethyl fumarate, cladribine), or were not given full consideration (e.g. rituximab), with reasons for their exclusion being unclear. In particular, the Committee noted the evidence presented in the application in relation to rituximab and considered that rituximab could have a relevant clinical role in the treatment of MS and recommended that any future application include evidence for rituximab versus active comparators, not just placebo. The Committee therefore did not recommend listing of glatiramer acetate, fingolimod or ocrelizumab at the time, and requested a revised application which comprehensively reviewed the relative roles of relevant available medicines for MS (*2*).

Public health relevance

MS is a chronic autoimmune disease characterized by inflammation of the central nervous system that leads to demyelination, axonal loss and progressive neuronal degeneration, resulting in irreversible disability and cognitive impairment (*3,4*). Common symptoms include pain, fatigue, mood and cognitive changes, mobility and sensory impairment, visual disturbances, and elimination dysfunction. Symptoms can vary in severity and can result in significant disability, and reduction in quality and length of life.

Data on the global prevalence of MS vary. The Global Burden of Disease study reported that globally, about 1.8 million people (23 per 100 000) had MS in 2019. Age-standardized prevalence per 100 000 population shows large variability across WHO regions, ranging from 4 cases per 100 000 in the Western Pacific Region to 60 per 100 000 in the European Region (*5*). The atlas of MS estimated that globally, about 2.8 million people (36 per 100 000) had MS in 2020 (*6*). The number of people with MS per 100 000 population also showed large variability across WHO regions, ranging from 5 per 100 000 in the African and Western Pacific regions to 133 per 100 000 in the European Region (*6*).

MS is most often diagnosed between the ages of 20 and 50 years, but the disease may also first manifest in older adults and children. Women are affected 2–3 times more than men (*7,8*).

MS is broadly divided into relapsing and progressive forms, classified in three different clinical phenotypic patterns based on the presence of transient attacks of neurological symptoms and/or a progressive worsening of the neurological function: relapsing-remitting MS, secondary progressive MS and primary progressive MS (*9*). Relapsing-remitting MS is characterized by relapses and remissions of

neurological symptoms, with relapses associated with new areas of inflammation in the central nervous system. Over time, most people with relapsing-remitting MS will transition to secondary progressive MS, marked by gradual worsening of neurological function with or without additional inflammatory events. Primary progressive MS is characterized by the absence of clearly defined relapses (*9,10*).

The course of MS is highly variable and unpredictable, and patients may have a broad range of neurological symptoms or signs, depending on the location and degree of central nervous system inflammation. Life expectancy for patients with MS is 5–10 years shorter than for the general population (*3,11,12*). Exposure to any disease-modifying therapy for MS is associated with a lower risk of death compared with no exposure (*13*).

MS has a substantial negative impact on health-related quality of life (*14–16*). People with MS have significantly lower health-related quality of life scores than people who have other chronic diseases, such as chronic ischaemic heart disease, gastro-oesophageal reflux disease, non-insulin-dependent diabetes mellitus, or inflammatory bowel disease (*17*). People with MS are less likely to be employed, more likely to take time off work when they are employed, and more likely to retire early than the general population (*18–20*).

Globally, an estimated 1 million people (unpaid spouses, partners, children, family members or friends) are involved in the overall care of people living with MS (*21*). Caregivers often stop working to care for the person with MS, further increasing the societal burden of the disease (*22*). Caregivers of people with MS also experience high levels of distress and reduced quality of life (*23, 24*).

Summary of evidence: benefits

The application presented a summary of evidence from pivotal studies of ocrelizumab in relapsing and primary progressive MS.

Relapsing MS

Two identically designed industry-sponsored, randomized, multicentre, active-controlled, double-blind, phase III studies (OPERA I and OPERA II) evaluated the efficacy and safety of ocrelizumab in 1651 adults with relapsing MS (*25*). Participants received ocrelizumab 600 mg by intravenous infusion every 6 months or subcutaneous interferon beta-1a 44 micrograms three times a week. The primary efficacy endpoint was annualized relapse rate over 96 weeks. Ocrelizumab treatment was associated with a statistically significant and clinically meaningful improvement in annualized relapse rate, compared with interferon.

- OPERA I: annualized relapse rate 0.16 versus 0.29 (rate ratio (RR) 0.54, 95% confidence interval (CI) 0.40 to 0.72; relative reduction 46%);
- OPERA II: annualized relapse rate 0.16 versus 0.29 (RR 0.53, 95% CI 0.40 to 0.71; relative reduction 47%).

Ocrelizumab treatment was also associated with statistically significant and clinically meaningful improvements compared with interferon for several secondary endpoints, including the proportion of patients with confirmed disability progression at 12 and 24 weeks and proportion of patients with no evidence of disease activity. Patients receiving ocrelizumab also had significantly lower mean numbers of T1 gadolinium-enhancing lesions and new and/or enlarging T2 lesions on magnetic resonance imaging (MRI).

Periodic analyses of efficacy data from patients in the OPERA I and II trials who continued on to the open-label extension phase reported that: the benefits of earlier initiation of ocrelizumab were maintained compared with patients switching from interferon (*26–28*); the risk of requiring a walking aid was lower (*29, 30*); and rates of upper- and lower-limb disability were lower (*31*).

In the phase IIIb ENSEMBLE study (1225 participants), most treatment-naïve patients with early-stage relapsing-remitting MS treated with ocrelizumab over 2 years showed minimal disease activity based on clinical and MRI measures – 86.5% had no evidence of clinical activity and 88.9% had no evidence of MRI activity. Expanded Disability Status Scale scores remained stable or showed improvements in most patients (87.4%) (*32*). In an analysis of 7-year open-label extension data from the OPERA I and II studies, 81% of treatment-naive patients with early MS had no disability progression over 7 years on treatment with ocrelizumab (*33*).

Progressive MS

The industry-funded phase III randomized, multicentre, double-blind, parallel-group, placebo-controlled ORATORIO trial evaluated the efficacy of ocrelizumab in the treatment of 732 patients with primary progressive MS (*34*). Participants were randomized 2:1 to receive ocrelizumab 600 mg by intravenous infusion every 6 months or placebo. The primary efficacy endpoint was the proportion of patients with 12-week confirmed disability progression. Secondary endpoints included 24-week confirmed disability progression, timed 25-foot walk, T2 lesion volume and total brain volume loss. The percentage of patients with 12-week confirmed disability progression was 32.9% with ocrelizumab versus 39.3% with placebo (hazard ratio (HR) 0.76, 95% CI 0.59 to 0.98). The percentage of patients with 24-week confirmed disability progression was 29.6% with ocrelizumab versus 35.7% with placebo (HR 0.75, 95% CI 0.58 to 0.98). By week 120, performance on the timed 25-foot walk worsened by 38.9% with ocrelizumab versus 55.1% with placebo; the total volume of brain lesions on T2-weighted MRI decreased by 3.4% with ocrelizumab and increased by 7.4% with placebo; and the percentage of brain volume loss was 0.90% with ocrelizumab versus 1.09% with placebo.

The ongoing CONSONANCE trial is a single-arm phase IIIb trial to evaluate the effectiveness and safety of ocrelizumab across the spectrum of progressive MS (i.e. in patients with either primary progressive MS or secondary progressive MS) (*35*). Primary outcomes are proportion of patients with no

evidence of progression, and the proportion of patients with no evidence of progression and no active disease. In the 2-year interim analysis, treatment with ocrelizumab was associated with comparable rates of no evidence of progression and no evidence of progression and no active disease in patients with secondary progressive MS and primary progressive MS and with functional improvement in about one third of patients.

Summary of evidence: harms

Pooled results for adverse events reported during the controlled treatment period of the pivotal phase III studies in relapsing MS (OPERA I and OPERA II (*25*)) are presented in Table 10.

Table 10

Adverse events in relapsing multiple sclerosis phase III studies in the controlled treatment period

Variable	OPERA I and OPERA II, no. (%)	
	IFNβ1a (*n* = 826)	OCR 600 mg (*n* = 825)
Patients with at least one adverse event	688 (83.3)	687 (83.3)
Total adverse events	4141	4194
Deaths	2 (0.2)	1 (0.1)
Patients with at least one:		
fatal adverse event	2 (0.2)	1 (0.1)
serious adverse event	72 (8.7)	57 (6.9)
serious adverse event leading to treatment discontinuation	9 (1.1)	6 (0.7)
adverse event leading to treatment discontinuation	51 (6.2)	29 (3.5)
Patients with malignancies	2 (0.2)	4 (0.5)
Patients with infections[a]	433 (52.4)	482 (58.4)
Patients with serious infections[a]	24 (2.9)	11 (1.3)
Patients with infusion-related reaction	80 (9.7)	283 (34.3)

IFNβ1a: interferon beta-1a; OCR: ocrelizumab.

[a] Infections are defined using adverse events falling into the Medical Dictionary for Regulatory Activities (MedDRA) (*36*) System Organ Class "Infections and Infestations.

Adverse events reported during the controlled treatment period of the phase III ORATORIO study (*34*) on primary progressive MS are presented in Table 11.

Table 11

Adverse events in primary progressive multiple sclerosis phase III study in the controlled treatment period

Variable	No. (%)	
	Placebo (*n* = 239)	**OCR 600 mg** (*n* = 486)
Patients with at least one adverse event	215 (90.0)	462 (95.1)
Total adverse events	1762	3690
Deaths	1 (0.4)	4 (0.8)
Patients with at least one:		
fatal adverse event	1 (0.4)	4 (0.8)
serious adverse event	53 (22.2)	99 (20.4)
serious infectiona	14 (5.9)	30 (6.2)
serious adverse event leading to withdrawal from treatment	6 (2.5)	13 (2.7)
serious adverse event leading to dose modification/ interruption	4 (1.7)	8 (1.6)
adverse event leading to withdrawal from treatment	8 (3.3)	20 (4.1)
adverse event leading to dose modification/ interruption	12 (5.0)	47 (9.7)
infusion-related reaction leading to withdrawal at first infusion	0	1 (0.2)
Patients with:		
malignancies[b]	2 (0.8)	11 (2.3)
infections[a]	162 (67.8)	339 (69.8)

OCR: ocrelizumab.

[a] Infections are defined using adverse events falling into the Medical Dictionary for Regulatory Activities (MedDRA) (*36*) System Organ Class "Infections and Infestations".

[b] Identified using the malignant tumours Standardized MedDRA Query. Non-serious relapses are excluded.

Notes: Investigator text for adverse events encoded using MedDRA version MedDRA v18.0.

Multiple occurrences of the same adverse events in one individual are counted only once except for the total number of adverse events row in which multiple occurrences of the same adverse events are counted separately.

A phase II, randomized placebo-controlled trial of ocrelizumab in relapsing-remitting MS found that treatment with 2 x 300 mg or 2 x 1000 mg of ocrelizumab was generally well tolerated (*37*). The adverse event profile of ocrelizumab during the open-label treatment period up to week 96 and during follow-up and monitoring/observation periods up to week 144 was consistent with observations during the first 24 weeks. The single most common adverse event was infusion-related reactions, reported more often in patients treated with ocrelizumab compared with patients given placebo (9.3% in placebo arm, 34.5% in the 300-mg x 2 arm and 43.6% in the 1000-mg x 2 arm, after the first infusion of day 1 of the study).

Safety data were pooled up to a clinical cut-off date of November 2020 from the phase II study and three pivotal phase III studies, and the "all-exposure population" including the same studies plus an additional seven phase IIIb studies. Safety findings, excluding coronavirus disease 2019 (COVID-19) infections, remain generally consistent with the controlled treatment period in the pooled relapsing MS/primary progressive MS population from the phase II study and pivotal phase III studies.

Very common (frequency ≥ 1/10) adverse drug reactions reported in association with the use of ocrelizumab in the pivotal phase III studies were infusion-related reactions, upper respiratory tract infections, nasopharyngitis and influenza. Common (frequency (≥ 1/100 to < 1/10) adverse drug reactions reported were sinusitis, bronchitis, cough, gastroenteritis, oral herpes, respiratory tract infection, viral infection herpes zoster, conjunctivitis and cellulitis.

The application reported that suspected or confirmed COVID-19 cases were identified from 10 ongoing Roche/Genentech clinical trials, as of 28 May 2021. Symptomatic COVID-19 was reported in 406 (9.9%) of 4089 patients treated with ocrelizumab across 10 clinical trials. Most cases of COVID-19 were non-serious (274/406, 67.5%) and most patients had recovered or were recovering at the time of the analysis (347/406, 85.5%). Eighteen patients (out of 406; 4.4%) had not recovered from COVID-19 and in 32/406 cases (7.9%), there was a fatal outcome. Most of the symptomatic COVID-19 cases (265/406, 65.3%) had a mild/moderate presentation, with 86 (21.2%) cases being classified as severe, 13 (3.2%) life-threatening and 32 (7.9%) fatal; information on severity was missing for 10 patients (2.5%).

WHO guidelines

WHO guidelines for the treatment of MS are not currently available.

Costs/cost–effectiveness

The application reported that in France, Germany, Italy, Spain and the United Kingdom, ex-factory prices for ocrelizumab range from €5125 to €6250 per vial, or €20 500 to €25 000 per patient per year. In upper and lower middle-income

countries and low-income countries, excluding countries with high foreign and exchange market rate fluctuations, the average ocrelizumab list price is €4450 per vial with the lowest list price starting at €1495 per vial.

Roche has implemented an international differential pricing model which is reported to apply in 75 upper and lower middle-income countries and low-income countries, either through public funding or the out-of-pocket paying sector, where pricing is added to non-pricing support in the form of patient assistance programmes. These programmes include components such as medicine doses, donations, patient awareness educational campaigns involving health care practitioners, patient assistance to treatment adherence, and health service delivery improvements. To date, and with the implementation of a greater price flexibility, as part of its international differential pricing model, Roche reports to have supported governments and private institutions in more than 30 upper and lower middle-income countries and low-income countries in providing access to patients for ocrelizumab in MS, including Argentina, Armenia, Belarus, Bosnia and Herzegovina, Brazil, Bulgaria, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, Egypt, El Salvador, Georgia, Ghana, Guatemala, Honduras, Jordan, Kazakhstan, Kenya, Kosovo, Lebanon, Libya, Malaysia, Mexico, Montenegro, Morocco, Namibia, Nicaragua, Nigeria, North Macedonia, Pakistan, Paraguay, Peru, South Africa, Tunisia, Türkiye, Ukraine, Uzbekistan and Venezuela (Bolivarian Republic of).

The use of ocrelizumab to treat MS was evaluated in health technology assessments and eventually resulted in positive reimbursement decisions in several high-income countries, following price negotiations and (confidential) pricing agreements (*38–43*).

The application did not present a review of published economic evaluations of ocrelizumab or other disease-modifying therapies for MS, arguing that comparability of results across studies and generalizability of conclusions are limited and affected by many factors, including different study parameters, inputs and modelling assumptions.

Availability

Ocrelizumab has marketing approval in more than 100 countries worldwide. Regulatory applications are currently being submitted in Asia. Approved indications are for treatment of adults with relapsing forms of MS and treatment of adults with primary progressive MS.

Other considerations

A separate application submitted by the Multiple Sclerosis International Federation, requesting individual listings for cladribine and glatiramer acetate, and a square box listing for rituximab, specifying ocrelizumab as a therapeutic alternative, was also considered by the Expert Committee at this meeting.

Committee recommendations

The Expert Committee noted that MS is the most common non-traumatic cause of neurological disability in young adults. About 2.8 million people are living with MS worldwide, with women affected 2–3 times more than men. The most common form is relapsing-remitting MS, characterized by relapses and remissions of neurological symptoms. Over time, most people with relapsing-remitting MS develop a secondary progressive course of the disease (secondary progressive MS) marked by gradual worsening with or without additional inflammatory events. Currently, there are no medicines specifically for the treatment MS included on the Model List. However, rituximab is included for other conditions, is widely available and is listed on many national essential medicines lists.

The Committee acknowledged the benefits of ocrelizumab in the management of relapsing-remitting and primary progressive forms of MS. However, there was no compelling evidence of its superiority over alternative treatments, specifically rituximab, which has the same molecular target (CD20). The Committee considered the option of listing ocrelizumab as alternative to rituximab, but also recognized the difference in current prices of the two products and the fact that off-label use of medicines is allowed in many countries, when robust evidence exists. The Committee concluded that including ocrelizumab as a therapeutic alternative to rituximab could result in considerable additional expenditure at the country level for patients and health systems, without offering additional clinical benefit. The Committee considered that inclusion only of the less expensive rituximab on the EML might serve to facilitate its use (albeit off-label) for MS.

The Committee recalled and reiterated the views expressed by the 2015 Expert Committee on consideration of medicines for inclusion on the Model Lists for off-label uses or indications: that is, labelling is the responsibility of national regulatory authorities and there may consequently be different labels for the same product in different countries, and there is thus no global standard for what is considered off-label. Furthermore, updating approved labels for older products may not be pursued by market authorization holder(s) if doing so is not considered commercially viable, and there are many examples of older products whose regulatory labels are inconsistent with current clinical evidence and current clinical practice. Consequently, the Expert Committee reaffirmed that off-label status of a medicine need not be a reason to exclude it from the Model Lists if it otherwise meets the criteria for inclusion. The Committee considered that the Model List can play an important role in identifying those medicines for which off-label use is supported by convincing evidence, complementing the assessment and labelling by jurisdictional authorities.

The Committee therefore did not recommend the inclusion of ocrelizumab as an individual medicine, or as a therapeutic alternative to rituximab under a square box listing, on the EML for the treatment of MS.

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Section 6: Anti-infective medicines

6.2 Antibacterials

6.2.1 Access group antibiotics

Amoxicillin + clavulanic acid – new formulation – EMLc

Amoxicillin + clavulanic acid	ATC code: J01CR02

Proposal

Addition of amoxicillin + clavulanic acid 200 mg + 28.5 mg dispersible tablet to the core list of the EMLc for the same indications for which other formulations of amoxicillin + clavulanic acid are currently listed.

Applicant

Sandoz International GmbH, Bavaria, Germany

WHO technical department

The Global Coordination and Partnership department within the Antimicrobial Resistance division reviewed and provided comments on the application, indicating its support for the addition of the proposed new dispersible tablet formulation of amoxicillin + clavulanic on the EMLc.

EML/EMLc

EMLc

Section

6.2.1 Access group antibiotics

Dose form(s) & strengths(s)

Tablet (dispersible): 200 mg (as trihydrate) + 28.5 mg (as potassium salt)

Core/complementary

Core

Individual/square box listing

Individual

Background

Multiple amoxicillin + clavulanic acid formulations in a 4:1 ratio are included on the EMLc as first- or second-choice empiric treatment for various bacterial infections.

- First choice: community-acquired pneumonia, complicated intra-abdominal infections, hospital acquired pneumonia, low-risk febrile neutropenia, lower urinary tract infections, sinusitis, and skin and soft tissue infections.
- Second choice: bone and joint infections, community-acquired pneumonia, otitis media and surgical prophylaxis.

In 2021, a higher strength formulation of amoxicillin + clavulanic acid in a 7:1 ratio (875 mg + 125 mg) was recommended for inclusion on the EML for treatment of community-acquired pneumonia and intra-abdominal infections in adults. In making its recommendation, the Expert Committee noted that a higher ratio of amoxicillin to clavulanic acid is generally associated with less diarrhoea, a recognized adverse effect of this combination (*1*).

Public health relevance

The public health relevance of age-appropriate formulations of essential medicines for children is well established. The Global Accelerator for Paediatric Formulations was developed in response to the World Health Assembly resolution 69.20 on promoting innovation and access to high quality medicines for children. In the 2022–2024 strategy, the Global Accelerator for Paediatric Formulations clearly stated that the development of dispersible tablets over bulky syrups or the enabling of formulary consolidation with flexible dosage forms should be one of the priority tasks (*2*).

Summary of evidence: benefits

The evidence of benefits presented by the applicants was mostly based on studies from the 1990s when the formulation of amoxicillin + clavulanic acid at a 7:1 ratio was first developed. No specific evidence on the efficacy of the dispersible formulation was included.

A randomized, observer-blinded, multicentre study conducted in the 1990s evaluated the efficacy of amoxicillin + clavulanic acid as twice daily dosing at a 7:1 ratio compared with three times daily dosing at a 4:1 ratio in 463 children, aged 2–12 years with acute otitis media (*3*). The two treatment groups demonstrated similar efficacy with clinical success rates at the end of therapy (10 days) of 91.8% for the twice-daily 7:1 group versus 90.5% for the three-times-daily 4:1 group. No significant difference was seen between treatment groups in the incidence of adverse events, however the incidence of diarrhoea was lower in the twice-daily group (6.7% versus 10.3%) group. Significantly more patients in the twice-daily group than the three-times-daily group were reported to have at least 80% compliance with treatment.

Another United States study from the 1990s randomized 868 children aged 2–12 years with acute otitis media to receive amoxicillin (45 mg) + clavulanic acid

(6.4 mg) twice daily for 10 days, 40/10 mg three times daily for 10 days or 45/6.4 mg twice daily for 5 days (*4*). Treatment successes (clinical cure or improvement) were reported as 86.5%, 78.7% and 71.1% in the three treatment groups, respectively. The incidence of diarrhoea was significantly greater in the three-times daily group (26.7%), than in the two twice-daily groups (9.6% and 8.7%).

A third randomized study from the 1990s of 415 children aged 2 months to 12 years with acute otitis media compared amoxicillin + clavulanic acid twice daily in a 7:1 ratio with three times daily in a 4:1 ratio given for 7 or 10 days (*5*). At the end of therapy (days 7–12), clinical success (cure) was achieved by about 94% of patients in both treatment groups. At follow-up (days 38–42), 93.3% of patients in the twice-daily group and 87.9% in the three-times-daily group continued to have a clinically successful response. Both treatment regimens were well tolerated, with most adverse events being of a mild-to-moderate and transient nature. Diarrhoea was reported in 7.2% and 10.7% of the twice-daily and three-times daily groups, respectively. Compliance with treatment was reported as 82.8% in the twice-daily group and 73.3% in the three-times-daily group.

Results of the three studies mentioned above were pooled in a subgroup analysis in a 2013 Cochrane systematic review (*6*). No significant differences were found between once- or twice- daily groups and the three-times daily group for: clinical cure rate at the end of therapy (risk ratio (RR) 1.03, 95% confidence interval (CI) 0.99 to 1.07); clinical cure rate during therapy (RR 1.00, 95% CI 0.70 to 1.42); clinical cure rate at post-treatment (RR 1.04, 95% CI 0.98 to 1.10); recurrent infection after completion of therapy (RR 1.01, 95% CI 0.39 to 2.60); overall adverse reactions (RR 0.92, 95% CI 0.52 to 1.63); diarrhoea (RR 0.70, 95% CI 0.48 to 1.00); skin adverse events (RR 0.72, 95% CI 0.44 to 1.17) or compliance rate (RR 1.05, 95% CI 0.98 to 1.13).

An observer-blinded, multicentre study conducted in the 1990s randomized 437 children aged 2–12 years with lower respiratory tract infections to receive 7 days of treatment with amoxicillin + clavulanic acid either twice daily in a 7:1 ratio or three times daily in a 4:1 ratio (*7*). Both regimens had similar clinical success (cure) rates (81.0% and 77.8%, respectively). Both regimens were well tolerated, and no statistically significant difference was found in the incidence of adverse events between the two groups. Compliance with study medication was high and similar for both groups (80% compliance was 90.0% and 87.0% for the twice-daily and three-times-daily groups, respectively).

Summary of evidence: harms

The safety profile of amoxicillin + clavulanic acid is well known. In children, the most frequently reported adverse events are mild gastrointestinal disturbances, with diarrhoea being largely attributed to clavulanic acid.

In the trials with a direct comparison between amoxicillin + clavulanic acid 4:1 versus 7:1 ratios, no significant difference was seen in the safety profile of the two products overall. Some trials reported a significantly lower incidence of diarrhoea in the twice-daily 7:1 groups, which is plausible due to the lower dose of clavulanic acid administered (*3*,*4*,*8*).

WHO guidelines

The WHO AWaRe (Access, Watch, Reserve) antibiotic book (*9*) provides guidance on the prescribing and use of antibiotics on the WHO Model Lists of Essential Medicines for the empiric treatment of common infections in adults and children. It reflects the recommendations for essential antibiotics made by the WHO Expert Committee on Selection and Use of Essential Medicines, incorporating the principles of the WHO AWaRe classification of antibiotics.

Costs/cost–effectiveness

The price of the proposed product is reported in the application as US$ 2.05 per pack of 32 dispersible tablets (US$ 0.064 per tablet).

Indicative prices for amoxicillin + clavulanic acid 4:1 formulations included in the UNICEF supply catalogue are:

- 250 mg/62.5 mg dispersible tablet: US$ 5.06 per pack of 50 tablets (US$ 0.10 per tablet);
- 125 mg/31.25 mg powder for oral suspension: US$ 1.87 per 100 mL bottle (US$ 0.09 per 125 mg amoxicillin dose).

Availability

Amoxicillin + clavulanic acid 200 mg + 28.5 mg dispersible tablet is not currently available in any markets. It has regulatory approval in Malawi. Submissions made to regulatory authorities for Kenya, Rwanda and Uganda are pending approval.

Other considerations

The EML Antimicrobial Working Group reviewed the application and advised that it supports the inclusion of amoxicillin + clavulanic acid dispersible tablets at a 7:1 ratio (200 mg + 28.5 mg) on the EMLc.

The Working Group noted that the 7:1 dispersible tablets proposed in the application offer several advantages over currently listed paediatric formulations such as ease of administration and heat stability at a similar price. The oral liquid formulations currently listed on the Model Lists must be refrigerated after reconstitution which is a challenge in many resource-constrained settings.

The Working Group acknowledged that amoxicillin + clavulanic acid was identified as one of the priority antibiotics during the WHO meeting on paediatric

drug optimization for antibiotics in November–December 2022. While UNICEF currently procures amoxicillin + clavulanic acid dispersible tablets at a 4:1 ratio (250 mg + 62.5 mg), which is also being proposed for inclusion on the EMLc as part of the EMLc formulation review in the context of the Global Accelerator for Paediatric Formulations project, it was considered that the additional availability of a dispersible tablet at a 7:1 ratio may offer certain advantages. These advantages include allowing higher doses of amoxicillin without dose-related side-effects associated with a higher clavulanic acid dose (e.g. in settings where penicillin non-susceptible pneumococci are prevalent).

The Working Group noted that the dispersible tablets proposed in this application did not receive regulatory approval from the European Medicines Agency as they did not meet its requirement of disintegration within 3 minutes, an issue which does not seem to affect hospital or community use or offset the key advantages. Given the public health need for this formulation, the Working Group did not consider this should preclude its addition to the EMLc.

Committee recommendations

The Expert Committee recognized the importance of age-appropriate formulations of essential medicines to better meet the dosing needs of children.

The Committee noted that the 7:1 ratio of amoxicillin to clavulanic acid is associated with similar efficacy to the 4:1 ratio but has a reduced frequency of gastrointestinal adverse effects. The dispersible tablet formulation also offers advantages over oral liquid formulations for ease of administration and heat stability.

The Committee therefore recommended the inclusion of the 200 mg + 28.5 mg dispersible tablet formulation of amoxicillin + clavulanic acid as an Access group antibiotic on the core list of the EMLc for treatment of bacterial infections in children – specifically those infections for which amoxicillin + clavulanic acid is already recommended on the EMLc.

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6.2.2 Watch group antibiotics

Flomoxef sodium – addition – EML and EMLc

Flomoxef sodium	**ATC code: J01DC14**

Proposal

Addition of flomoxef sodium to the core list of the EML and EMLc for the empiric treatment of mild/moderate community-acquired intra-abdominal infections and mild/moderate upper urinary tract infections in adults and children at high risk of infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacterales.

Applicant

Global Antibiotic Research and Development Partnership (GARDP)

WHO technical department

The Global Coordination and Partnership department within the Antimicrobial Resistance division reviewed and provided comments on the application. The technical department acknowledged that flomoxef sodium could have an added role in the treatment of the indications outlined and could potentially be a viable carbapenem-sparing option for the treatment of resistant bacterial infections caused by ESBL-producing Enterobacterales, especially in settings with a high prevalence of ESBL-producing Enterobacterales. However, the technical department considered that more in vivo data were needed to support its inclusion on the Model Lists. Additionally, it was noted that flomoxef sodium may be of interest for the management of neonatal sepsis but that a determination in this regard is currently premature. However, flomoxef sodium could be considered for inclusion in the future once more data become available, including from the ongoing GARDP neonatal sepsis trials.

EML/EMLc

EML and EMLc

Section

6.2.2 Watch group antibiotics

Dose form(s) & strengths(s)

Powder for injection: 0.5 g, 1 g in vial

Core/complementary

Core

Individual/square box listing

Individual

Background

Flomoxef sodium has not been previously considered for inclusion on the EML. It has been classified as a watch group antibiotic under the AWaRe (Access, Watch, Reserve) classification.

Flomoxef sodium is an oxacephem antibiotic belonging to the oxacephem subclass of second-generation cephalosporins that are not inactivated by ESBL and narrow spectrum β-lactamases. However, flomoxef sodium is inactivated by carbapenemases and class C β-lactamases (AmpC). It has good activity against Gram-positive (except *Enterococcus* spp.) and Gram-negative bacteria (except *Pseudomonas aeruginosa*, *Acinetobacter* and Enterobacterales producing AmpC) and against anaerobes.

Public health relevance

There is currently no efficacious and safe alternative to the use of carbapenems for patients who are not severely ill but need treatment for intra-abdominal infections and upper urinary tract infections caused by ESBL-producing Enterobacterales, which are often quinolone resistant. However, overuse of carbapenems has caused increasing levels of carbapenem resistance, especially in pathogens that are transmitted in hospitals, increasing the urgency for alternative carbapenem-sparing options especially for non-severe infections.

Cephamycins have been identified as potential definitive treatments of non-severe urinary tract infections caused by ESBL-producing Enterobacterales in a recent systematic review (*1*) and in two narrative reviews on this topic (*2,3*).

Summary of evidence: benefits

Flomoxef sodium was first approved in 1988, based on clinical studies that were conducted between 1983 and 1988. Given the age of the antibiotic and the old pivotal trials that were conducted with different standards of rigor, the applicants compiled the evidence of efficacy based on a combination of in vitro susceptibility studies, clinical trials literature review and recommendations in guidelines.

In-vitro studies

The application reported the main findings of 14 studies (mostly conducted in Asia) that assessed the in vitro activity of flomoxef sodium against clinical isolates (*4–17*). They demonstrated a wide range of species susceptible to flomoxef sodium, both Gram-positive and Gram-negative organisms, including ESBL-producing Enterobacterales (especially the enzymes from the CTX-M group). However, flomoxef sodium did not exhibit antibacterial activity against Enterobacterales

with inducible chromosomal AmpC (e.g. *Enterobacter cloacae*, *Serratia marcescens* and *Citrobacter freundii*) and it was inhibited by carbapenemases. It was also not active against *Enterococcus* spp., *Pseudomonas* spp. and *Acinetobacter* spp. The application stated that based on these in vitro studies, flomoxef displays potentially better activity than both third- and fourth-generation cephalosporins and piperacillin-tazobactam" and that flomoxef activity is inferior to the activity of all carbapenems.

In vitro susceptibility studies conducted by GARDP

In 2018, susceptibility to flomoxef sodium was evaluated and compared with meropenem in 40 Enterobacterales from the International Health Management Associates repository (collected from worldwide locations between 2013 and 2016) (*18*). Flomoxef sodium showed potent activity against the 26 ESBL-producing Enterobacterales, with a minimum inhibitory concentration (MIC) to inhibit growth of 50% of organisms (MIC$_{50}$) at 0.06/0.12 mg/L, and an MIC to inhibit growth of 90% of organisms (MIC$_{90}$) at 8 mg/L but it was inactive against the three carbapenem-resistant *Klebsiella pneumoniae* and AmpC producers. A second study tested flomoxef sodium on about 1000 Enterobacterales isolates collected between 2019 and 2021, of which 80% were resistant to third-generation cephalosporins – (70% of these were ESBL producers (*19*). Susceptibility to flomoxef sodium was observed in 816 isolates (82%). In comparison, susceptibility to cefuroxime was 17%, susceptibility to ceftazidime 21% and susceptibility to piperacillin-tazobactam 41%. Amikacin and fosfomycin also exhibited potent activity against the isolates of the panel, with 90% of them being susceptible. Resistance to flomoxef sodium was mainly due to AmpC and/or carbapenemase expression, although 17 (2%) ESBL-producing isolates were resistant to flomoxef sodium.

Data from preapproval studies and postmarketing use

Data were derived from the interview form version 11 (February 2022) (*20*) which, in Japan, the market authorization holder is required to provide to complement the information in the package insert. Data from preapproval studies were pooled, about 1500 patients including all indications. For urinary tract infections the pooled cure rate was 63.0% and for acute prostatitis 95.0%. For intra-abdominal infections (peritonitis and intra-abdominal abscess), the pooled cure rate was 81.6% (71.8% for cholecystitis and cholangitis).

Data from postmarketing use included almost 25 000 patients. Reported pooled cure rates were 84.2% for upper urinary tract infections and 89.5% for prostatitis/urethritis. For intra-abdominal infections (peritonitis and intra-abdominal abscess), pooled cure rates were 84.6% (83.4% for cholecystitis and cholangitis) and 91.3% in children. Cure rates were lower for severe compared to mild infections (67.9% versus 84.6% for urinary tract infections, 76.4% versus

87.2% for intra-abdominal infections) and for bloodstream/systemic infections (44.8% cure rates for severe systemic infections versus 78.7% for mild systemic infections).

Systematic review

GARDP conducted a systematic literature review for the purpose of the application, with the primary objective of identifying clinical efficacy and safety data for flomoxef sodium in adults, children and neonates. They included 37 studies from English databases and 176 from a Japanese database. Most studies were published before 2000, were uncontrolled and included patients with multiple sources of infection within the same study. A meta-analysis could therefore not be performed due to the low quality of studies. However, the applicants performed a targeted analysis of the subset of studies focused on intra-abdominal and urinary tract infections. Results were presented by type of infection.

Intra-abdominal infections

Eight studies (one randomized controlled trial, four single-arm trials and three observational studies) were identified. The randomized, double-blind, multicentre trial compared flomoxef sodium (1 g every 12 hours for 10 days) with cefotiam (1 g every 12 hours for 10 days) in 296 patients aged 16 years and older with postoperative infections (*21*). This was one of the pivotal trials that led to the approval of the medicine in Japan. As the trial was conducted in the 1987, no patients had intra-abdominal infections caused by ESBL-producing Enterobacterales. The per-protocol analysis included 253 evaluable patients. The clinical cure rate in the overall population was 71.4% (90/126; 95% confidence interval (CI) 63.5% to 79.3%) for flomoxef sodium and 62.2% (79/127; 95% CI 53.8% to 70.6%) for cefotiam, with no statistically significant difference. Of note, in patients with postoperative infections of the abdominal cavity and retroperitoneal space, the cure rate was significantly higher for flomoxef sodium (67.3% (37/55); 95% CI 54.9% to 79.7%) than for cefotiam (49.2% (30/61); 95% CI 36.6% to 61.7%).

Results from observational studies of flomoxef sodium for the treatment of postsurgical intra-abdominal infections reported high cure rates of > 90% (*22–24*). A single-arm study, including only patients with biliary tract infections, reported an overall cure rate of 77.8%. The cure rate was higher for the cholecystitis subgroup (90.0%) but lower for the cholangitis subgroup (70.6%) (*25*). Two other single-arm studies in women reported overall cure rates of 89.4% and 90.5% for pelvic infections treated with flomoxef sodium (*26,27*).

Urinary tract infections

Sixteen studies (one randomized controlled trial, three single-arm trials and 12 observational studies) were identified. The randomized controlled trial

was a double-blind, multicentre trial in adults with complicated urinary tract infections where flomoxef sodium (1 g given every 12 hours for 5 days) was compared with latamoxef (1 g given every 12 hours for 5 days) (*28*). The primary outcome was clinical cure. Clinical response was rated on a three-point scale (excellent, moderate or poor) based on the presence or absence of pyuria and/or bacteriuria at day 5 or end of treatment. The clinical cure rate was 68.2% (60/88, 95% CI 58.5% to 77.9%) for flomoxef sodium and 69.6% (78/112, 95% CI 61.1% to 78.2 %) for latamoxef when including all pathogens except *P. aeruginosa*. When only *Escherichia coli* infections were included, cure rates were higher in both groups (90.6% with flomoxef sodium versus 92.6% with latamoxef). As the trial was conducted in 1987, no infections were caused by extended-spectrum β-lactamase Enterobacterales.

Of the 15 remaining uncontrolled studies, five had more than 25 patients (*29–33*) and showed varying clinical cure rates ranging from 50% (*31*) to 72% in patients with strains susceptible to flomoxef sodium (*32*). Ten studies included fewer than 25 patients (*27,34–40*) with clinical cure rates ranging from 45% to 100% with most having rates in the overall population of about 65%. The applicants noted that results of most of these observational trials were difficult to interpret as they enrolled few patients with infections in different sites and of varying severity.

Bloodstream infections

Five observational retrospective studies assessed the efficacy of flomoxef sodium monotherapy for the treatment of bloodstream infections caused by ESBL-producing Enterobacterales. Data for only four studies were available, three of which compared flomoxef sodium with a carbapenem, and one had no comparator (*41–44*). Overall, the conclusions were that the appropriateness of flomoxef sodium seems to depend on the MIC and severity of disease. One study compared flomoxef sodium (1 g given every 6 hours) with carbapenems (*43*). The 30-day all-cause mortality was 28.8% (95% CI 21.2% to 37.3%) in the flomoxef sodium group and 12.8% (95% CI 9.0% to 17.6%) in the carbapenem group ($P < 0.01$). However, a subgroup analysis showed that with a flomoxef sodium MIC of < 1 mg/L, no statistically significant difference was seen in the 30-day all-cause mortality between the two groups (8.7% with flomoxef sodium and 6.4% with meropenem, $P = 0.73$). However, the difference was statistically significant for flomoxef sodium MIC levels of 2–8 mg/L (38.4% with flomoxef sodium and 15.6% with carbapenems, $P < 0.01$). In another study comparing flomoxef sodium with ertapenem for the treatment of adults with sepsis with a confirmed bacteraemia due to ESBL-producing Enterobacterales (*42*), no statistically significant difference in the 28-day all-cause mortality was observed between treatment groups – 20.7% (95% CI 11.2% to 33.4%) for flomoxef sodium and 15.4% (95% CI 10.6% to 21.4%)

for ertapenem, *P* = 0.42). In a study comparing flomoxef sodium and ertapenem in adult patients with haemodialysis and bacteraemia due to ESBL-producing *K. pneumoniae*, there was a statistically significant difference in the 14-day mortality between flomoxef sodium and ertapenem (73.0% versus 47.0%, *P* < 0.05) (*44*).

Efficacy in children

According to the applicants, efficacy of flomoxef sodium in children is challenging to interpret as most studies are old, uncontrolled, have small sample sizes and included patients with multiple sources of infections in the same study. The application focused on the efficacy of flomoxef sodium for the treatment of urinary tract and intra-abdominal infections. Only two studies with more than 10 patients were available and reported data on the efficacy of flomoxef sodium for the treatment of urinary tract infections (*45,46*). In both cases, clinical cure rates were 100%, but due to the small sample sizes (13 and 10 patients, respectively), the results were difficult to interpret. No studies with more than 10 patients were available for intra-abdominal infections. The applicants concluded that, given that urinary tract and intra-abdominal infections present similarly in children and adults, extrapolation of efficacy for these indications is generally accepted by regulatory authorities.

Pharmacokinetic (PK) and pharmacodynamics (PD) studies

Evidence in adults comes from two recent studies. The optimal dosage for the treatment of urinary tract infections caused by ESBL-producing Enterobacterales was 1 g every 6 hours with normal renal function (taking 70% time above MIC as PK/PD index) (*47*). For intra-abdominal infections, PK/PD simulations showed the dosing regimens of 1 g 3–4 times a day had a bactericidal effect in all tissues (at an MIC of 1 mg/L and using 40% time above MIC as the PK/PD index (*48*). PK/PD data for neonates presented in the application suggest three different doses in the first month of life (20 mg/kg given every 12 hours in the first week, then every 6 to 8 hours in the second week and then 40 mg/kg given every 6 to 8 hours in the third and fourth week of life) (*49*).

Of note, there is no MIC breakpoint available for flomoxef sodium and physicians in countries where flomoxef sodium is available are using the latamoxef or moxalactam MIC breakpoint, which is available from the Clinical and Laboratory Standards Institute but not from the European Committee on Antimicrobial Susceptibility Testing. Moxalactam is no longer in use and latamoxef is only used in Japan.

The application concluded that the available evidence suggests flomoxef sodium is effective for the treatment of mild and moderate urinary tract and intra-abdominal infections. However, most evidence comes from old studies that were often not as methodologically rigorous as would be required today. Additionally, all data (including PK data) come from Asia, and it is unclear if differences may

exist in different populations. Importantly, flomoxef sodium monotherapy for the indication of bloodstream/systemic infections showed lower efficacy with increasing severity, suggesting that this agent on its own may not be appropriate in cases with severe infections.

Summary of evidence: harms

Safety data are derived both from patients exposed in clinical trials (about 3400 patients exposed before 1988) and patients exposed in the postmarketing setting (estimated 20.6 million patients based on sales data between 1988 and 2022). In general, the safety of flomoxef sodium is comparable to other cephalosporins and the incidence of adverse events in children and adults is similar. As with other cephalosporins, frail elderly patients who may have concomitant vitamin deficiencies, particularly vitamin K deficiencies, must be monitored closely for bleeding disorders when treated with flomoxef sodium. In pregnant and breastfeeding women, the safety of flomoxef sodium has not yet been established.

Safety data in adults were extrapolated from the Japanese Flumarin® information sheet (*50*) and the Shionogi & Co. Interview Form v11 (February 2022) (*20*). According to these documents, the incidence of adverse reactions was 12.7% (414/3267 patients) in clinical trials and 2.9% (810/27 651) in a 6-year postmarketing observational survey. Seven types of clinically significant adverse reactions are reported, however no incidence data are available – shock/anaphylaxis, acute renal injury, pancytopenia/agranulocytosis/ thrombocytopenia/haemolytic anaemia, pseudomembranous colitis, toxic epidermal necrolysis/Stevens–Johnson syndrome, interstitial pneumonia/ pulmonary infiltration with eosinophilia, and hepatic dysfunction/jaundice. The applicants hypothesize that these adverse reactions are rare events (< 0.1% of patients) based on previous versions of the Interview Form. Less than 5% of patients treated with flomoxef sodium had at least one adverse event in the nine small trials included in the systematic review performed by GARDP. Diarrhoea was reported in 1.4–4.4% of participants.

Safety data in children are very limited. In the 6-year postmarketing observational survey, the incidence of adverse events was higher in infants (4.4%, 16/360) compared with older children up to 15 years (2.6% (74/2840). The incidence of adverse events tended to increase with longer treatment even though most children (97%) in the cohort were treated for < 14 days. Most adverse events were classified as gastrointestinal disorders. In the systematic review performed by GARDP, the overall incidence of adverse events in children was < 5%, with diarrhoea being the most frequent adverse event reported.

WHO guidelines

Flomoxef sodium is not currently included in existing WHO guidelines.

Costs/cost–effectiveness

No published cost–effectiveness studies are available for flomoxef sodium. The application included a summary of available data of the wholesale prices of flomoxef sodium in some markets where it is available. Reported prices were US$ 5.16 (for 0.5 g) and US$ 10.35–10.38 (for 1 g).

Availability

Flomoxef sodium is off-patent and is currently available only in a small number of Asian countries. The three manufactures are all located in Asia and Shionogi & Co. has about 60% of the total market share.

Other considerations

The EML Antimicrobial Working Group reviewed the application and advised that it did not support the inclusion of flomoxef sodium for the treatment of intra-abdominal and upper urinary tract infections in adults and children at high risk of infection caused by ESBL-producing Enterobacterales on the EML and EMLc at this time.

The Working Group acknowledged that flomoxef sodium is associated with some positive characteristics such as activity against most strains of ESBL-producing Enterobacterales. It therefore could be used as an alternative to carbapenems for empiric or targeted use of infections suspected or known to be caused by these organisms in certain situations. The Working Group also noted that there was considerable real-life experience of effective and safe use of this antibiotic over several decades in millions of patients in some countries in Asia.

The Working Group noted, however, that: clinical data specifically for the efficacy of flomoxef sodium for the treatment of infections by ESBL-producing Enterobacterales were limited (especially for severe infections where it would be most useful); clinical trial data mostly predate the period when ESBL-producing Enterobacterales emerged as a common pathogen; clinical experience was mostly limited to a few Asian countries where the medicine is currently approved; validated clinical breakpoints for susceptibility testing were not available from the Clinical and Laboratory Standards Institute or the European Committee for Antimicrobial Susceptibility Testing; and a trial funded by the applicant studying flomoxef sodium in combination with another antibiotic for neonatal sepsis (an indication not requested in this application) was still ongoing, with active recruitment. Furthermore, the Working Group considered that there were also other β-lactam antibiotics that could be used as carbapenem-sparing options due to their activity against ESBL-producing Enterobacterales (e.g. temocillin, cefoxitin) that have not been evaluated for addition to the Model Lists.

Committee recommendations

The Committee noted that while the available in vitro studies demonstrate that flomoxef sodium has activity against most strains of ESBL-producing Enterobacterales, validated clinical breakpoints for susceptibility testing were not currently available. The Committee also noted that most clinical trials of flomoxef sodium were performed before the emergence of ESBL-producing Enterobacterales as a common pathogen, and that evidence for the efficacy of flomoxef sodium in severe infections, where it may be of greatest value, was limited. The Committee also considered that clinical evidence for flomoxef sodium in comparison with other potentially carbapenem-sparing antibiotics in the treatment of infections caused by ESBL-producing Enterobacterales was not available.

The Committee also noted that real-life experience of effective and safe use of flomoxef sodium was considerable, albeit limited to few countries in Asia. Furthermore, the Committee noted that the current market availability of flomoxef sodium was similarly limited to a small number of Asian countries.

Because of these limitations, the Expert Committee considered the evidence for flomoxef sodium was uncertain, and therefore did not recommend its inclusion on the EML and EMLc for empiric treatment of community-acquired mild/moderate intra-abdominal and upper urinary tract infections caused by ESBL-producing Enterobacterales.

However, the Committee acknowledged the need for effective carbapenem-sparing treatments for infections caused by ESBL-producing Enterobacterales, especially in settings where the pathogen is highly prevalent. Given this need, the Committee considered that future evaluation of flomoxef sodium may be worthwhile once more data are available, including those from the ongoing trial in neonatal sepsis.

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6.2.3 Reserve group antibiotics

Ceftolozane + tazobactam – addition – EML and EMLc

Ceftolozane + tazobactam	ATC code: J01DI54

Proposal

Addition of ceftolozane + tazobactam to the complementary list of the EML and EMLc as a reserve antibiotic for use in the treatment of confirmed or suspected infections due to multidrug-resistant organisms.

Applicant

Merck, Sharp & Dohme, Rahway, NJ, United States of America

WHO technical department

The Global Coordination and Partnership department within the Antimicrobial Resistance division reviewed the application and advised that it supported the inclusion of ceftolozane + tazobactam on the Model Lists as a reserve group antibiotic. The technical department stressed that the use of ceftolozane + tazobactam must always be informed by evidence-based guidance and strong stewardship activities, and that access and affordability of the medicine must be considered, particularly for patients in low- and middle-income countries.

EML/EMLc

EML and EMLc

Section

6.2.3 Reserve group antibiotics

Dose form(s) & strengths(s)

Powder for injection: 1 g + 0.5 g in vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Ceftolozane + tazobactam was previously considered for inclusion on the EML for treatment of infections due to carbapenem-resistant *Pseudomonas aeruginosa*. Inclusion was not recommended at the time, with the Expert Committee noting

that although ceftolozane + tazobactam was active against some strains of carbapenem-resistant *P. aeruginosa*, it lacked activity against carbapenemase-producing Enterobacteriaceae, which is more prevalent in the community and represents a greater public health threat (*1*).

Public health relevance

According to data from the United States Centers for Disease Control and Prevention, from 2015 to 2017, *Escherichia coli*, *Klebsiella pneumoniae* and *P. aeruginosa* represented over 30% of all pathogens associated with health care-associated infections in US hospitals (*2*).

A recent study estimated that drug-resistant *E. coli*, *K. pneumoniae*, and *P. aeruginosa* were directly responsible for almost 500 000 deaths globally in 2019 (*3*). Rates of resistance of these pathogens to carbapenems and third-generation cephalosporins show wide global variability. For example, resistance of *P. aeruginosa* to carbapenems is reported to range from 8% in Australia and the United Kingdom, to 30% in India and South Africa, to 87% in Belarus (*4*).

In 2017, WHO designated carbapenem-resistant *P. aeruginosa* and carbapenem-resistant and third-generation cephalosporin-resistant Enterobacterales critical priority pathogens in need of new therapeutic options (*5*).

Summary of evidence: benefits

The applicants conducted a comprehensive review of the available evidence for ceftolozane + tazobactam. A summary of the included evidence published since the 2019 EML application is reported below. A summary of the evidence considered in the 2019 application is reported in the technical report of the 2019 Expert Committee meeting (*1*).

Randomized clinical trials

ASPECT-NP was a randomized, double-blind, non-inferiority, phase III trial assessing the efficacy and safety of ceftolozane + tazobactam (3 g every 8 hours) compared with meropenem (1 g every 8 hours) for the treatment of adults with Gram-negative nosocomial pneumonia – ventilated hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) (*6*). Antibiotic treatment was given for 8–14 days. The primary efficacy endpoint was all-cause mortality at day 28 in the intention-to-treat population. Mortality at 28 days was 24.0% in the ceftolozane + tazobactam group and 25.3% in the meropenem group with a weighted treatment difference of 1.1% (95% confidence interval (CI) −5.1% to 7.4%). Ceftolozane + tazobactam met the criteria for non-inferiority to meropenem with a prespecified 10% margin. In the VAP subgroup, 28-day mortality was 24% in the ceftolozane + tazobactam group and 20.3% in the meropenem group with a weighted treatment difference of −3.6% (95% CI −10.7%

to 3.5%). Of note, the lower limit of the 95% CI included the 10% non-inferiority margin (i.e. results inconclusive), but the authors stated that this analysis was not powered for non-inferiority testing. The key secondary endpoint was clinical response 7–14 days after the end of therapy. Clinical cure was achieved in 54% of patients in the ceftolozane + tazobactam group and 53% in the meropenem group with a weighted treatment difference of 1.1% (95% CI –6.2% to 8.3%) demonstrating non-inferiority of ceftolozane + tazobactam with a prespecified 12.5% margin.

A substudy of the ASPECT-NP trial investigated the emergence of non-susceptibility and found that all 59 isolates that were susceptible to ceftolozane + tazobactam at baseline remained susceptible, while 22.4% (13/58) of those initially susceptible to meropenem became resistant during treatment (*7*).

A randomized, single-centre, open-label trial compared the efficacy and safety of ceftolozane + tazobactam (1.5 g every 8 hours plus vancomycin, daptomycin or linezolid) with standard of care (cefepime, piperacillin + tazobactam or meropenem plus vancomycin, daptomycin or linezolid) for the empiric treatment of febrile neutropenia in 100 adults with haematological malignancies (*8*). The duration of treatment was between 3 and 14 days. The primary efficacy endpoint was favourable clinical response at the end of intravenous treatment in the modified intention-to-treat population. The non-inferiority margin for the primary outcome was 10%. At the end of intravenous treatment, the proportion of patients with a favourable clinical response was higher in the ceftolozane + tazobactam group than the standard of care group (87% versus 72%, $P = 0.1$). From the 1-sided non-inferiority analysis, non-inferiority of ceftolozane + tazobactam was concluded because the lower limit of the 95% CI for favourable clinical response was –1.4% (i.e. it did not cross the prespecified –10% non-inferiority margin). All-cause 30-day mortality was 4% in both treatment groups with no deaths attributed to the infection.

Observational studies

A retrospective study using data collected from 20 hospitals in the United States investigated outcomes in 205 patients who received ceftolozane + tazobactam for the treatment of multidrug-resistant P. aeruginosa infections from any source (pneumonia in 59% of cases) (*9*). The primary outcome was 30-day and inpatient mortality. Secondary outcomes were clinical success and microbiological cure. Death occurred in 39 patients (19.0%), clinical success in 151 (73.7%) and microbiological cure in 145 (70.7%). Of note the median time from culture collection to treatment initiation was 9 days. Commencement of treatment with ceftolozane + tazobactam more than 4 days after culture collection was associated with worse outcomes in the multivariable analysis (odds ratio (OR) 5.5, 95% CI 2.1 to 14.4) although a causative association cannot be assumed. High doses of ceftolozane + tazobactam (3 g every 8 hours) were used in 47.3% of patients.

Another retrospective study reported outcomes in 101 adult patients with severe *P. aeruginosa* infections from any source (pneumonia in 31.7% of cases) treated with ceftolozane + tazobactam in 22 hospitals across Italy (*10*). Just over half (52.5%) of the patients were infected with an extensively drug-resistant or pandrug-resistant isolate, 17.8% with a multidrug-resistant isolate and 29.7% were classified as non-multidrug-resistant. The primary outcome was clinical success at the end of treatment which occurred in 83.2% of cases – 77.7% of cases with multidrug-resistant infections, 81.1% with extensively drug-resistant or pandrug-resistant infections, and 90% with non-multidrug-resistant infections. Predictive factors for clinical failure included sepsis (OR 3.02, *P* = 0.05) and continuous renal replacement therapy (OR 4.50, *P* = 0.02). High doses of ceftolozane + tazobactam (3 g every 8 hours) were used in 65.6% of patients.

A case–control study in Spain compared patients with haematological malignancy and *P. aeruginosa* infection treated with ceftolozane + tazobactam (19 cases) or other antibiotics (38 controls) (*11*). A higher proportion of cases than controls had neutropenia (63.2% versus 52.6%) and were infected with extensively drug-resistant pathogens (47.4% versus 21.1%). Patients treated with ceftolozane + tazobactam had higher clinical success rates than controls (89.5% versus 71.1%) and lower mortality (5.3% versus 28.9%).

Another retrospective, multicentre observational cohort study compared ceftolozane + tazobactam with treatment with either polymyxins or aminoglycosides-based regimens for infections due to drug-resistant *P. aeruginosa* (*12*). Baseline characteristics were similar between the two groups and the outcomes assessed were clinical cure, acute kidney injury and in-hospital mortality. Clinical cure was 81% in the ceftolozane + tazobactam group and 61% in the comparator group. In-hospital mortality was 20% with ceftolozane + tazobactam and 25% in the comparator group. The development of acute kidney injury occurred in 6% of patients treated with ceftolozane + tazobactam and 34% of patients in the comparator group. After adjusting for differences between groups, treatment with ceftolozane + tazobactam was independently associated with clinical cure (adjusted OR 2.63, 95% CI 1.31 to 5.30) and protection against acute kidney injury (adjusted OR 0.08, 95% CI 0.03 to 0.22). No difference between the groups was seen for in-hospital mortality.

The ZENITH study was a matched case–control study that compared ceftolozane + tazobactam with other antibiotics with anti-pseudomonas activity for the treatment of bloodstream infections due to *P. aeruginosa* in neutropenic haematological patients (*13*). Matching was done on the multidrug-resistance profile of the *P. aeruginosa* isolate, closest date of bloodstream infection, underlying disease and polymicrobial infection. A total of 44 cases (treated with ceftolozane + tazobactam as empiric and/or targeted therapy) and 88 controls (treated with other antibiotic regimens) were analysed. Among the cases, 91%

of infections were caused by multidrug-resistant *P. aeruginosa*. The primary endpoints were 7- and 30-day case fatality rates. At both time points, the case fatality rate was lower in the ceftolozane + tazobactam group (day 7: 6.8% versus 34.1%; day 30: 22.7 % versus 48.9%). After adjusting for potential confounders, the odds of dying from the *Pseudomonas* infection were lower in the ceftolozane + tazobactam group compared with the control group both at day 7 (adjusted OR 0.16, 95% CI 0.04 to 0.58) and day 30 (adjusted OR 0.19, 95% CI 0.07 to 0.55).

Summary of evidence: harms

The application reported that among patients in the randomized trials, ceftolozane + tazobactam was generally well tolerated and the overall safety profile and tolerability were similar to the comparator in the ASPECT-cUTI (*14*), ASPECT-cIAI (*15*) and ASPECT-NP (*6*) trials. The safety results of the ASPECT-NP trial are reported below. Safety results from ASPECT-cUTI and ASPECT-cIAI trials considered by the Expert Committee were previously reported in 2019 (*1*).

In ASPECT-NP, the incidence of treatment-emergent and severe adverse events, discontinuation due to adverse events, and death were comparable between treatment groups (*6*). Overall, 11% of patients in the ceftolozane + tazobactam group experienced at least one treatment-related adverse event compared with 8% in the meropenem group. The most frequently reported treatment-related adverse events in the ceftolozane + tazobactam group were liver function test abnormalities, *Clostridioides difficile* colitis and diarrhoea. The most common treatment-emergent adverse events were anaemia, urinary tract infections, diarrhoea and decubitus ulcers (*16*). The proportion of severe treatment-related events was the same in both groups (1%) as was the proportion of treatment-related adverse events leading to drug discontinuation (1% in both groups). No treatment-related adverse event resulted in death (*6*).

The application presented safety data for ceftolozane + tazobactam in the paediatric population. Two randomized, double-blind, phase II trials compared ceftolozane + tazobactam and meropenem in treatment of paediatric patients with complicated urinary tract infections (*17*) and intra-abdominal infections (*18*). In the trial including patients with complicated urinary tract infections, 133 children were included and the proportion of patients with treatment-related adverse events was similar in the two groups (14.0% with ceftolozane + tazobactam versus 15.2% with meropenem) with no serious treatment-related adverse events. In the trial including patients with complicated intra-abdominal infections, 91 patients were included and the proportion of treatment-related adverse events was higher with ceftolozane + tazobactam (plus metronidazole) than with meropenem (18.6% versus 14.3%). Overall adverse events were also higher in the ceftolozane + tazobactam group (80.0% versus 61.9%).

Additional evidence

The ASPIRE-ICU team recently published a study where resistance to ceftolozane + tazobactam in *P. aeruginosa* isolates from mechanically ventilated patients in the intensive care unit was 23.4% (*19*). In the study, 723 isolates obtained from respiratory samples or perirectal swabs from 402 patients in 11 European countries were analysed.

WHO guidelines

Ceftolozane + tazobactam is not currently included in existing WHO guidelines.

The Infectious Diseases Society of America guidelines (*20*) and the European Society of Clinical Microbiology and Infectious Diseases guidelines (*21*) include ceftolozane + tazobactam as a preferred treatment option for drug resistant *P. aeruginosa* infections. In particular, the US guidelines recommend it for difficult-to-treat *Pseudomonas* infections and as a reasonable alternative for moderate-to-severe infections caused by carbapenem-resistant *Pseudomonas* susceptible to traditional β-lactams (*20*). The European Society of Clinical Microbiology and Infectious Diseases guidelines recommend ceftolozane + tazobactam for difficult-to-treat carbapenem-resistant *P. aeruginosa*, if active in vitro (*21*).

Costs/cost–effectiveness

A cost–effectiveness analysis was performed comparing ceftolozane + tazobactam to meropenem to treat hospital-acquired pneumonia and ventilator-associated pneumonia in Italy (*22*). Cost–effectiveness of both empiric and targeted use were analysed. The study concluded that ceftolozane + tazobactam was cost-effective compared with meropenem with an incremental cost–effectiveness ratio (ICER) of €1913 to €2203 (for empiric treatment) and €6163 to €6597 (for targeted treatment) per quality-adjusted life year (QALY) gained. The same comparison was done from the perspective of the US health care sector (*23*) and showed that in the confirmed treatment setting, the ICER for ceftolozane + tazobactam compared with meropenem for the treatment of ventilated hospital-acquired pneumonia or ventilator-associated pneumonia was US$ 12 126 per QALY. The ICER decreased to US$ 4775 per QALY when used early (before susceptibility results).

A cost–effectiveness analysis compared ceftolozane + tazobactam with piperacillin + tazobactam for the empiric treatment of complicated urinary tract infection in Taiwan, China (*24*). Empiric use of ceftolozane + tazobactam resulted in higher total costs per patient compared with piperacillin + tazobactam (US$ 4199 versus US$ 3594) but a higher gain in QALYs (4.80 versus 4.78 QALYs). The additional cost per discounted QALY gained associated with the empiric use of ceftolozane + tazobactam was US$ 32 521. The same comparison was done from the perspective of the United States health care sector (*25*), and

showed that treatment with ceftolozane + tazobactam had higher costs than piperacillin + tazobactam (US$ 36 413 versus US$ 36 028), a higher QALY gained (9.19 versus 9.13 QALY) and an ICER of US$ 6128/QALY. The authors concluded that ceftolozane + tazobactam remained cost-effective at a willingness to pay of US$ 100 000 per QALY compared with piperacillin + tazobactam.

Another cost–effectiveness analysis compared ceftolozane + tazobactam (plus metronidazole) with piperacillin + tazobactam for the empiric treatment of patients with nosocomial complicated intra-abdominal infections at risk of infection with resistant pathogens (*26*). The authors concluded that based on national antimicrobial resistance surveillance data in the United States, ceftolozane + tazobactam with metronidazole was associated with lower costs per patient compared to piperacillin + tazobactam (US$ 44 226 versus US$ 44 811) and a higher QALY gain (12.85 versus 12.70 QALYs). They concluded that ceftolozane + tazobactam was more likely to be an appropriate empiric therapy for complicated intra-abdominal infections in the US. The same comparison was done in the United Kingdom, which showed that ceftolozane + tazobactam (plus metronidazole) was cost-effective compared with piperacillin + tazobactam with an ICER of £4350 per QALY and 0.36 hospitalization days saved per patient (*27*). Treatment with ceftolozane + tazobactam was associated with higher costs per patient compared with piperacillin + tazobactam (£2576 versus £2168) and a higher QALY gain (14.31 versus 14.21).

Availability

Ceftolozane + tazobactam is manufactured by Merck, Sharp & Dohme and has regulatory approval from the United States Food and Drug Administration and the European Medicines Agency. It is currently available in 27 European countries, 17 Asian countries and nine countries in the Americas. In Africa, it is only available in Egypt and South Africa. It is also available in Australia and New Zealand.

Other considerations

The EML Antimicrobial Working Group reviewed the application and advised that it supported the inclusion of ceftolozane + tazobactam on the EML and EMLc as reserve antibiotic for the treatment of infections caused or suspected to be caused by carbapenem-resistant *P. aeruginosa*, but emphasized the importance of associated stewardship interventions to ensure its appropriate use.

The Working Group highlighted that ceftolozane + tazobactam has particularly high activity against carbapenem-resistant *P. aeruginosa*, a critical priority pathogen on the WHO priority pathogens list, which in some settings is a common cause of severe pneumonia in ventilated patients in intensive care, including patients with coronavirus disease 2019 (COVID-19).

The Working Group noted that clinical trial and observational data suggest that ceftolozane + tazobactam is as effective in patients with nosocomial pneumonia as other commonly used older antibiotics. However, high levels of resistance to the most widely used antibiotics in high-risk settings are increasingly common and alternative antibiotics are needed to provide wider treatment options.

The Working Group also noted that ceftolozane + tazobactam was generally well tolerated, with no specific safety concerns. Published phase I pharmacokinetic and phase II safety studies also support the safety of ceftolozane + tazobactam in paediatric patients (28,29).

The Working Group commented that ceftolozane + tazobactam was notably more expensive than other antibiotics for which generics are available. The primary patent is due to expire in 2023, but secondary patents will be active until 2035. The Working Group also noted that limited cost–effectiveness data were available from low- and middle-income settings.

Committee recommendations

The Expert Committee recognized the global health importance of effective new treatments for infections caused by multidrug-resistant pathogens, especially those designated as critical priority on the WHO priority pathogens list, for which few effective treatment options exist or are in development.

The Committee noted that clinical trial evidence for efficacy of ceftolozane + tazobactam against carbapenem-resistant *P. aeruginosa* and Enterobacterales specifically was positive, albeit limited, and that the medicine had shown good activity against carbapenem-resistant *P. aeruginosa* in in vitro studies. The Committee considered that data presented from observational studies also supported the efficacy of ceftolozane + tazobactam in the treatment of infections caused by drug-resistant *P. aeruginosa*. The Committee noted no serious safety or tolerability concerns associated with ceftolozane + tazobactam, in both adult and paediatric patients. Overall, the Committee considered that the availability of carbapenem-sparing alternatives for treatment of drug-resistant *P. aeruginosa* was important as part of the strategy to limit and prevent further emergence and spread of carbapenem-resistant organisms.

The Committee noted the higher price of ceftolozane + tazobactam compared with other antibiotics, but also that it had generally been found to be acceptably cost-effective in high-income settings.

Given the seriousness of infections due to carbapenem-resistant *P. aeruginosa*, particularly hospital-acquired and ventilator-associated pneumonia, and the limited number of effective treatment options available, the Committee considered that inclusion of ceftolozane + tazobactam on the Model Lists was sufficiently justified. The Expert Committee therefore recommended the addition

of ceftolozane + tazobactam as a reserve group antibiotic on the complementary list of the EML and EMLc for the treatment of infections caused or suspected to be caused by carbapenem-resistant *P. aeruginosa*. The Committee also emphasized the importance of associated stewardship activities to ensure its appropriate use.

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Imipenem + cilastatin + relebactam – addition – EML

Imipenem + cilastatin + relebactam	ATC code: J01DH56

Proposal

Addition of imipenem + cilastatin + relebactam to the complementary list of the EML as a reserve antibiotic for use in the treatment of confirmed or suspected infections due to multidrug-resistant organisms.

Applicant

Merck, Sharp & Dohme, Rahway, NJ, United States of America

WHO technical department

The Global Coordination and Partnership department within the Antimicrobial Resistance division reviewed the application and advised that it supported the inclusion of imipenem + cilastatin + relebactam on the EML as a reserve group antibiotic. The technical department stressed that the use of imipenem + cilastatin + relebactam must be always informed by evidence-based guidance and strong stewardship activities, and that access and affordability of the medicine must be considered, particularly for patients in low- and middle-income countries.

EML/EMLc

EML

Section

6.2.3 Reserve group antibiotics

Dose form(s) & strengths(s)

Powder for injection: 500 mg (as monohydrate) + 500 mg (as sodium) + 250 mg (as monohydrate) in vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Imipenem + cilastatin + relebactam has not previously been considered for inclusion on the EML. It has been classified as a reserve group antibiotic under the AWaRe (Access–Watch–Reserve) classification.

Public health relevance

Worldwide in 2019, an estimated 4.95 million people died of drug-resistant bacterial infections, of which 1.27 million were directly attributable to resistant infections, most of these were concentrated in low- and middle-income countries. Drug-resistant *Pseudomonas aeruginosa* was responsible for 84 600 deaths, of which almost half were carbapenem-resistant, drug-resistant *Klebsiella pneumoniae* was responsible for 193 000 deaths, of which almost 30% were carbapenem-resistant and drug-resistant *Escherichia coli* was responsible for 219 000 deaths, of which almost 15% were carbapenem-resistant (*1*).

Antibiotic resistance among Gram-negative pathogens is a problem worldwide. The European Centre for Disease Prevention and Control reported increasing trends of carbapenem resistance in invasive isolates of *K. pneumoniae* (+ 20% in 2021 compared with the previous year) with a population-weighted mean of 11.7%, (range 0–73.7%) in 2021 (*2*). Population-weighted mean resistance percentages among *K. pneumoniae* invasive isolates were also very high for other antibiotic classes, in particular for third-generation cephalosporins (34.3%), fluoroquinolones (33.6%) and aminoglycosides (23.7%) with about a third of *K. pneumoniae* cases (34.3%) in the European Union/European Economic Area resistant to at least one antimicrobial class under surveillance in 2021. For *P. aeruginosa*, no increasing trend of carbapenem-resistance in the 2017–2021 period was reported, even though levels remain high in some countries, with a mean of 18.1% among invasive isolates in the European Union/European Economic Area in 2021 and wide intercountry variation (3.5% to 45.9%). Additionally, 18.7% of isolates were resistant to at least one antimicrobial classes under surveillance.

In the United States, the proportions of carbapenem-resistant *K. pneumoniae* and *P. aeruginosa* isolates have decreased overall since 2011 among tracked health care-associated infections. In 2020, the mean national resistance level was 4.8% for *Klebsiella* and 12.9% for *Pseudomonas* (compared to 9.8% and 20.0%, respectively in 2011); however, wide variation exist across states (*3*).

In 2017, WHO designated carbapenem-resistant *P. aeruginosa* and carbapenem-resistant and third-generation cephalosporin-resistant Enterobacterales critical priority pathogens in need of new therapeutic options (*4*).

Summary of evidence: benefits

Randomized clinical trials

RESTORE-IMI 1 was a randomized, double-blind, multicentre, phase III trial that investigated the activity of imipenem + cilastatin + relebactam (500 mg + 500 mg + 250 mg every 6 hours) compared with colistin (300 mg loading dose, then 150 mg every 12 hours) plus imipenem + cilastatin relebactam (500 mg + 500 mg every 6 hours) for the treatment of complicated intra-abdominal and urinary tract infections and hospital acquired pneumonia, including ventilator-

associated pneumonia (*5*). The primary efficacy endpoint was overall response, however the study was not powered to infer statistically significant differences in efficacy between treatment arms. The trial only included patients with infections caused by imipenem non-susceptible (but colistin susceptible) Gram-negative pathogens in adults and excluded patients with *Acinetobacter* spp. infections. There were 31 and 16 patients in the intervention group and comparator group, respectively. The primary outcome was calculated on the microbiological modified intention-to-treat population which included 21 and 10 patients in the intervention and comparator groups, respectively. These were patients with a positive culture for an imipenem-resistant Gram-negative pathogen that had received at least one dose of the study medicine. Most patients had *Pseudomonas* infections – 80% in the comparator group and 76% in the intervention group. Overall, the β-lactamases most frequently detected were AMPc (84%) and extended-spectrum β-lactamases (35%). Carbapenemases were detected in a minority of patient with Klebsiella pneumoniae carbapenemase detected in five patients (of whom four were randomized to imipenem + cilastatin + relebactam) and OXA-48 in one patient randomized to the control group. Despite being protocol-required, only nine patients had baseline blood cultures and only two of those had a bacteraemia. A favourable overall response was reported in 71.4% and 70.0% of patients in the intervention and comparator groups, respectively. The overall adjusted difference for favourable response was –7.3% (90% confidence interval (CI) –27.7% to 21.4%), favouring the comparator group. Definitions of overall response differed by type of infection: for hospital-acquired pneumonia/ventilator-associated pneumonia, it was survival at day 28; for complicated intra-abdominal infections it was clinical response at day 28; and for complicated urinary tract infections it was clinical plus microbiological response 5–9 days after the end of therapy. A favourable clinical response at day 28 was reported in 71.4% and 40.0% of patients in the intervention and comparator groups, respectively (adjusted difference 26.3%, 90% CI 1.3% to 51.5%). Among secondary endpoints, all-cause mortality at day 28 was lower in the intervention group (9.5% versus 30%; adjusted difference –17.3%, 90% CI –46.4% to 6.4%). Results by type of infection showed that for hospital-acquired pneumonia/ventilator-associated pneumonia 28-day survival was 20.8% higher with imipenem + cilastatin + relebactam (87.5% versus 66.7%). None of the four patients with a complicated intra-abdominal infections had a favourable response at day 28 while for complicated urinary tract infections, results for the primary efficacy endpoint favoured the comparator group with an adjusted difference of –27.3% (90% CI –52.8% to 12.8%). Of the two patients with bacteraemia (randomized one to each group) only the one in the comparator group had a favourable response.

The RESTORE-IMI 2 was a randomized controlled, double-blind, multicentre, non-inferiority, phase III trial comparing imipenem + cilastatin + relebactam (500 mg + 500 mg + 250 mg every 6 hours) with piperacillin + tazobactam (4 g + 500 mg every 6 hours) for the treatment of hospital-acquired

pneumonia/ventilator-associated pneumonia in adults (*6*). Treatment duration was 7–14 days. In total, 537 patients were included, 268 in the intervention group and 269 in the comparator group. The primary and secondary outcomes were evaluated in the modified intention-to-treat population, which excluded patients where only Gram-positive cocci were isolated at baseline. Results for the primary endpoint of 28-day all-cause mortality showed lower mortality in the intervention group (15.9% versus 21.3%) with an adjusted difference of –5.3% (95% CI –11.9% to 1.2%). With a prespecified 10% margin, non-inferiority was concluded. The key secondary endpoint was favourable clinical response at early follow-up (7–14 days after the end of treatment). Results favoured the intervention group (61.0% versus 55.8%) with an adjusted difference of 5.0% (95% CI –3.2% to 13.2%). With a prespecified 12.5% margin, non-inferiority was concluded. At day 28, a favourable clinical response was reported in 51.9% of patients in the intervention group and 50.6% in the comparator group, with an adjusted difference of 1.1% (95% CI –7.2% to 9.4%).

The application also presented findings from a series of post-hoc and secondary analyses of the RESTORE-IMI 2 trial presented at conferences that reported results for imipenem + cilastatin + relebactam in patients with imipenem-resistant infections, in critically ill patients, in patients with renal augmentation or impairment, and in patients with polymicrobial hospital-acquired pneumonia/ventilator-associated pneumonia infections (*7–10*).

A randomized, double-blind, multicentre, non-inferiority, dose-ranging, phase II study compared the efficacy of relebactam 250 mg, relebactam 125 mg or placebo each given with imipenem + cilastatin for the treatment of 351 adult patients with complicated intra-abdominal infections regardless of baseline susceptibility of the pathogen (*11*). The primary efficacy endpoint was favourable clinical response at discontinuation of therapy (5–9 days after the start of therapy) and at late follow-up (28–42 days). With a prespecified non-inferiority margin of 15%, both doses of relebactam with imipenem + cilastatin were non-inferior to imipenem + cilastatin monotherapy for the primary efficacy endpoint. A similar study was conducted in adult patients with complicated urinary tract infections regardless of baseline susceptibility of the pathogen (*12*). Again, with a prespecified non-inferiority margin of 15%, both doses of relebactam with imipenem + cilastatin were non-inferior to imipenem + cilastatin monotherapy for the primary efficacy endpoint of the proportion of patients who achieved a favourable microbiological response.

Observational studies

A retrospective case series described outcomes in 21 adult patients with mixed infection sources (52% were pulmonary infections) who were treated with imipenem + cilastatin + relebactam. Most infections were caused by *P. aeruginosa* (16/21, 76%), of which all except one were multidrug-resistant. Survival at 30 days

was observed in 67% of patients. Two patients experienced adverse events, neither of which led to treatment discontinuation. Imipenem + cilastatin + relebactam was used as combination therapy in 29% of cases (6/21), with tobramycin as the most common concomitant antibiotic (*13*).

Summary of evidence: harms

The applicants presented the safety data for imipenem + cilastatin + relebactam for each interventional study in the previous section.

In the RESTORE-IMI 1 trial, adverse events were recorded during therapy and in the 14-day follow-up period. Overall, the incidence of adverse events, deaths, serious adverse events, drug-related adverse events and discontinuations due to adverse events was lower with imipenem + cilastatin + relebactam than with colistin plus imipenem + cilastatin; however, the trial was not powered to detect statistical significance in safety outcomes. Drug-related adverse events were reported in 16.1% (5/31) of patients treated with imipenem + cilastatin + relebactam and in 31.3% (5/16) of patients in the comparator group. Two patients discontinued treatment in the comparator group because of a drug-related adverse event and none discontinued in the imipenem + cilastatin + relebactam group. No serious drug-related adverse events were reported in either group. Treatment-emergent nephrotoxicity was significantly lower with imipenem + cilastatin + relebactam than with colistin plus imipenem + cilastatin: 3/29 (10.3%) versus 9/16 (56.3%), $P = 0.002$ (*5*).

In the RESTORE-IMI 2 trial, adverse events were recorded during therapy and in the 14-day follow-up period. The incidence of adverse events, deaths, serious adverse events, drug-related adverse events and discontinuations due to adverse events were comparable between patients who received imipenem + cilastatin + relebactam and those who received piperacillin + tazobactam. Drug-related adverse events were reported in 11.7% of patients treated with imipenem + cilastatin + relebactam and in 9.7% of patients in the comparator group. In total 10 patients had to discontinue therapy due to a drug-related adverse event – 6/266, 2.3% in the imipenem + cilastatin + relebactam and 4/269, 1.5% in the comparator group. Five serious drug-related adverse event were reported, three in the imipenem + cilastatin + relebactam (of whom two had to discontinue therapy) and two with piperacillin + tazobactam (with therapy discontinued in one) (*6*).

In the dose-ranging study in patients with complicated intra-abdominal infections, drug-related adverse events occurred in 13.7% (16/117) of patients treated with imipenem + cilastatin + relebactam 250 mg, 13.8% (16/116) of patients treated with imipenem + cilastatin + relebactam 125 mg and in 9.6% (11/114) of patients treated with imipenem cilastatin monotherapy. In total, four patients discontinued therapy due to a drug-related adverse event, three in the monotherapy group and one in the imipenem + cilastatin + relebactam 125 mg group. One patient in the monotherapy group had a serious drug-related adverse event necessitating discontinuation of therapy (*11*).

In the dose-ranging study in patients with complicated urinary tract infections, drug-related adverse events occurred in 10.1% (10/99) of patients treated with imipenem + cilastatin + relebactam 250 mg, 9.1% (9/99) of patients treated with imipenem + cilastatin + relebactam 125 mg and in 9.0% (9/100) of patients treated with imipenem + cilastatin monotherapy. Four patients discontinued therapy due to a drug-related adverse event, of whom one was in the monotherapy group. Two serious drug-related adverse events were reported, one in the imipenem + cilastatin + relebactam 250 mg and one in the monotherapy group (*12*).

WHO guidelines

Imipenem + cilastatin + relebactam is not currently included in WHO guidelines. WHO recognized its usefulness against carbapenem-resistant Enterobacterales but noted the uncertainty on its activity against *P. aeruginosa* due to inconclusive data (*14*).

Costs/cost–effectiveness

The application presented the findings of a cost–effectiveness analysis of imipenem + cilastatin + relebactam compared with colistin plus imipenem + cilastatin using clinical data from the RESTORE-IMI 1 trial. On average, a patient treated with imipenem + cilastatin + relebactam gained additional 3.7 quality adjusted life years (QALYs) over their lifetime. Higher drug acquisition costs for imipenem + cilastatin + relebactam were offset by shorter length of hospital stay and lower costs related to adverse events, which resulted in net savings of US$ 11 015 per patient. Sensitivity analyses suggested that imipenem + cilastatin + relebactam had a high likelihood of being cost-effective at a US willingness-to-pay threshold of US$ 100 000–150 000 per QALY (*15*).

A second cost–effectiveness analysis compared imipenem + cilastatin + relebactam and piperacillin + tazobactam using clinical data from the RESTORE-IMI 2 trial. QALYs gained were reported as 7.92 and 7.08 for imipenem + cilastatin + relebactam and piperacillin + tazobactam, respectively. Total treatment costs were US$ 185 254 and US$ 170 513 for imipenem + cilastatin + relebactam and piperacillin + tazobactam, respectively. This resulted in an incremental cost per QALY gained of US$ 17 529, which is lower than the typical US willingness-to-pay threshold. The authors concluded that imipenem + cilastatin + relebactam may be a cost-effective treatment for payers and a valuable option for clinicians (*16*).

Availability

Imipenem + cilastatin + relebactam is manufactured by Merck and has regulatory approval from the United States Food and Drug Administration and the European Medicines Agency. It is currently available in 19 European countries, in the United States and in Japan. Market availability is currently pending in Argentina, Belgium, Denmark, Ireland, Palau and Spain.

Other considerations

The EML Antimicrobial Working Group reviewed the application and advised that it supported the inclusion of imipenem + cilastatin + relebactam on the EML as a reserve antibiotic for the treatment of infections caused by multidrug-resistant organisms, but emphasized the importance of associated stewardship interventions to ensure its appropriate use.

The Working Group highlighted that imipenem + cilastatin + relebactam has broad activity against extended-spectrum β-lactamase-producing Enterobacterales, some carbapenemase-producing Enterobacterales (mainly Class A Klebsiella pneumoniae carbapenemase and Class C AmpC, but not Class B metallo-β-lactamases and Class D OXA) and carbapenem-resistant *P. aeruginosa*. Although New Delhi metallo-β-lactamases and Class D OXA carbapenemases are globally the most common genotypes associated with carbapenem resistance in Enterobacterales, Klebsiella pneumoniae carbapenemase remains an important cause in some low- and middle-income countries, where treatment options are limited. Infections caused by carbapenem-resistant Enterobacterales and carbapenem-resistant *P. aeruginosa* are a major public health concern and in many low- and middle-income countries settings, antibiotic treatment options are now very limited; indeed, the only options may be older agents with important toxicity concerns, such as colistin.

The Working Group noted that some clinical trial and observational data suggest that imipenem + cilastatin + relebactam had clinical efficacy in patients with infections caused by multidrug-resistant pathogens. Although the medicine has limited activity against some types of carbapenem resistance, it has good activity against other types seen in both high-income countries and low- and middle-income countries. The Working Group also noted that the medicine is well tolerated, with no specific safety concerns. However, imipenem + cilastatin + relebactam is significantly more expensive than antibiotics for which generics are available and there are few cost–effectiveness data in low- and middle-income settings.

Committee recommendations

The Expert Committee recognized the global health importance of effective new treatments for infections caused by multidrug-resistant pathogens, especially those designated as critical priority on the WHO priority pathogens list, for which few effective treatment options exist or are in development.

The Committee noted that imipenem + cilastatin + relebactam has broad in vitro activity against multidrug-resistant Gram-negative pathogens but lacks in vitro activity against the carbapenemase genotypes most commonly associated with carbapenem resistance in Enterobacterales globally. The Committee also noted that other Reserve antibiotic options which have a similar spectrum of

activity are already included on the EML for the treatment of other types of carbapenem-resistance in Enterobacterales (e.g. cefiderocol, ceftazidime + avibactam and meropenem + vaborbactam).

The Committee considered that the available clinical trial evidence for efficacy of imipenem + cilastatin + relebactam was generally positive, albeit limited, and noted that no serious safety or tolerability concerns were identified. The Committee also noted the high price of the medicine compared with older antibiotics, but also that it has been found to be acceptably cost-effective at willingness-to-pay thresholds in high-income settings.

Based on these considerations, the Expert Committee did not recommend the inclusion of imipenem + cilastatin + relebactam as a Reserve group antibiotic for the treatment of infections caused by multidrug-resistant organisms on the EML.

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Tedizolid phosphate – addition – EML

Tedizolid phosphate	ATC code: J01XX11

Proposal

Addition of tedizolid phosphate to the complementary list of the EML as a reserve group antibiotic for use in the treatment of confirmed or suspected acute skin and skin structure infections caused by susceptible Gram-positive bacteria, including multidrug-resistant strains.

Applicant

Merck, Sharp & Dohme, Rahway, NJ, United States of America

WHO technical department

The AMR Global Coordination department reviewed the application and advised that it supported the inclusion of tedizolid phosphate on the EML as a reserve group antibiotic for treatment of confirmed or suspected infections caused by multidrug-resistant Gram-positive organisms. The technical department stressed that the use tedizolid phosphate must be always informed by evidence-based guidance and strong stewardship activities, and that access and affordability of the medicine must be considered, particularly for patients in low- and middle-income countries.

EML/EMLc

EML

Section

6.2.3 Reserve group antibiotics

Dose form(s) & strengths(s)

Powder for injection: 200 mg in vial

Tablet: 200 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Tedizolid phosphate has not previously been considered for inclusion on the EML. It is classified as a Reserve group antibiotic under the AWaRe (Access–Watch–Reserve) classification.

Public health relevance

Worldwide in 2019, an estimated 4.95 million people died with drug-resistant bacterial infections. Of these deaths, 1.27 million were directly attributable to resistant infections and most were concentrated in low- and middle-income countries. Methicillin-resistant *Staphylococcus aureus* (MRSA) remains one of the most important causes of antimicrobial resistance and hospital-acquired infections worldwide. In 2019, it was estimated that drug-resistant *S. aureus* infections were responsible for 178 000 deaths globally – almost a quarter of all deaths caused by drug-resistant organisms (*1*).

In 2017, WHO designated vancomycin-resistant *S. aureus* and MRSA as high priority pathogens in need of new therapeutic options (*2*).

Summary of evidence: benefits

In-vitro studies

The application stated that tedizolid (the active metabolite of the prodrug tedizolid phosphate) has demonstrated at least four-fold greater potency in vitro against susceptible strains of staphylococci (including MRSA), enterococci and streptococci compared with linezolid, based on a minimum inhibitory concentration to inhibit growth of 90% of organisms (MIC_{90}) (*3*,*4*). There is no cross-resistance with linezolid-resistant cfr-positive *S. aureus* in the absence of chromosomal mutations (*5*).

Randomized clinical trials

ESTABLISH 1 was a randomized, double-blind, non-inferiority, phase III trial comparing oral tedizolid (200 mg once daily for 6 days) with oral linezolid (600 mg twice daily for 10 days) for the treatment of 667 adults with acute bacterial skin and skin structure infections (*6*). The primary endpoint was clinical response defined as ≥ 20% decrease from baseline in lesion area at 48–72 hours. Results of the sensitivity analysis in all randomized patients (i.e. intention-to-treat population) showed that 78.0% of patients in the tedizolid group and 76.1% in the comparator group met the primary endpoint (absolute treatment difference 1.9%, 95% confidence interval (CI) –4.5% to 8.3%) favouring tedizolid but with no statistically significant difference between the two groups. Tedizolid met the criteria for non-inferiority to linezolid with a prespecified 10% margin. Of note, the sensitivity analysis excluded temperature 37.6 °C at 48–72 hours as a variable for the definition of clinical response.

For the intention-to-treat population, sustained clinical response measured at the end of treatment (day 11 relative to the first dose) was 69.3% in the tedizolid group and 71.9% in the linezolid group (absolute treatment difference –2.6%, 95% CI –9.6% to 4.2%). Clinical response 7–14 days after the end of treatment was 85.5% in the tedizolid group and 86.0% in the linezolid group (difference –0.5%, 95% CI –5.8% to 4.9%).

ESTABLISH 2 was a randomized, double-blind, non-inferiority, phase III trial comparing the same regimens compared in the ESTABLISH 1 trial but with an intravenous to oral switch. A total of 666 patients were randomized to receive either tedizolid ($n = 332$) or linezolid ($n = 334$) (*7*). All baseline pathogens were susceptible to vancomycin and linezolid. For the primary efficacy endpoint ($\geq 20\%$ decrease from baseline in lesion area at 48–72 hours), in the intention-to-treat population, 85% (283/332) in the tedizolid group and 82.6% in the comparator group responded to treatment (treatment difference 2.6%, 95% CI –3.0% to 8.2%). Tedizolid met the criteria for non-inferiority to linezolid with a prespecified 10% margin. Other endpoints evaluated in the intention-to-treat population included clinical success 7–14 days after the end of treatment (88.0% in the tedizolid group and 87.7% in the comparator group; treatment difference 0.3%, 95% CI –4.8% to 5.3%) and clinical success at the day 11 end of treatment (87.0% in the tedizolid group and 88.0% in the linezolid group; treatment difference –1.0%, 95% CI –6.1% to 4.1%).

The primary efficacy endpoint in patients with MRSA infections was evaluated by pooling ESTABLISH 1 and ESTABLISH 2 results in the microbiological intention-to-treat population. In this subgroup analysis, clinical success was reported in 83.7% (118/141) of patients in the tedizolid group and 81.5% (119/146) in the comparator group. In these trials, MRSA was the causative pathogen in 16–27% of all patients and 27–43% of patients with a positive culture.

Observational studies

The application reported the results of a case series of four patients with cellulitis and wound infections treated with tedizolid phosphate (*8*). Two were obese patients with severe cellulitis complicated by sepsis and myositis: one patient received tedizolid after failure of first-line therapy with cefalotin, clindamycin and imipenem, and the other was started on tedizolid and clindamycin but clindamycin was stopped on day 3 due to an adverse event. Both patients improved within 72 hours of starting tedizolid with normalized laboratory results within a week. A third patient had a surgical site infection and was treated empirically with tedizolid for 7 days because of a history of previous MRSA bacteraemia; this patient and had a clinical response within 72 hours. The fourth patient also had a surgical site infection treated with tedizolid for 14 days and also improved within 72 hours.

Summary of evidence: harms

Safety data from the ESTABLISH 1 and ESTABLISH 2 trials were reported in the application (*6,7*). Overall, the proportion of patients experiencing drug-related treatment-emergent adverse events was similar between groups (22.4% and 27.9% in the tedizolid phosphate and linezolid groups, respectively). Less than 0.5% were serious (0 events with tedizolid and 2 with linezolid). Fewer patients in the tedizolid group had gastrointestinal adverse events (16.0% versus 23.0%) and low platelet counts (< 150 000 cells/mm3) during the postbaseline period (6.5% with tedizolid versus 12.6% with linezolid). Tedizolid was not associated with nephrotoxicity or postbaseline serum creatinine, and blood urea nitrogen increase was low (< 0.5%) in both treatment groups.

Tedizolid is a weak and reversible inhibitor of monoamine oxidase. The interaction with monoamine oxidase inhibitors could not be evaluated in the phase III trials as the patients receiving these medicines were excluded because linezolid has a warning in its prescribing information against use in patients using serotonergic psychiatric medications because of the potential risk of serotonin syndrome. However, based on a murine serotonergic model, tedizolid has not shown a propensity for serotonergic effects when given at doses up to almost 30 times higher than the human equivalent (*9*). Based on this evidence, the United States Food and Drug Administration has not put any warning or restriction for the use of tedizolid with serotonergic medications.

Additional evidence

A randomized, double-blind, phase III study compared tedizolid phosphate with linezolid for treatment of 726 ventilated patients with Gram-positive hospital-acquired or ventilator-associated bacterial pneumonia (*10*). The overall incidence of MRSA was 31.3%. The primary efficacy endpoints were day 28 all-cause mortality and investigator-assessed clinical response at test of cure in the intention-to-treat population. All-cause mortality at 28 days was 28.2% and 26.4% in the tedizolid and linezolid arms, respectively (treatment difference –1.8%, 95% CI –8.2% to 4.7%). Non-inferiority of tedizolid was demonstrated using a non-inferiority margin of 10%. For investigator-assessed clinical response at test of cure, rates were 56.3% and 63.9% for tedizolid and linezolid groups, respectively (treatment difference –7.6, 97.5% CI –15.7% to 0.5%). Non inferiority of tedizolid was not demonstrated for this outcome measure based on a non-inferiority margin of 12.5%.

WHO guidelines

Tedizolid phosphate is not currently included in existing WHO guidelines.

Tedizolid phosphate is included as a treatment option for MRSA skin and soft tissue infections in guidelines issued by the World Society for Emergency

Surgery (*11*), the Surgical Infection Society (*12*) and in a consensus statement by the Italian Infectious Diseases Society (*13*).

Costs/cost–effectiveness

Information regarding the cost and comparative cost–effectiveness of tedizolid phosphate was not presented in the application.

Availability

Tedizolid phosphate has regulatory approval in 43 countries globally, however market availability is limited to only 14 upper middle- and high-income countries.

Other considerations

The EML Antimicrobial Working Group reviewed the application and advised that it supported the inclusion of tedizolid phosphate on the EML as a reserve antibiotic for the treatment of infections caused by multidrug-resistant organisms as a therapeutic alternative to linezolid. The indications for use of tedizolid should be aligned with those for linezolid as described in the WHO AWaRe antibiotic book (*14*).

The Working Group highlighted that MRSA remains a major global public health concern as a cause of severe bacterial infections, with significant mortality associated with invasive disease as noted in the recent Global Research on Antimicrobial Resistance Project (GRAM) study (*1*).

The Working Group also noted that tedizolid is given only once daily, and generally for shorter treatment courses than linezolid, which is given twice daily. Tedizolid has good bioavailability and has both an intravenous and oral preparation, encouraging oral treatment only or rapid switch from intravenous to oral treatment in stable patients. No dose adjustments need to be made in patients with hepatic or renal disease. The Working Group considered that the main advantage of tedizolid over linezolid was the significantly lower incidence of bone marrow suppression and gastrointestinal toxicity.

The Working Group noted that tedizolid is more expensive than generic linezolid, however shorter treatment courses may affect the relative costs. Based on current patent status, generic versions of tedizolid are unlikely to be widely available before the 2030s. Cost–effectiveness data are scarce in low- and middle-income settings.

Committee recommendations

The Expert Committee noted that MRSA remains a major cause of severe bacterial infections in many settings, and that the pathogen is designated by WHO as high priority for which new therapeutic options are needed.

The Committee acknowledged the activity of tedizolid phosphate against high-priority drug-resistant Gram-positive pathogens, mainly *S. aureus* including

MRSA and also vancomycin-resistant enterococci. The Committee noted that clinical trial data suggest tedizolid phosphate is non-inferior to linezolid for the treatment of acute bacterial skin and skin structure infections, including infections caused by MRSA. The Committee also noted the advice of the EML Antimicrobial Working Group that tedizolid phosphate is associated with less bone marrow suppression and gastrointestinal toxicity than linezolid and that it is administered once daily for generally shorter treatment courses than linezolid which is administered twice daily .

The Committee noted that the application failed to include any information on the cost and cost–effectiveness of tedizolid phosphate. The Expert Committee also noted the advice of the EML Antimicrobial Working Group that tedizolid phosphate is more expensive than linezolid and is still under patent protection (either primary or secondary) until at least 2030, whereas linezolid is already available in generic versions.

Taking these issues into consideration, the Expert Committee recommended the inclusion of tedizolid phosphate as a Reserve group antibiotic on the EML as a therapeutic alternative to linezolid under a square box listing. The representative medicine should be linezolid because of its wider availability and lower price. The Committee noted that the application requested inclusion specifically for treatment of acute bacterial skin and skin structure infections. However, the Committee recommended that tedizolid phosphate be included on the EML for the same indications as linezolid, which are currently pathogen- rather than infection-based, namely infections caused by MRSA, vancomycin-resistant *S. aureus* and vancomycin-resistant enterococci.

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6.2.5 Antituberculosis medicines

Ethionamide – new indication – EML and EMLc

Ethionamide	ATC code: J04AD03

Proposal

Inclusion of ethionamide on the core list of the EML and EMLc for the new indication of treatment of drug-susceptible tuberculosis meningitis in children and adolescents.

Applicant

WHO Global Tuberculosis Programme

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EML and EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strengths(s)

Tablet: 250 mg

Tablet (dispersible): 125 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Ethionamide is currently included on the complementary list of the EML and EMLc for use in the treatment of multidrug-resistant tuberculosis.

Public health relevance

Tuberculous meningitis is the most lethal form of tuberculosis. Globally in 2019, there were an estimated 164 000 cases and 78 200 deaths due to tuberculous meningitis (*1*). Mortality and severe permanent disabilities remain high in both children and adults, particularly in people living with HIV (*2,3*).

Summary of evidence: benefits

The application referenced a systematic review and meta-analysis of seven cohort studies comparing the effectiveness of shorter regimens including at a minimum isoniazid, rifampicin and pyrazinamide, versus the WHO-recommended 12-month regimen of isoniazid, rifampicin, ethambutol and pyrazinamide in children and adolescents with drug-susceptible tuberculosis meningitis (*4*). This meta-analysis informed a 2022 WHO guideline recommendation in favour of the shorter regimen (conditional recommendation; very low-certainty evidence). Details of the findings of the systematic review were not provided in the application but are summarized below.

Three of the included studies (724 patients) evaluated a 6-month intensive regimen of isoniazid, rifampicin, pyrazinamide and ethionamide. This regimen was associated with a lower pooled proportion of death (5.5%, 95% confidence interval (CI) 2.1% to 13.4%) compared with the 12-month regimen (23.9%, 95% CI 17.5% to 31.7%). The pooled proportions of treatment success were 94.6% (95% CI 73.9% to 99.1%) for the 6-month intensive regimen and 75.4% (95% CI 68.7% to 81.1%) for the 12-month regimen. For survivors who completed treatment and who had neurological sequalae the pooled proportions were 66.0% (95% CI 55.3% to 75.3%) for the 6-month regimen and 36.3% (95% CI 30.1% to 43.0%) for the 12-month regimen, although there was substantial heterogeneity for both regimens. For survivors who completed treatment and who did not have neurological sequalae, the pooled proportions were 29.9% (95% CI 20.4% to 41.4%) and 47.9% (95% CI 42.1% to 53.7%) for the 6-month and 12-month regimens, respectively.

Summary of evidence: harms

Harms associated with the use of ethionamide were not discussed in the application.

From one of the studies included in the systematic review that evaluated 6- and 9-month intensified regimens of isoniazid, rifampicin, pyrazinamide and ethionamide in children with tuberculosis meningitis, treatment-induced hepatotoxicity was reported in 5% of the children (*5*).

WHO guidelines

Current WHO guidelines for the management of tuberculosis in children and adolescents include a conditional recommendation (very low-certainty evidence) that in children and adolescents with bacteriologically confirmed or clinically diagnosed tuberculosis meningitis (without suspicion or evidence of multidrug- or rifampicin-resistant tuberculosis), a 6-month intensive regimen of isoniazid, rifampicin, pyrazinamide and ethionamide may be used as an alternative to the 12-month regimen of isoniazid, rifampicin, ethambutol and pyrazinamide (*6*).

Costs/cost–effectiveness

No information was provided in the application.

The 2023 Global Drug Facility catalogue reports the price of ethionamide 250 mg tablets as US$ 9.16 for 100 tablets, and of ethionamide 125 mg dispersible tablets as US$ 13.30–14.48 for 100 tablets.

Availability

Ethionamide tablets and dispersible tablets are available through the Stop TB Partnership's Global Drug Facility.

Other considerations

In adults, WHO guidelines recommend that drug-susceptible tuberculosis meningitis be treated with the same regimen used for pulmonary tuberculosis, that is, a 6-month regimen composed of 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin, noting that some expert groups suggest longer therapy (7).

Committee recommendations

The Expert Committee noted that tuberculosis meningitis is responsible for considerable morbidity and mortality, and that a shorter, intensified ethionamide-containing treatment regimen in children and adolescents has shown favourable outcomes in comparison with the alternative WHO-recommended 12-month regimen of isoniazid, rifampicin, pyrazinamide and ethambutol.

The Committee therefore recommended the inclusion of ethionamide on the core list of the EML and EMLc for the new indication of drug-susceptible tuberculosis meningitis in children and adolescents, consistent with the recommendations in current WHO guidelines for management of drug-susceptible tuberculosis meningitis in children and adolescents.

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Pretomanid – addition – EML

Pretomanid	ATC code: J04AK08

Proposal

Addition of pretomanid to the complementary list of the EML for use in combination with bedaquiline and linezolid, with or without moxifloxacin, for the treatment of patients aged 14 years and older with multidrug-resistant or rifampicin-resistant tuberculosis.

Applicant

Global Alliance for TB Drug Development

WHO technical department

The WHO Global Tuberculosis Programme department reviewed and provided comments on the application. The proposed inclusion of pretomanid for treatment of drug-resistant tuberculosis on the EML is supported by the technical department, to be used as a component of a 6-month regimen composed of bedaquiline, pretomanid and linezolid, with or without moxifloxacin.

EML/EMLc

EML

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strengths(s)

Tablet: 200 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Pretomanid has not previously been evaluated for inclusion on the EML.

Bedaquiline, linezolid and moxifloxacin are currently included for treatment of multidrug- and rifampicin-resistant tuberculosis. These medicines are used in combination in the bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) and bedaquiline, pretomanid, linezolid (BPaL) regimens.

Treatment duration is 26 weeks. The BPaL regimen may be extended to 9 months (39 weeks) if necessary.

Public health relevance

In 2021, an estimated 10.6 million people fell ill with tuberculosis worldwide, and there were 1.6 million deaths. Also in 2021, an estimated 450 000 new cases of rifampicin-resistant tuberculosis occurred. In 2019, tuberculosis was the 13th leading cause of death. Multidrug-resistant tuberculosis (MDR-TB) remains a public health crisis and a health security threat. Only about one in three people with drug-resistant tuberculosis accessed treatment in 2020 (*1*).

Existing drug-resistant tuberculosis treatment regimens often include five to seven medicines and more than 14 000 pills taken over a duration of up to 18 months or sometimes longer. High rates of non-adherence are common, which often result in unfavourable outcomes, emergence of drug resistance, continued spread of the disease and increased mortality. The introduction of the BPaLM and BPaL regimens provides efficacious, safe, well tolerated treatment options that have shortened overall treatment duration and improved compliance and favourable outcomes.

Summary of evidence: benefits

The Nix-TB study was an open-label, single-arm study conducted at three South African sites, investigating treatment with (BPaL in patients with highly drug-resistant pulmonary tuberculosis (*2*). The primary endpoint was the incidence of an unfavourable outcome, defined as treatment failure (bacteriological or clinical) or relapse, through 6-months follow-up after the end of treatment. Participants were classified as having a favourable outcome at 6 months after the end of treatment if they had resolution of clinical disease, a negative culture status, and had not already been classified as having had an unfavourable outcome. Other efficacy endpoints and safety were also evaluated. The study enrolled 109 participants, and 107 participants were included in the modified intent-to-treat population for evaluation of efficacy. Six months after the end of treatment, nine (8%) participants had an unfavourable outcome and 98 (92%) had a favourable outcome (95% confidence interval (CI) 84.6% to 96.0%). Of the nine participants with unfavourable outcomes, six died during treatment, one withdrew (not for treatment failure) during treatment and two relapsed during follow-up.

The ZeNix study was a randomized controlled, partially-blinded, multicentre, phase III trial to evaluate the efficacy, safety and tolerability of various doses and durations of linezolid plus bedaquiline and pretomanid in 181 patients with pulmonary extensively drug-resistant tuberculosis, pre-extensively drug-resistant tuberculosis, or treatment intolerant or non-responsive MDR-TB (*3*). Patients were randomized to receive various doses and durations of linezolid

(1200 mg or 600 mg daily; 26 weeks or 9 weeks) plus bedaquiline and pretomanid for 26 weeks. The primary endpoint was the incidence of bacteriological failure or relapse or clinical failure 6 months after the end of treatment. Other efficacy endpoints and safety were also evaluated. The modified intent-to-treat population was used for the primary efficacy analysis and included 178 participants. Among participants who received BPaL with linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks, 93%, 89%, 91% and 84%, respectively, had a favourable outcome 6 months after the end of treatment. Six of the seven unfavourable microbiological outcomes up to 78 weeks after the end of treatment occurred in participants assigned to the 9-week linezolid groups. The 1200 mg linezolid 26-week group had the highest percentage of participants who required linezolid dose modifications. The overall risk–benefit ratio favoured the group that received BPaL with linezolid at a dose of 600 mg for 26 weeks, with a lower incidence of adverse events reported and fewer modifications to the linezolid dose.

The TB-PRACTECAL study was a randomized, open-label, phase II/III study evaluating the safety and efficacy of regimens containing bedaquiline and pretomanid in combination with existing and repurposed drugs for the treatment of pulmonary MDR-TB (*4*). The study was conducted in Belarus, South Africa and Uzbekistan, and enrolled participants 15 years and older. In the first stage, equivalent to a phase IIB study, participants were randomly assigned to one of four regimens. The three investigational regimens included oral bedaquiline, pretomanid and linezolid. Additionally, two of the regimens also included moxifloxacin (arm 1) and clofazimine (arm 2). Treatment was administered for 24 weeks in the investigational arms. The phase III stage evaluated the treatment regimen of BPaLM compared with the local standard of care at the participating sites. The primary efficacy outcome was a composite endpoint of the percentage of unfavourable outcomes at 72 weeks after randomization. The secondary outcomes included safety outcomes and the percentage of grade 3 or 4 and serious adverse events in the investigational regimens compared with the standard of care. Enrolment was terminated based on a Data Safety Monitoring Board interim analysis of available data through week 72, which demonstrated that the BPaLM arm was significantly outperforming the standard of care arm in the percentage of unfavourable outcomes. Safety outcomes also favoured the BPaLM arm in this analysis (*5*).

The United States Centers for Disease Control and Prevention (CDC) analysed data submitted by health departments and clinicians on patients with tuberculosis in the US who began treatment with BPaL between August 2019 and September 2020. At follow up 12 months after treatment with BPaL was started, 19/20 (95%) patients had completed treatment, and there had been no treatment failures, recurrences or deaths (*6*).

Positive country experiences from Kyrgyzstan, South Africa and Ukraine with implementing the BPaL regimen under operational research conditions were reported at the Union World Conference on Lung Health in 2022 (unpublished).

Summary of evidence: harms

As of May 2022, 2550 participants have been exposed to pretomanid across pretomanid clinical studies.

The application described adverse events associated with the BPaL and BPaLM regimens from the Nix-TB, ZeNix and TB-PRACTECAL studies.

In the Nix-TB study, participants received the BPaL regimen with linezolid dosed at 1200 mg daily for 26 weeks. At least one treatment-emergent adverse event was reported by all 109 participants. In total, 50 (46%) participants interrupted linezolid due to an adverse event and resumed at the same or lower dose, and 30 participants (28%) permanently discontinued linezolid due to an adverse event. The most common adverse events were peripheral neuropathy (81%), myelosuppression (48%), optic neuropathy (13%), cardiac rhythm disturbances (11%) and myalgia (10%). Most peripheral neuropathy events were mild to moderate and were managed through linezolid dose adjustments. Twelve (11%) participants had transaminase increases > 3 times the upper limit of normal – 12 had an alanine aminotransferase elevation and 11 participants had an aspartate aminotransferase elevation. Two of these participants had alanine and aspartate aminotransferase elevations of > 3 times the upper limit of normal as well as direct and total bilirubin elevations of > 2 times the upper limit of normal. In both cases, the study drug regimen was interrupted. In total, eight participants had their regimen interrupted for hepatic adverse events, but all resumed and completed the full 26 weeks of treatment. The maximum mean increase in the QT interval by the Fridericia method was 10 ms at week 16; no participant had a QT interval > 480 ms (*2*).

During the ZeNix study, participants received the BPaL regimen for 26 weeks with linezolid dosed at 1200 mg or 600 mg daily for 26 weeks or 9 weeks. Treatment emergent adverse events were reported in 156 of 181 participants (86.2%), with the overall percentages comparable across treatment groups. One participant (0.6%) died due to a treatment-emergent adverse event (in the 1200 mg linezolid 9-week group), but this event was deemed not to be related to the study drug. The linezolid dose was modified (interrupted, reduced or discontinued) in 51%, 30%, 13%, and 13% of participants who received linezolid 1200 mg for 26 weeks, 1200 mg for 9 weeks, 600 mg for 26 weeks and 600 mg for 9 weeks, respectively. Adverse effects associated with linezolid include peripheral neuropathy, optic neuropathy and myelosuppression. For participants who received linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks, peripheral neuropathy occurred in 38%, 24%, 24% and 13%

of participants, respectively, and myelosuppression occurred in 29%, 15%, 13% and 16% of participants, respectively. Optic neuropathy developed in four (9%) participants who received linezolid at a dose of 1200 mg for 26 weeks; all the cases resolved. Optic neuropathy was not reported by participants in any other treatment groups (*3*).

Data from TB-PRACTECAL were shared with WHO to inform the updated treatment guideline recommendations. Interim results showed that the BPaLM regimen had favourable efficacy and safety when compared with the regimens given in the control arm.

The CDC analysed data submitted by health departments and clinicians on 20 patients with tuberculosis in the US who began treatment with BPaL between August 2019 and September 2020. At follow-up 12 months after treatment with BPaL was started, 19 (95%) patients had completed treatment. With regard to side-effects, 12 (60%) patients reported at least one side-effect during treatment (with the combination regimen or another medication). Side-effects included peripheral neuropathy (six patients), depression (five patients), vestibular dysfunction (three patients), vision changes (three patients), nausea (two patients) and hearing loss (two patients). The timing of side-effects could not be correlated to a specific antituberculosis drug. At the time treatment began, therapy with linezolid was initiated in 18 (90%) patients at a dose lower than the 1200 mg daily approved by the United States Food and Drug Administration (most received 600 mg daily), and in 18 patients (90%), measurement of linezolid levels was used to attain therapeutic levels while minimizing toxic effects (*6*).

Testicular toxicity was observed in male mice and rats in all repeat-dose studies but was not observed in male monkeys in any repeat-dose study. New data on the safety of pretomanid based on hormone evaluations in four clinical studies and a paternity survey were assessed by the WHO Guideline Development Group in early 2022. These data have largely alleviated previous concerns on reproductive toxicity observed in animal studies, suggesting that adverse effects on human male fertility are unlikely. Four studies with exposure to pretomanid ranging from 2 to 6 months provided an assessment of serum hormone levels relevant to male reproductive health, including follicle-stimulating hormone, luteinizing hormone, inhibin B and testosterone (*7*). These hormone assessments demonstrated an improvement in the underlying hypogonadism, as reflected by increases in the testosterone and inhibin B levels in all treatment arms, which is consistent with improvements in the underlying disease state. In addition, a search for adverse events associated with fertility disorders across the 19 studies in the pretomanid clinical development programme identified no events in any male participant and one event in a female participant (irregular menstruation). None of the changes observed suggested testicular damage.

WHO guidelines

Based on data from the TB-PRACTECAL and ZeNix studies, the 2022 WHO consolidated guidelines on tuberculosis suggest the use of a 6-month BPaLM treatment regimen (bedaquiline, pretomanid, linezolid 600 mg and moxifloxacin) rather than the standard 9- or 18-month regimens for patients with MDR-TB/rifampicin-resistant TB (conditional recommendation, very low certainty of evidence) (*8*). The BPaL regimen may be used in cases of documented resistance to fluoroquinolones.

Pretomanid should be administered in combination with bedaquiline and linezolid, with or without moxifloxacin, as follows:

- Pretomanid 200 mg orally (1 tablet of 200 mg), once daily, for 26 weeks.
- Bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg three times a week, with at least 48 hours between doses for 24 weeks, for a total of 26 weeks of treatment. Alternatively, bedaquiline 200 mg orally once daily for 8 weeks followed by 100 mg once daily for 18 weeks, for a total of 26 weeks of treatment.
- Linezolid 600 mg orally once daily for 26 weeks with potential for dose reduction depending on tolerance.
- Moxifloxacin 400 mg orally once daily for 26 weeks in patients without baseline resistance to fluoroquinolones.

Treatment with the BPaL combination may be extended to 39 weeks if necessary.

Costs/cost–effectiveness

Based on current costs reported in the Global Drug Facility catalogue, for patients with body weight of 40–70 kg, drug costs for treatment with BPaLM and BPaL regimens for 26 weeks is US$ 725 and US$ 720, respectively. In comparison, MDR-TB regimens of 9–11 months would cost between US$ 564 and US$ 639. The costs of medicines for longer regimens vary by patient and country and would be between US$ 875 and US$ 942.

Drug costs are only one part of the total cost of treatment and non-drug costs of delivering care and managing patients are significant. The lowest published total cost of administering shorter, 9-month MDR-TB regimens in India, which accounts for about 30% of all MDR-TB patients treated, is at least US$ 2600, while treatment with longer regimens lasting up to 18 months is US$ 5500. Comparable costs in South Africa are US$ 4700 and US$ 8400, respectively. Due to volume driven cost economies, costs in India are lower; costs are likely to be higher in other middle- or high-income countries, especially those with a relatively lower burden of disease (*9*).

While the BPaLM and BPaL regimens are similar in drug cost compared with 9- to 11 month regimens, the difference in cost–effectiveness becomes apparent when the total cost of treatment is considered. A study found that the BPaLM and BPaL regimens would save about 40% over the cost of 9- to 11-month MDR-TB regimens (US$ 1000–2000 saving per patient) and about 75% compared with longer regimens (US$ 4000–6000 saving per patient) (*9,10*). Similarly, the estimated savings associated with using BPaL for pre-extensively drug-resistant tuberculosis would range between 80% and 90% (up to US$ 12 000 per patient) (*10–12*). These studies considered only the cost of drugs and cost of care and estimated that global savings could reach US$ 740 million annually if all patients were to, hypothetically, transition to BPaLM or BPaL regimens immediately. If patient costs are added, the savings from implementation of BPaLM and BPaL will be larger.

Two additional studies investigated the comparative cost of introducing pretomanid as part of the BPaL regimen to treat drug-resistant tuberculosis versus the standard treatment across six countries. All analyses in all countries estimated that the introduction of BPaL would lead to cost savings (*11,12*).

Availability

Pretomanid 200 mg tablets, manufactured by Viatris, have regulatory approval in the United States, European Economic Area countries and a further 20 countries globally. Pretomanid 200 mg tablets, manufactured by Mylan Laboratories, were prequalified by WHO in November 2020. Additional manufacturers are reported to have applied or plan to apply for marketing authorization in China and India.

Committee recommendations

The Expert Committee noted that tuberculosis, including drug-resistant tuberculosis, remains a significant public health threat and is responsible for considerable morbidity and mortality. The Committee also noted that treatment for drug-resistant tuberculosis often carries a high pill-burden over a long treatment duration, and that non-compliance with treatment is common, leading to unfavourable outcomes for both individuals and the community.

High rates of non-adherence to standard treatment regimens for MDR-TB are common, which often result in unfavourable outcomes, emergence of further drug resistance, continued spread of disease and increased mortality. The introduction of the BPaLM and BPaL regimens provides efficacious, safe, well tolerated treatment options that have shortened overall treatment duration and improved compliance and favourable outcomes.

The Committee considered that the available evidence from clinical trials supports the efficacy and safety of pretomanid, as part of the BPaLM and BPaL regimens, and noted experiences reported from countries where these regimens have been introduced in tuberculosis treatment programmes. The Committee

also noted that the BPaL and BPaLM regimens have a shorter overall treatment duration compared with alternative regimens, which may contribute to improved treatment adherence and more favourable outcomes.

The Committee noted that use of the BPaLM and BPaL regimens is recommended in current WHO guidelines for treatment of MDR-TB.

Based on these considerations, the Committee therefore recommended the inclusion of pretomanid on the complementary list of the EML for use as part of a combination regimen with bedaquiline and linezolid with or without moxifloxacin for the treatment of multidrug-resistant or rifampicin-resistant tuberculosis in patients aged 14 years and older.

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Bedaquiline – age restriction – EML and EMLc

Bedaquiline	ATC code: J04AK05

Proposal

Removal of the age limit from the listing for bedaquiline in the EML and EMLc.

Applicant

WHO Global Tuberculosis Programme

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EML and EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strengths(s)

Tablet: 20 mg, 100 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Bedaquiline tablets for use in the treatment of multidrug-resistant tuberculosis (MDR-TB) have been listed on the EML and EMLc since 2015 and 2019, respectively. When bedaquiline was added to the EMLc in 2019, an age limit of ≥ 6 years was included, in line with WHO guideline recommendations at the time. The age limit was amended to ≥ 5 years in 2021, in line with updated WHO guidelines.

Public health relevance

The public health relevance of effective treatments for MDR-TB is well established.

In 2021, the estimated incidence of tuberculosis disease in children younger than 15 years was 1.15 million (*1*). While the exact burden of MDR-TB in children is still unknown, more than 30 000 cases are estimated to occur

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globally each year (*2,3*). In 2021, 5506 children and young adolescents (0–14 years) were initiated on second-line treatment for MDR-TB or rifampicin-resistant tuberculosis (RR-TB).

Summary of evidence: benefits

A descriptive analysis of data from a paediatric MDR-TB/RR-TB individual patient dataset included 40 children younger than 6 years and 68 children aged 6–12 years who received bedaquiline off-label under programmatic conditions. In a matched analysis, bedaquiline was associated with significantly shorter treatment duration and a lower adjusted odds ratio (OR) of injectable tuberculosis drug use (*4*). The certainty of evidence was very low of no statistically significant difference in successful treatment outcomes between children younger than 6 years receiving an all-oral bedaquiline-based regimen compared with children not receiving bedaquiline (OR 0.94, 95% confidence interval (CI) 0.09 to 10.30). In absolute terms, this represents two fewer treatment successes per 1000 children treated (95% CI 203 fewer to 24 more) (*5*).

Population pharmacokinetic models from two phase II trials of bedaquiline in children – TMC207-C211 (*6*) and IMPAACT P1108 (*7*) – suggest that drug exposures observed in adults can be reached in most children receiving bedaquiline, however some dose modification may be necessary for some children depending on age and weight (*4*).

Summary of evidence: harms

The most common adverse effects of bedaquiline include headache, nausea, liver dysfunction, QT interval prolongation and arthralgia.

Available interim data from IMPAACT P1108 were based on a small sample size (*n* = 12) but did not suggest distinct cardiac safety signals with bedaquiline in children 0–6 years compared with cardiac safety reported in adults (*4*). No children had QT prolongation in any categories of ≥ 60 ms. Three children experienced QT prolongation of between 3 ms and 60 ms. However, the safety review was not complete as not all children enrolled had completed the full course of bedaquiline treatment (24 weeks).

At this time, long-term safety and adverse event data are lacking for children younger than 6 years receiving bedaquiline.

WHO guidelines

WHO guidelines for the management of tuberculosis in children and adolescents include a conditional recommendation (very low-certainty evidence) that an all-oral treatment regimen containing bedaquiline may be used in children younger than 6 years with MDR-TB and RR-TB (*4*).

Costs/cost–effectiveness

Information on the cost and cost–effectiveness of bedaquiline has been presented and considered previously. No new information is available.

Availability

Information on the market availability of bedaquiline has been presented and considered previously. No new information is available.

Other considerations

In October 2021, WHO convened an expert consultation on bedaquiline dosing in young children. By accounting for age, body weight and other known covariates, an adult population pharmacokinetic model was used to simulate dose–exposure scenarios for a virtual representative paediatric population. Using these population pharmacokinetic methods and trial-based paediatric bedaquiline pharmacokinetic data, a combined age- and weight-based approach to bedaquiline dosing was developed for children weighting 3 to < 16 kg, and is included in the WHO operational handbook on tuberculosis (*8*). Bedaquiline is metabolized by CYP3A4, and children younger than 6 months have immature enzyme function resulting in lower bedaquiline clearance. Doses are therefore adjusted based also on age to avoid excessively high bedaquiline concentrations and resultant risk of toxicity.

Committee recommendations

The Expert Committee recommended the removal of the age restriction from the listing of bedaquiline on the EML and EMLc, consistent with the recommendations for use of bedaquiline in current WHO guidelines for management of tuberculosis in children and adolescents.

References

1. Global tuberculosis report 2022. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/363752, accessed 6 October 2023).

2. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Pérez-Vélez CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014;383(9928):1572–9.

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7.   Evaluating the pharmacokinetics, safety, and tolerability of bedaquiline in HIV-infected and HIV-uninfected infants, children, and adolescents with multidrug-resistant tuberculosis. ClinicalTrials.gov identifier: NCT02906007. Washington, DC: US National Library of Medicine; 2016 (https://clinicaltrials.gov/ct2/show/NCT02906007, accessed 6 October 2023).

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Delamanid – age restriction – EML and EMLc

Delamanid	ATC code: J04AK06

Proposal

Removal of the age limits from the listing for delamanid in the EML and EMLc.

Applicant

WHO Global Tuberculosis Programme

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EML and EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strengths(s)

Tablet (dispersible): 25 mg

Tablet: 50 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Delamanid tablets for use in the treatment of multidrug-resistant tuberculosis (MDR-TB) have been listed on the EML and EMLc since 2015 and 2019, respectively. When bedaquiline was added to the EMLc in 2019, an age limit of ≥ 6 years was included, in line with WHO guideline recommendations at the time. The age limit was amended to ≥ 5 years in 2021, in line with updated WHO guidelines.

Public health relevance

The public health relevance of effective treatments for MDR-TB is well established.

In 2021, the estimated incidence of tuberculosis disease in children younger than 15 years was 1.15 million (*1*). While the exact burden of MDR-TB in

children is still unknown, more than 30 000 cases are estimated to occur globally each year (*2,3*). In 2021, 5506 children and young adolescents (0–14 years) were initiated on second-line treatment for MDR-TB or rifampicin-resistant tuberculosis (RR-TB).

Summary of evidence: benefits

A phase I, open-label, age de-escalation study, followed by a phase II 6-month extension study assessed the pharmacokinetics, safety and tolerability of delamanid administered twice daily for 10 days in children with MDR-TB/RR-TB aged birth to 17 years on treatment with an optimized background regimen (*4*). Twelve children were included in the 0–2-year cohort. Exposures in this age group were lower than predicted from pharmacokinetic modelling of older age groups, and lower than target exposures in adults, necessitating a modelling/simulation approach to dosing.

A descriptive analysis of data from a paediatric MDR-TB/RR-TB individual patient dataset included seven children younger than 3 years treated with delamanid, 14 children aged 3–6 years and 69 children aged 6–12 years. All 21 children younger than 6 years were successfully treated (*5*).

These data were reviewed by the Guideline Development Group responsible for updating the WHO guidelines on the management of tuberculosis in children and adolescents, which made a conditional recommendation based on very low certainty of evidence that delamanid may be used as part of longer regimens in children younger than 3 years with - or rifampicin-resistant tuberculosis (*5–7*).

Summary of evidence: harms

From the evidence described above, no cardiac safety signals distinct from those reported in adults were observed in children 0–2 years of age. However, children had lower drug exposures compared with adults. Pharmacodynamic simulations suggested that clinically meaningful changes in QT (i.e. prolongation) would be unlikely in children younger than 3 years, even if higher doses were used to reach drug exposures comparable to those achieved in adults.

Central nervous system effects, including paraesthesia, tremors, anxiety, depression and insomnia, are potential safety concerns associated with delamanid in both adults and children. Hallucinations have been associated with delamanid and are reported to be more prevalent in children than in adults (*7*).

Overall, the Guideline Development Group considered the balance between desirable and undesirable effects of delamanid in children younger than 3 years probably favoured the intervention (*7*).

WHO guidelines

WHO guidelines for the management of tuberculosis in children and adolescents include a conditional recommendation (very low-certainty evidence) that delamanid may be used as part of longer regimens in children younger than 3 years with MDR-TB and RR-TB (*5*).

Costs/cost–effectiveness

Information on the cost and cost–effectiveness of delamanid has been presented and considered previously. No new information is available.

Availability

Information on the market availability of delamanid has been presented and considered previously. No new information is available.

Other considerations

In October 2021, WHO convened an expert consultation on delamanid dosing in young children. During this consultation, it was noted that since safety concerns about a possible risk of metabolite accumulation largely applied to infants (younger than 3 months) with immature cytochrome P450 enzyme function, it was advised that dosing for infants weighing 5 kg to less than 10 kg should use a combined age- and weight-based approach, with doses for children younger than 3 months being lower than doses for children aged 3 months and older. Dosing guidance for delamanid in children is provided in the WHO operational handbook on tuberculosis (*8*). Use of the 25 mg dispersible tablet formulation is preferred in infants and young children, rather than manipulation of the 50 mg tablet.

Committee recommendations

The Expert Committee recommended the removal of the age restrictions from the listing of delamanid on the EML and EMLc, consistent with the recommendations for use of delamanid in current WHO guidelines for management of tuberculosis in children and adolescents.

References

1. Global tuberculosis report 2022. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/363752, accessed 6 October 2023).

2. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Pérez-Vélez CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014;383(9928):1572–9.

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8.   WHO operational handbook on tuberculosis: module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/352523, accessed 6 October 2023).

Antituberculosis medicines – formulations for deletion – EML and EMLc

Antituberculosis formulations – deletions	ATC code: various

Proposal

Deletion of various antituberculosis medicine formulations from the EML and EMLc.

Applicant

WHO Global Tuberculosis Programme

WHO technical department

Global Tuberculosis Programme

EML/EMLc

EML and EMLc

Section

6.2.5 Antituberculosis medicines

Dose form(s) & strengths(s)

Amikacin – Injection: 100 mg/2 mL (as sulfate) in 2 mL vial (EML and EMLc)

Ethambutol – Oral liquid: 25 mg/mL (EMLc)

Ethionamide – Tablet: 125 mg (EML and EMLc)

Isoniazid – Oral liquid: 50 mg/5 mL (EMLc)

Linezolid – Powder for oral liquid: 100 mg/5 mL (EML and EMLc)

p-aminosalicylic acid – Granules: 4 g in sachet (EML and EMLc)

Pyrazinamide – Oral liquid: 30 mg/mL (EMLc)

Core/complementary

Core and complementary

Individual/square box listing

Individual

Background

At its meeting in 2021, the Expert Committee considered an application for deletion of various antituberculosis medicine formulations from the EML and EMLc, including ethambutol, ethionamide and pyrazinamide oral liquid,

and ethionamide 125 mg tablets. The Committee recognized that dispersible tablet formulations are preferred child-friendly formulations and provide flexible dosing options. However, because of concerns about limited uptake and availability of dispersible tablets formulations of ethambutol, ethionamide, isoniazid and pyrazinamide in some countries, the Committee did not recommend the deletion of oral liquid formulations of ethambutol, isoniazid and pyrazinamide, nor the 125 mg tablet formulation of ethionamide at that time. To allow countries time to transition to the adoption of the preferred, listed dispersible-tablet formulations, the Committee advised that these formulations would be deleted from the Model Lists in 2023 without further consideration, unless an application was received to support their ongoing inclusion (*1*).

No application to support ongoing inclusion has been received.

Public health relevance

Not applicable

Summary of evidence: benefits

The rationale presented in the applications for the requested deletions is summarized below.

Amikacin injection 100 mg/2 mL

Amikacin is recommended by WHO for the treatment of multidrug-resistant tuberculosis in people aged 18 years and older where susceptibility has been demonstrated. There is no current recommendation for its use in children and adolescents younger than 18 years due to an unfavourable benefit–risk balance and poor tolerability. In rare situations, amikacin may be used as salvage therapy, for which the dosage for children older than 2 years is 15–20 mg/kg a day, which can be achieved using the alternative listed strength of amikacin injection (250 mg/mL). This alternative strength is also more appropriate for dosing adults with multidrug-resistant tuberculosis, where higher doses are used (750–1000 mg a day).

Linezolid powder for oral liquid 100 mg/5 mL

This formulation is reported to be the subject of supply and availability issues, and to be more expensive than the alternative listed formulation of linezolid 150 mg dispersible tablets. The powder for oral liquid requires reconstitution before administration and contains a number of excipients associated with safety concerns. Linezolid 150 mg dispersible tablets have been included on the EMLc since 2019 and are included in the list of finished pharmaceutical products prequalified by WHO.

p-aminosalicylic acid granules 4 g

The application reports that p-aminosalicylic acid granules 4 g have been discontinued by the sole manufacturer because of high production costs and decreasing demand. An alternative product containing the equivalent of 4 g p-aminosalicylic acid as 5.52 g p-aminosalicylate sodium is available and is proposed in the application to replace the 4 g p-aminosalicylic acid formulation being proposed for deletion.

Ethambutol oral liquid 25 mg/mL; ethionamide tablet 125 mg; isoniazid oral liquid 50 mg/5 mL; pyrazinamide oral liquid 30 mg/mL

Refer to the Background section, above.

WHO guidelines

The proposed changes are aligned with recommendations in current WHO guidelines for the treatment of drug-susceptible and drug-resistant tuberculosis.

Costs/cost–effectiveness

Not applicable

Availability

Not applicable

Committee recommendations

The Expert Committee accepted the rationale and justifications presented by the Global Tuberculosis Programme and recommended the deletion of the following formulations of antituberculosis medicines from the EML and/or EMLc as requested in the application:

- amikacin injection 100 mg/2 mL (as sulfate) in 2 mL vial
- linezolid powder for oral liquid 100 mg/5 mL
- p-aminosalicylic acid granules 4 g in sachet.

The Committee recommended the inclusion of a new formulation of p-aminosalicylate sodium (powder for oral solution: 5.52 g in sachet (equivalent to 4 g p aminosalicylic acid)) on the complementary list of the EML and EMLc to replace the deleted formulation of p-aminosalicylic acid, which has been discontinued by the only manufacturer.

The Expert Committee recalled the recommendation of the 2021 Committee on the deletion of the following formulations of antituberculosis medicine formulations and recommended their removal from the EML and EMLc. The Committee noted that deletion of these formulations is supported by

the Global Tuberculosis Programme, and that no application had been received to support their ongoing inclusion on the Model Lists:

- ethambutol: oral liquid 25 mg/mL (EMLc)
- ethionamide: tablet 125 mg (EML and EMLc)
- isoniazid: oral liquid 50 mg/5 mL (EMLc)
- pyrazinamide: oral liquid 30 mg/mL (EMLc).

References

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2021 (including the 22nd WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1035; https://apps.who.int/iris/handle/10665/351172, accessed 6 October 2023).

6.4 Antiviral medicines

6.4.4.2 Medicine for hepatitis C

Ravidasvir – addition – EML

Ravidasvir	ATC code: not available

Proposal

Addition of ravidasvir to the core list of the EML for the treatment of chronic hepatitis C virus infection in adults.

Applicant

Ministry of Health, Putrajaya, Malaysia

WHO technical department

WHO Global Hepatitis Programme

EML/EMLc

EML

Section

6.4.4.2.1 Pangenotypic direct-acting antiviral combinations

Dose form(s) & strengths(s)

Tablet: 200 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Ravidasvir has not previously been evaluated for inclusion on the EML.

Ravidasvir was developed through an innovative drug development pathway involving multiple stakeholders including the Drugs for Neglected Disease Initiative (DNDi), Pharco Pharmaceuticals (a pharmaceutical company in Egypt) and Pharmaniaga, a manufacturer from Malaysia. An access agreement was formed under this collaboration. Malaysia as the co-founder of DNDi took part in the decision-making process and funded the development of the drug through the running of clinical trials in Malaysia. As a result, ravidasvir

was registered in Malaysia in 2021 and its use in combination with sofosbuvir was granted conditional approval by the National Pharmaceutical Regulatory Authority of Malaysia.

Public health relevance

An estimated 58 million people are chronically infected with hepatitis C virus (HCV) worldwide, with higher burden in low- and middle-income countries (*1*). However, in 2019 about 79% of people infected with HCV were unaware of their infection status and only about 13% of all infected people received treatment (*1*). An estimated 290 000 people died as a result of hepatitis C in 2019, mostly from liver cancer and cirrhosis caused by untreated HCV infections. In this context, the WHO goal is still to eliminate HCV as a public health threat by 2030, that is, a 90% reduction in chronic infections and 65% reduction in mortality compared with 2015.

Summary of evidence: benefits

The application reported the results of four phase II/III clinical trials of ravidasvir, conducted mainly in countries in Asia and the Middle East.

The Pyramid 1 trial was a randomized, phase IIb/IIIa clinical trial conducted in 298 patients in Egypt (*2*). This study assessed the efficacy and safety of ravidasvir plus sofosbuvir (with or without ribavirin) in patients with chronic HCV (genotype 4) infection. The study included both treatment naïve (149 patients, 59/149 with cirrhosis) and treatment experienced (149 patients, 70/149 with cirrhosis) patients. Patients without cirrhosis received ravidasvir (200 mg once a day) plus sofosbuvir (400 mg once a day) with or without ribavirin for 12 weeks. Patients with cirrhosis received ravidasvir (200 mg once a day) plus sofosbuvir (400 mg once a day) plus ribavirin for either 12 or 16 weeks. The primary efficacy endpoint was sustained virological response at 12 weeks after treatment. The response rate was 95.3% overall, higher in patients without cirrhosis (98.9% in the treatment-naïve group and 97.5% in the treatment-experienced group) and lower in those with cirrhosis (91.5% in the treatment-naïve group and 94.3% in the treatment-experienced group that was treated for 16 weeks). The response rate was lower (88.6%) in treatment-experienced patients with cirrhosis who were treated for 12 weeks.

The STORM-C-1 trial (*3*) was a multicentre, two-stage, open-label, single arm, phase II/III trial conducted in Malaysia and Thailand which included 301 patients (stage 1) and 302 patients (stage 2) with chronic HCV infection regardless of genotype. The study assessed the efficacy of ravidasvir (200 mg) plus sofosbuvir (400 mg) given for 12 weeks (patients without cirrhosis) or 24 weeks (patients with cirrhosis). The primary efficacy endpoint was sustained virological response at 12 weeks after treatment. The overall response rate in stage 1 was 97%

(95% confidence interval (CI) 94% to 99%), 96% in patients with cirrhosis and 97% in genotype 3 HCV infections. Of note, 30% of the patients were co-infected with HIV. Preliminary results of stage 2 were consistent with those of stage 1. The reported overall response rate was 96.8% (95% CI 95.1% to 98.1%).

The EVEREST trial was an open-label, single-arm, phase II trial in 38 treatment-naïve, HCV genotype 1 patients without cirrhosis (4). The study assessed the efficacy and safety of ravidasvir (200 mg once a day) plus ritonavir-boosted danoprevir (100 mg/100 mg every 12 hours) and ribavirin for 12 weeks. The primary efficacy endpoint was sustained virological response at 12 weeks after treatment. The response rate was 100%. Six patients had NS5A resistance-associated variants at baseline, all of whom achieved sustained virological response at week 12.

The ASC-ASC16-II/III-CTP-1-01 trial was a randomized, double-blind, placebo-controlled, multicentre phase II/III trial conducted in China in 424 treatment-naïve, HCV genotype 1 patients without cirrhosis (5). Patients were randomized to receive ravidasvir (200 mg once a day) plus ritonavir-boosted danoprevir (100 mg/100 mg every 12 hours) and ribavirin for 12 weeks (n = 318) or placebo (n = 106). Patients in the placebo arm received active treatment after week 12. The primary efficacy endpoint was sustained virological response at 12 weeks after treatment. The overall response rate was 99% in the per-protocol analysis in both groups.

The application presented the efficacy results for overall sustained virological response for ravidasvir (combined with sofosbuvir) from the STORM-C-1 trial and compared them with efficacy data for other regimens taken from a meta-analysis on pangenotypic direct-acting antiviral medicines (6), stratifying results by genotype (Table 12). Results stratified by cirrhosis and HIV status were also presented in the application (data not shown).

Table 12

Proportion of overall sustained virological response at week 12 for combinations of direct-acting antivirals (all comers, all treatment experience), by genotype

Genotype	Per cent				
	Sofosbuvir + velpatasvir	Sofosbuvir + daclatasvir	Glecaprevir + pibrentasvir	Sofosbuvir + ledipasvir	Sofosbuvir + ravidasvir
1	96	96	98	97	99
2	99	94	98	86	100
3	89	89	95	65	97
4	99	97	97	96	95

Summary of evidence: harms

In the Pyramid trial (*2*), safety endpoints were assessed until 4 weeks after the last dose of treatment. Adverse events were reported in 69% (204/298) of patients and half of which were considered to be unrelated to the study treatment. Most adverse events were mild to moderate and were headache (31%), pruritus (29%), fatigue (18%) and abdominal pain (10%). Serious adverse events were reported in 4% (11/298) of patients, with only two considered to be related to the study treatment, one case of hearing impairment and one case of transient symptomatic bradycardia.

In the STORM-C-1 trial (*3*), safety endpoints were assessed until 24 weeks after the end of treatment. Treatment-emergent adverse events were reported in 64% (192/301) of patients. Treatment-related adverse events were reported in 29% (87/301) of patients. The most common adverse events were pyrexia (12%), cough (9%), upper respiratory tract infection (8%) and headache (7%). Serious adverse events were reported in 6% (19/301) of patients with only one considered to be related to the study treatment. In patients with HCV–HIV co-infections, no clinically significant drug–drug interactions between ravidasvir and commonly used antiretrovirals were reported.

No treatment-related serious adverse events, discontinuations due to adverse events or deaths were reported during the EVEREST trial (*4*).

In the ASC-ASC16-II/III-CTP-1-01 trial (*5*), safety endpoints were assessed until 4 weeks after the last dose of treatment. In this trial, adverse events were reported in 94% (298/318) of patients in the intervention group and 79% (84/106) of patients in the placebo group. Most adverse events were mild. Serious adverse events were reported in 2% (7/318) and 5% (5/106) of patients in the intervention and placebo groups, respectively.

The application presented a comparison of safety data for ravidasvir combined with sofosbuvir with safety results for other regimens taken from a meta-analysis on pangenotypic direct acting antivirals, reporting the pooled proportions of patients experiencing events (Table 13) (*6*).

Table 13
Pooled proportions of adverse effects of direct-acting antivirals (all treatment experience)

Measure	Per cent				
	Sofosbuvir + Velpatasvir	Sofosbuvir + Daclatasvir	Glecaprevir + Pibrentasvir	Sofosbuvir + Ledipasvir	Sofosbuvir + Ravidasvir
Serious adverse event	3	3	2	2	8[a]
Discontinuation due to adverse event	0	1	1	0	< 1

[a] Indirect comparison based on the STORM C-1 (*3*) and Pyramid 1 (*2*) trials.

WHO guidelines

Ravidasvir is not currently included in WHO guidelines for the treatment of chronic HCV infection.

Costs/cost–effectiveness

The application reported that the current cost of one tablet of ravidasvir was US$ 7.30 in China and US$ 3.60 in Malaysia. No cost data were available for high- and low-income countries. In Malaysia, the cost of a course of ravidasvir + sofosbuvir was reported to be US$ 300. Pharco and DNDi have publicly announced that the sofosbuvir and ravidasvir combination will be available for US$ 294 or less per treatment course (*7*).

A cost–utility analysis comparing ravidasvir + sofosbuvir to daclatasvir + sofosbuvir and sofosbuvir + velpatasvir was conducted in the Brazil and Argentina. In Brazil, all three regimens were considered cost-effective when compared to no direct-acting antiviral regimen. Compared with ravidasvir + sofosbuvir, sofosbuvir + daclatasvir was not cost-effective for genotype 3 HCV infections and sofosbuvir + velpatasvir was not cost-effective for all HCV genotypes. In Argentina, ravidasvir + sofosbuvir was found to be cost-effective for all HCV genotypes (*8*).

The application also presented comparisons of price per tablet of direct-acting antivirals (Table 14) and treatment cost by regimen (Table 15) in Malaysia and by country income level.

Table 14
Price comparison for direct-acting antivirals in Malaysia and high-, middle- and low-income countries and areas

Antiviral	US$ per tablet			
	Malaysia	**High income[a]**	**Middle income[b]**	**Low income[c]**
Daclatasvir 30 mg	4.84	No data	No data	1.34
Daclatasvir 60 mg	0.39	48.44	0.83	6.39
Dasabuvir 250 mg	No data	No data	5.46	No data
Glecaprevir 100 mg + pibrentasvir 40 mg	No data	111.94	107.07	No data
Ravidasvir 200 mg	3.59	No data	7.33	No data
Ribavirin 200 mg	1.40	1.22	0.45	0.17
Sofosbuvir 400 mg	0.75	444.66	2.30[d]	6.78
Sofosbuvir 400 mg + ledipasvir 90 mg	No data	272.04	2.33	14.79
Sofosbuvir 400 mg + velpatasvir 100 mg	2.19	232.19	5.63	14.34

[a] Australia, Taiwan, China, Germany, Japan, New Zealand, Saudi Arabia, Republic of Korea, Sweden and United Kingdom.
[b] Argentina, Azerbaijan, Brazil, China, Egypt, Romania, South Africa, Thailand and Türkiye.
[c] India, Indonesia and Viet Nam.
[d] Data only from China.

Table 15
Comparison of treatment costs for direct-acting antiviral regimens, by country income level

Antiviral regimen	US$		
	High income	**Middle income**	**Low income**
Glecaprevir + pibrentasvir (minimum treatment duration)	18 806.62	19 503.74	No data
Glecaprevir + pibrentasvir (maximum treatment duration)	37 613.25	35 976.84	No data
Sofosbuvir + daclatasvir (minimum treatment duration)	41 421.07	262.78	1106.22

Table 15 *continued*

Antiviral regimen	US$		
	High income	Middle income	Low income
Sofosbuvir + daclatasvir (maximum treatment duration)	82 842.14	1 278.17	2212.43
Sofosbuvir + ravidasvir (minimum treatment duration)	No data	808.95	No data
Sofosbuvir + ravidasvir (maximum treatment duration)	No data	2370.34	No data
Sofosbuvir + velpatasvir (minimum treatment duration)	19 503.74	472.54	1204.48
Sofosbuvir + velpatasvir (maximum treatment duration)	39 007.47	945.09	2408.95

Availability

Ravidasvir currently has regulatory approval and market availability in China, Egypt and Malaysia.

In 2017, the Medicines Patent Pool and Pharco Pharmaceuticals signed a licence and technology agreement for ravidasvir, with the aim of improving access to ravidasvir in 19 low- and middle-income countries with a high prevalence of HCV infection, namely Algeria, Azerbaijan, Belarus, Djibouti, Egypt, Ethiopia, Iran (Islamic Republic of), Iraq, Jordan, Kazakhstan, Lebanon, Libya, Morocco, occupied Palestinian territory, Russian Federation, Syrian Arab Republic, Tunisia, Ukraine and Yemen (*9*).

Other considerations

The Committee acknowledged that the Ministry of Health of Malaysia (the applicant) had taken an active role in the development and manufacturing of ravidasvir in a public-private partnership with pharmaceutical contractors and the DNDi. The Committee considered that this type of approach may offer a path forward for countries looking to address the challenge of high medicine prices. The Committee recognized the importance of identifying and supporting effective strategies to reduce prices far below current market prices for direct-acting antiviral medicines in countries with limited resources and a high HCV burden to increase affordable to hepatitis C treatments.

Committee recommendations

The Expert Committee recognized the public health importance of effective and safe treatments for HCV infection, especially in settings with high disease burden.

The Committee also noted that the availability of pangenotypic regimens has overcome the requirement for genotype testing, but that rapid diagnostic testing is still required to identify patients eligible for treatment. Rapid diagnostic tests to screen for HCV infection are included on the WHO Model List of Essential In-Vitro Diagnostics.

The Committee considered that the evidence presented in the application from four clinical trials supported the effectiveness and safety of ravidasvir, when used in combination with sofosbuvir, and showed results similar to those seen with other pangenotypic direct-acting antiviral regimens. However, the Committee noted that comparative studies versus other pangenotypic direct-acting antiviral regimens were lacking, and that ravidasvir + sofosbuvir is not included among the recommended pangenotypic regimens for adults in current WHO guidelines for hepatitis C.

The Committee noted that the global availability of ravidasvir is currently limited but considered that inclusion of ravidasvir on the EML would provide an additional treatment option for national selection and procurement in countries where it is available. The Committee also noted that ravidasvir had been licensed to the Medicines Patent Pool, which may facilitate affordable access in low- and middle-income countries.

The Committee therefore recommended the inclusion of ravidasvir on the core list of the EML, for use in combination with sofosbuvir, as a therapeutic alternative under the square box listing for pangenotypic direct-acting antivirals for the treatment of chronic HCV infection in adults.

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Dasabuvir, ombitasvir + paritaprevir + ritonavir, pegylated interferon alfa
(2a & 2b) – deletion – EML

Dasabuvir	**ATC code: J05AP09**
Ombitasvir + paritaprevir + ritonavir	**ATC code: J05AP53**
Pegylated interferon alfa (2a & 2b)	**ATC code: L03AB11/L03AB10**

Proposal

Deletion of dasabuvir; ombitasvir + paritaprevir + ritonavir; and pegylated interferon alfa 2a and 2b for the treatment of chronic hepatitis C virus (HCV) infection from the EML.

Applicant

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Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

EML/EMLc

EML

Section

6.4.4.2.2 Non-pangenotypic direct-acting antiviral combinations

6.4.4.2.3 Other antivirals for hepatitis C

Dose form(s) & strengths(s)

Dasabuvir – Tablet: 250 mg

Ombitasvir + paritaprevir + ritonavir – Tablet: 12.5 mg + 75 mg + 50 mg

Pegylated interferon alfa 2a – Vial or prefilled syringe: 180 micrograms

Pegylated interferon alfa 2b – Vial or prefilled syringe: 80 micrograms, 100 micrograms

Core/complementary

Core (dasabuvir, ombitasvir + paritaprevir + ritonavir)

Complementary (pegylated interferon alfa)

Individual/square box listing

Individual

Background

Pegylated interferon alfa has been included on the EML for use in combination with ribavirin for the treatment of chronic HCV infection since 2013. Dasabuvir and the fixed-dose combination of ombitasvir + paritaprevir + ritonavir were added in 2015.

Listings of antivirals on the EML for the treatment of chronic HCV infection were differentiated in 2019, to distinguish between pangenotypic and non-pangenotypic treatments. With pangenotypic regimens now recommended by WHO as the standard of care, the Expert Committee recommended that non-pangenotypic treatments could be considered for future deletion from the EML (*1*).

Public health relevance

It is estimated that 58 million people are chronically infected with HCV worldwide, with higher burdens in low and middle-income countries (*2*). However, in 2019 about 79% of people infected with HCV were unaware of their infection status and only about 13% of all infected people received treatment (*2*). An estimated 290 000 people died as a result of hepatitis C in 2019, mostly from liver cancer and cirrhosis caused by untreated HCV infections. In this context, the WHO goal is still to eliminate HCV as a public health threat by 2030, that is, a 90% reduction in chronic infections and 65% reduction in mortality compared to 2015.

Summary of evidence: benefits

In 2018, WHO issued updated guidelines on care and treatment of chronic HCV infection (*3*). Key changes made were the following.

- The adoption of a "treat all" approach: the use of safe and highly effective direct-acting antiviral regimens for all persons with HCV infection improves the balance of benefits and harms of treating persons with little or no fibrosis, thus supporting a strategy of treating all persons with chronic HCV infection, rather than reserving treatment for persons with more advanced disease.
- The recommendation for the use of three pangenotypic direct-acting antiviral regimens for the treatment of persons with chronic HCV infection aged 18 years and above:
  - sofosbuvir/velpatasvir 12 weeks
  - sofosbuvir/daclatasvir 12 weeks and
  - glecaprevir/pibrentasvir 8 weeks.

In 2022, this was updated to include adolescents and children down to the age of 3 years (*4,5*).

Since 2016, several new, pangenotypic direct-acting antiviral medicines had been approved by at least one stringent regulatory authority, reducing the need for genotyping to guide treatment decisions. A WHO-commissioned systematic review identified 142 clinical studies that evaluated the safety and efficacy of various direct-acting antiviral regimens approved by the United States Food and Drug Administration and the European Medicines Agency. In 2018, the Guidelines Development Group made a recommendation to use pangenotypic regimens for the treatment of HCV infection. The Guidelines Development Group acknowledged that the potential clinical benefits of pangenotypic regimens were similar to those of non-pangenotypic regimens. However, pangenotypic regimens present an opportunity to simplify the care pathway by removing the need for expensive genotyping and so simplifying procurement and supply chains. These regimens offer an important opportunity to facilitate treatment expansion worldwide. These factors shift the balance of benefits and harms in favour of the use of pangenotypic regimens. Interferon-based regimens also have low efficacy and are associated with considerable toxicity.

Summary of evidence: harms

Pegylated interferon alfa and ribavirin are associated with prominent side-effects during treatment and potentially irreversible long-term side-effects, such as thyroid disease, type 1 diabetes, ophthalmological complications and growth impairment in children (*5*).

WHO guidelines

Pegylated interferon alfa 2a and 2b and the non-pangenotypic regimen of dasabuvir with ombitasvir + paritaprevir + ritonavir are no longer recommended treatments in current WHO guidelines for treatment of chronic HCV infection (*3*,*4*).

Costs/cost–effectiveness

Not applicable

Availability

Not applicable

Other considerations

Dasabuvir, ombitasvir, paritaprevir and ritonavir have been removed from expressions of interest issued for WHO prequalification of active pharmaceutical ingredients and finished pharmaceutical products.

Committee recommendations

The Expert Committee noted that pangenotypic direct-acting antiviral regimens are now the standard for treatment of chronic HCV infection as recommended

in current WHO guidelines for treatment of HCV infection. They offer the advantages of simplifying the care pathway by removing the need for genotype testing and focusing procurement, thereby facilitating treatment expansion worldwide.

The Committee noted that dasabuvir, used in combination with ombitasvir + paritaprevir + ritonavir, is not a pangenotypic regimen. The Committee also noted that interferon-based regimens have low efficacy and are associated with significant toxicity. These treatments are no longer recommended in WHO guidelines.

The Committee therefore recommended the deletion from the EML of dasabuvir, ombitasvir + paritaprevir + ritonavir, and pegylated interferon alfa 2a and 2b from the core list of the EML.

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6.7 Medicines for Ebola virus disease

Anti-Ebola virus disease monoclonal antibodies – addition – EML and EMLc

Ansuvimab-zykl	**ATC code: J06BD04**
Atoltivimab + maftivimab + odesivimab-ebgn	**ATC code: not available**

Proposal

Addition of the monoclonal antibody therapeutics ansuvimab-sykl (mAb114) and atoltivimab + maftivimab + odesivimab-ebgn (REGN-EB3) to the core list of the EML and EMLc for the treatment of Ebola virus disease caused by *Zaire ebolavirus*.

Applicant

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Health Care Readiness

EML/EMLc

EML and EMLc

Section

6.7 Medicines for Ebola virus disease

Dose form(s) & strengths(s)

Ansuvimab-zykl – Powder for injection: 400 mg

Atoltivimab + maftivimab + odesivimab-ebgn – Injection: 241.7 mg + 241.7 mg + 241.7 mg in 14.5 mL vial

Core/complementary

Core

Individual/square box listing

Individual

Background

Anti-Ebola virus disease monoclonal antibodies have not previously been evaluated for inclusion on the Model Lists.

Public health relevance

Ebola virus disease (EVD) is a life-threatening disease caused by Ebola virus (*Zaire ebolavirus*). During early EVD, patients present with a non-specific febrile illness, followed by gastrointestinal signs and symptoms that frequently lead to hypovolaemia, metabolic acidosis, hypoglycaemia, and multiorgan failure (*1*). EVD case fatality is high, with a pooled case fatality rate of 60% (95% confidence interval (CI) 47% to 73%) in outbreaks from 2010 to 2020 (*2*). In recent years, several outbreaks of EVD have occurred in Africa, including the prolonged 2013–2016 outbreak in West Africa, outbreaks in the Democratic Republic of the Congo (2018–2020, 2020, 2021, 2022), and in Guinea (2021) (*3*).

Summary of evidence: benefits

The PALM study was a randomized, multicentre study of four investigational EVD therapeutics undertaken in the Democratic Republic of the Congo (*4*). All patients received standard care, which consisted of administration of intravenous fluids, daily clinical laboratory testing, correction of hypoglycaemia and electrolyte imbalances, and administration of broad-spectrum antibiotic agents and antimalarial agents as indicated. Patients were assigned in a 1:1:1:1 ratio to receive intravenous administration of the triple monoclonal antibody 2G4, 4G7, 13C6 (ZMapp; the control group), the antiviral remdesivir, the single mAb114, or the triple monoclonal antibody REGN-EB3. Patients of any age, including pregnant women, were eligible if they had a blood specimen positive for Ebola virus by real-time polymerase-chain-reaction (RT-PCR) assay. Neonates < 7 days of unconfirmed EVD status were also eligible if they were born to a mother with documented EVD. Patients were stratified according to baseline PCR cycle threshold values for the virus (≤ 22 versus > 22), with lower cycle threshold values corresponding to higher viral load. The primary endpoint was 28-day mortality.

A total of 681 patients were enrolled from 20 November 2018 to 9 August 2019. An interim analysis of data from 499 patients on 9 August 2019 led to the data and safety monitoring board recommending terminating random assignment to ZMapp and remdesivir on the basis of results showing that the REGN-EB3 group crossed an interim boundary for efficacy with respect to a surrogate endpoint for death at 28 days, and an analysis of mortality that showed clear differences between the mAb114 and REGN-EB3 groups and the ZMapp and remdesivir groups. A total of 673 patients were included in the primary analyses. At 28 days, 290 deaths had occurred (in 18.8% and 76.1% of patients with low and high viral loads, respectively).

The difference in 28-day mortality of mAb114 compared with ZMapp was −14.6 percentage points (95% confidence interval (CI) −25.2 to −1.7). The difference in 28-day mortality with REGN-EB3 compared with ZMapp was −17.8 percentage points (95% CI −28.9 to −2.9).

From an indirect comparison of mAb114 versus standard care, via ZMapp, informed by data from the PALM (*4*) and PREVAIL (*5*) studies, there was moderate-certainty evidence that mAb114 reduced mortality (relative risk (RR) 0.42, 95% CI 0.19 to 0.93). In absolute terms, this represents 229 fewer deaths per 1000 patients (95% CI 320 to 28 fewer) using the lowest baseline risk estimate, and 383 fewer deaths per 1000 patients (95% CI 535 to 46 fewer) using the highest baseline risk estimate (*6*).

From an indirect comparison of REGN-EB3 versus standard care, via ZMapp, informed by data from the PALM (*4*) and PREVAIL (*5*) studies, there was moderate-certainty evidence that REGN-EB3 reduced mortality (RR 0.40, 95% CI 0.18 to 0.89). In absolute terms, this represents 237 fewer deaths per 1000 patients (95% CI 324 to 43 fewer) using the lowest baseline risk estimate, and 396 fewer deaths per 1000 patients (95% CI 541 to 73 fewer) using the highest baseline risk estimate (*6*).

A direct comparison of REGN-EB3 versus mAb114 informed by data from the PALM study (*4*) showed low-certainty evidence of there being little or no difference between the two treatments for mortality outcomes (RR 0.96, 95% CI 0.71 to 1.29). In absolute terms, this represents 7 fewer deaths per 1000 patients (95% CI 48 fewer to 48 more) using the lowest baseline risk estimate, and 11 fewer deaths per 1000 patients (95% CI 80 fewer to 80 more) using the highest baseline risk estimate (*6*).

Summary of evidence: harms

Adverse events that were reported in >10% of patients in the PALM trial from a predefined list of signs and symptoms that occurred during mAb114 and REGN-EB3 infusion are shown in Table 16. The adverse event profiles in adult and paediatric participants treated with mAb114 or REGN-EB3 were similar.

The evaluation of adverse events in participants may have been confounded by the signs and symptoms of the underlying Zaire ebolavirus infection.

Table 16

Adverse events occurring during infusion in > 10% of adult and paediatric participants in the PALM trial

Adverse event	% of participants		
	mAb114 (*7*) (*n* = 173)	REGN-EB3 (*8*) (*n* = 154)	Control (*n* = 168)
Pyrexia	17	54	58
Tachycardia	9	39	32
Diarrhoea	9	20	18

Table 16 *continued*

Adverse event	% of participants		
	mAb114 (*7*) (*n* = 173)	REGN-EB3 (*8*) (*n* = 154)	Control (*n* = 168)
Vomiting	8	19	23
Hypotension	8	19	31
Tachypnoea	6	15	28
Chills	5	11	33
Hypoxia	3	10	11

mAb114: monoclonal antibody ansuvimab-sykl; REGN-EB3: atoltivimab + maftivimab + odesivimab-ebgn.

WHO guidelines

The 2022 WHO guideline on therapeutics for Ebola virus disease includes a strong recommendation for treatment with either mAb114 or REGN-EB3 for patients with RT-PCR confirmed EVD and for neonates of unconfirmed EVD status, 7 days old or younger, born to mothers with confirmed EVD. The recommendation applies only to EVD caused by Ebola virus (*Zaire ebolavirus*) (*6*).

Costs/cost–effectiveness

The price of the two therapeutics is currently unknown. No cost–effectiveness studies have been undertaken.

Availability

Both mAb114 (Ridgeback Pharmaceuticals) and REGN-EB3 (Regeneron) have regulatory approval from the United States Food and Drug Administration (*7,8*). As of 1 October 2022, no commercial product is available. The two therapeutics are currently used under an expanded access/compassionate use protocol.

In 2021, given the evidence of efficacy of the two therapeutics, WHO opened an expression of interest to manufacturers of the therapeutics for product evaluation and prequalification (*9*). As of March 2023, no therapeutics for EVD have been prequalified by WHO.

The International Coordinating Group agreed in October 2021 to build a stockpile of the two therapeutics with 5000 treatments. However, no commercial batches are available. WHO procurement issued a Request for Quotations and invited the two manufacturers to make offers. Ridgeback Pharmaceuticals responded that the company does not have the capacity to produce mAb114 commercially and is in the process of agreeing a commercial partner to produce it, and it is estimated to be on the market in 2024/2025. Regeneron has not yet submitted an offer.

The United States government's Biomedical Advanced Research and Development Authority has an agreement with Regeneron to procure REGN-EB3 for the US National Strategic Stockpile.

Committee recommendations

The Expert Committee accepted that effective treatments for EVD are of public health relevance, particularly in the context of outbreaks. EVD caused by *Zaire ebolavirus* is a life-threatening disease with a high case-fatality rate for which early diagnosis and initiation of treatment are essential to reduce mortality.

The Committee agreed that although limited, the clinical trial evidence for mAb114 and REGN-EB3 demonstrated important reductions in mortality at 28 days, and that evidence from indirect comparisons of the two therapeutics suggested little or no difference in mortality outcomes between them. The Committee also noted that based on the same evidence presented in the application, the 2022 WHO guidelines on therapeutics for EVD include a strong recommendation for treatment with either of these therapeutics, with the choice of which agent to use depending on availability.

The Committee noted with concern that access to these therapeutics is challenging, with no current commercial availability and supply only through expanded access or compassionate use protocols. Furthermore, the price of these agents is unknown and no cost–effectiveness studies have been undertaken. Since late 2021, mAb114 and REGN-EB3 have been included in an expression of interest to manufacturers for WHO prequalification, but to date, no products have been prequalified. Additionally, efforts made by WHO to build a stockpile of the two therapeutics, through requests for quotations from the two manufacturers, have not yet been successful. The Committee requested an update on availability for review in 2025.

The Committee considered that inclusion of these therapeutics on the Model Lists represents a strong equity and advocacy message, fully aligned with WHO guidelines, which could contribute to broader actions being undertaken to ensure reliable and affordable access to quality-assured therapeutics for EVD.

The Expert Committee therefore recommended the addition of the monoclonal antibodies mAb114 (ansuvimab-sykl) and REGN-EB3 (atoltivimab + maftivimab + odesivimab-ebgn) to the core list of the EML and EMLc, in a new subsection on medicines for EVD, for the treatment of EVD caused by *Zaire ebolavirus* in patients (adults and children) with confirmed EVD, and in neonates of unconfirmed infection status aged 7 days or younger, born to mothers with confirmed infection.

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6.8 Medicines for COVID-19

Data from 11 January 2023 report that globally, cumulative cases of COVID-19 were more than 660 million, with almost 6.7 million deaths (*1*). Vaccination is having a substantial impact on hospitalizations and deaths in a number of high-income countries, but limitations in global access to COVID-19 vaccines mean that many populations remain vulnerable. More effective treatments for COVID-19 are still needed.

The Expert Committee considered five applications for inclusion of medicines for COVID-19 on the Model Lists: baricitinib, molnupiravir, nirmatrelvir and ritonavir, remdesivir, and tocilizumab. Summaries of the evidence presented and considered by the Expert Committee for each medicine are in the following sections. The recommendations made by the Expert Committee are applicable to all proposed medicines and are presented below.

Committee recommendations

The Expert Committee noted that the evidence presented in the applications for each medicine was the same as that considered by the WHO Guideline Development Group for COVID-19 therapeutics, which informed the following recommendations in WHO living guidelines for COVID-19 (*2*).

- Baricitinib: strong recommendation for the use of baricitinib for patients with severe or critical COVID-19
- Molnupiravir: conditional recommendation for use of molnupiravir for treatment of patients with non-severe COVID-19 at highest risk of hospitalization
- Nirmatrelvir and ritonavir: strong recommendation for the use of nirmatrelvir and ritonavir for treatment of patients with non-severe COVID-19 at highest risk of hospitalization
- Remdesivir: conditional recommendation for the use of remdesivir for treatment of patients with non-severe COVID-19 at highest risk of hospitalization or with severe COVID-19
- Tocilizumab: strong recommendation for the use of IL-6 inhibitors (namely tocilizumab and sarilumab) for adults and children with severe or critical COVID-19

Given the global recognition of the need for effective therapeutics to prevent and treat COVID-19, as well as the need to ensure adequate and affordable access globally to these treatments, the Expert Committee recommended that effective and safe therapeutics for COVID-19 be considered as essential medicines and therefore be prioritized by countries for national selection and procurement.

The Expert Committee acknowledged that new variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have emerged, and continue to emerge, affecting the epidemiology, clinical characteristics and, most importantly, the response to treatment of the disease. The Committee considered that predicting how mutations carried by new virus variants modify the response to available treatments is difficult, if not impossible. Furthermore, the evolution of the pathogen combined with the evolving immunity in the population over time (through previous natural infection or vaccination) may influence the severity of the disease, thus potentially affecting the relative and absolute benefits associated with the use of COVID-19 therapeutics. Data on COVID-19 and hospitalization rates are fluctuating, with countries reporting surges, often in association of new variants or subvariants. However, the Committee noted that increases in COVID-19 cases do not always lead to increased severity of the disease or hospital admissions. COVID-19 data have shown lower hospitalization rates in more recent waves compared with previous ones (*3*). Nevertheless, new variants may further mutate and potentially cause more severe disease.

With this in mind, the Committee considered that the advantages of adding a medicine for the treatment of COVID-19 to the Model Lists must be evaluated against potential risks. The WHO Model Lists are updated every 2 years and national essential medicines lists are often updated less frequently. In the context of rapidly evolving public health emergencies, there is therefore a risk of including a medicine on the Model Lists that later has to be removed because it is no longer relevant for the reasons outlined above, a scenario that should be avoided. The Committee considered that WHO's timeline and process of selecting essential medicines is not ideally suited to rapidly evolving public health emergencies, where the prioritization of health care interventions needs to be adjusted according to the evolving evidence base. The Committee recognized the important role of WHO and national guidelines as tools for countries to orient prioritization of medicines during public health emergencies.

The Committee also commended the role of adaptive trial platforms as a basis to guide clinical decision-making during a public health emergency. During the COVID-19 pandemic, adaptive platform trials were rapidly created at national (e.g. RECOVERY) and international (e.g. Solidarity) levels, which contributed to the generation of evidence on critically relevant outcomes, such as preventing deaths or hospitalizations. These adaptive trial platforms were characterized by high external and internal validity, prioritization of relevant research questions and use of robust methods. These elements contributed to the rapid implementation of their results in routine clinical care. The Committee encouraged the strengthening of national infrastructure to successfully conduct adaptive platform trials, noting that their use need not be limited to public health emergencies, but should also be extended to other priority health care questions.

The Expert Committee therefore recommended that a new section be added to the EML and EMLc for COVID-19 therapeutics, but that individual medicines should not be specifically listed. Rather, the Committee recommended that this section of the Model Lists should serve to direct national decision-makers to the WHO living guidelines for COVID-19 therapeutics, which are being revised and updated regularly. Importantly, these living guidelines also include recommendations for the use of other medicines already included on the Model Lists (e.g. dexamethasone, oxygen), as well as recommendations against the use of medicines that are included on the Model Lists for other indications (e.g. hydroxychloroquine, lopinavir-ritonavir).

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Baricitinib – addition – EML and EMLc

Baricitinib	ATC code: L04AA37

Proposal

Addition of baricitinib to the complementary list of the EML and EMLc for the treatment of patients with severe or critical COVID-19.

Applicant

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WHO technical department

Country Readiness Strengthening

EML/EMLc

EML and EMLc

Section

6.8 Medicines for COVID-19

Dose form(s) & strengths(s)

Tablet: 2 mg, 4 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Baricitinib has not previously been evaluated for inclusion on the Model Lists.

Summary of evidence: benefits

Evidence for the benefits of baricitinib for severe or critical COVID-19 was derived from a living network meta-analysis considered by the WHO Guideline Development Group for COVID-19 therapeutics (*1*). The meta-analysis included four randomized trials comparing baricitinib with usual care in 10 915 adult patients in the hospital setting (*2–5*). There was high-certainty evidence that baricitinib reduced mortality (odds ratio (OR) 0.83, 95% confidence interval (CI) 0.74 to 0.93). In absolute terms, this represents 20 fewer deaths per 1000 people

(95% CI 8 fewer to 30 fewer). There was also moderate-certainty evidence that treatment with baricitinib reduced mechanical ventilation (OR 0.89, 95% CI 0.80 to 0.99), duration of hospitalization (mean difference (MD) 1.4 fewer days, 95% CI 2.4 to 0.4 fewer), and duration of mechanical ventilation (MD 3.2 fewer days, 95% CI 5.9 to 0.5 fewer).

Additionally, a subgroup analysis based on one study of 2659 patients already receiving treatment with interleukin (IL) inhibitors showed an independent mortality benefit of treatment with baricitinib (OR 0.79, 95% CI 0.63 to 0.97), representing 24 fewer deaths per 1000 people (*2*).

A 2022 Cochrane systematic review of six randomized trials (11 145 participants) compared systemic Janus kinase inhibitors plus usual care to usual care alone in hospitalized patients with moderate-to-severe COVID-19 (*6*). Baricitinib was the most often evaluated Janus kinase inhibitor (four studies, 10 815 participants). The authors concluded that there was moderate-certainty evidence that systemic Janus kinase inhibitors decreased all-cause mortality at up to day 28 (risk ratio (RR) 0.72, 95% CI 0.57 to 0.91).

Summary of evidence: harms

From the meta-analysis considered by the WHO Guideline Development Group, there was moderate-certainty evidence that treatment with baricitinib resulted in little or no increase in serious adverse events (*1*).

The Cochrane review found moderate-certainty evidence from three studies (1885 participants) of little or no difference in the rate of adverse events (any grade) with Janus kinase inhibitors compared with placebo (RR 0.97, 95% CI 0.88 to 1.08). For serious adverse events, there was moderate-certainty evidence from four studies (2901 participants) of a decreased risk for serious adverse events in patients treated with Janus kinase inhibitors compared with placebo (RR 0.79, 95% CI 0.68 to 0.92). There was low-certainty evidence from four studies (10 041 participants) of little or no difference in the rate of secondary infection between treatment with Janus kinase inhibitors and standard of care (*6*).

WHO living guidelines for COVID-19 note that risks of immunosuppression exist, particularly when multiple immunosuppressants are used concurrently (e.g. baricitinib with corticosteroids and IL-6 inhibitors). The guidelines also noted that the risk of serious bacterial and fungal infections may vary considerably across settings depending on the background prevalence of other infections (e.g. tuberculosis). The Guideline Development Group noted that this risk may not be so important given the short course of baricitinib treatment for COVID-19, but that evidence was currently limited because of the narrow geographic spread of the trials included and short follow-up periods (*1*).

The most common adverse events associated with baricitinib when used in chronic conditions and for durations not representative of use when indicated

for treatment of COVID-19 are increased low-density lipoprotein cholesterol (26.0%), upper respiratory tract infections (16.9%), headache (5.2%), herpes simplex infection (3.2%) and urinary tract infections (2.9%) (*7*).

Another Janus kinase inhibitor, tofacitinib, has been associated with serious adverse events, including heart attack or stroke, cancer, blood clots and death (*8*). However, data from randomized trials evaluating the safety of short-term use of baricitinib in patients with COVID-19 have not shown any significant safety signals, including thrombosis.(*2–4,9*).

WHO guidelines

The WHO therapeutics and COVID-19 living guideline, 13 January 2023 includes a strong recommendation for the use of baricitinib for patients with severe or critical COVID-19 (1). The applicability of this recommendation to children is still uncertain, as none of the randomized controlled trials considered by the WHO Guideline Development Group enrolled children.

Costs/cost–effectiveness

No formal cost–effectiveness analysis was conducted as part of the WHO guideline development process. The high cost of baricitinib compared with other candidate treatments for COVID-19 was noted by the Guideline Development Group, along with concerns about access and exacerbation of health inequity, particularly in resource-constrained areas (*1*).

Non-peer-reviewed work by researchers from Harvard University estimated the cost of generic baricitinib to be US$ 2 per treatment course (4 mg daily x 14 days), compared with the list price from Eli Lilly of US$ 1109.92 per treatment course (*10*).

Availability

Currently, baricitinib is provided commercially by Eli Lilly, which has been granted patents in more than 50 countries. It is included on the 8th expression of interest for prequalification of COVID-19 therapeutics. As of April 2023, no baricitinib products are prequalified by WHO.

Baricitinib is not currently the subject of licensing agreements between the patent holder and the Medicines Patent Pool. It is not being procured through the ACT Accelerator programme at this time.

Other considerations

Baricitinib has been authorized for emergency use by the United States Food and Drug Administration for treatment of COVID-19 in hospitalized paediatric patients (aged 2 to < 18 years) requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (*11*).

Committee recommendations

See beginning of section 6.8 Medicines for COVID-19.

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Molnupiravir – addition – EML

Molnupiravir	ATC code: J05AB18

Proposal

Addition of molnupiravir to the core list of the EML for the treatment of adult patients with non-severe COVID-19 at highest risk of hospitalization.

Individuals at highest risk of hospitalization are those older than 60 years, those with immunosuppression and/or chronic disease and those unvaccinated against COVID-19.

Applicant

Clinical Management Unit; WHO Department of Country Readiness Strengthening, Geneva, Switzerland

WHO technical department

Country Readiness Strengthening

EML/EMLc

EML

Section

6.8 Medicines for COVID-19

Dose form(s) & strengths(s)

Capsule: 200 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Molnupiravir has not previously been evaluated for inclusion on the Model Lists.

Summary of evidence: benefits

Evidence for the benefits of molnupiravir for non-severe COVID-19 is derived from a living network meta-analysis considered by the WHO Guideline Development Group for COVID-19 therapeutics (*1*). The meta-analysis included six studies comparing molnupiravir plus usual care with usual care alone in 4796 adult patients with non-severe COVID-19 in the outpatient setting.

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There was moderate-certainty evidence that treatment with molnupiravir reduced hospital admissions (odds ratio (OR) 0.54, 95% confidence interval (CI) 0.30 to 0.89). In absolute terms, among highest risk patients, this represents 43 fewer hospital admissions per 1000 people (95% CI 68 to 10 fewer). There was also moderate-certainty evidence that molnupiravir reduced time to symptom resolution (mean difference (days) 3.4 fewer, 95% CI 4.8 to 1.7 fewer), and low-certainty evidence that molnupiravir reduced mortality (OR 0.06, 95% CI 0 to 0.4). The effect of molnupiravir on mechanical ventilation was very uncertain.

Summary of evidence: harms

From the meta-analysis considered by the WHO Guideline Development Group, there was high-certainty evidence of no important difference between molnupiravir and placebo in adverse effects leading to drug discontinuation (*1*).

Another rapid review and meta-analysis (four randomized controlled trials, 1823 participants) investigated adverse events associated with molnupiravir (*2*). No significant difference was found between molnupiravir 800 mg and placebo for the outcomes of any adverse events (risk ratio (RR) 0.94, 95% CI 0.83 to 1.06), serious adverse events (RR 0.80, 95% CI 0.59 to 1.08) and adverse events leading to death (RR 0.47, 95% CI 0.17 to 1.28). In each case, rates of adverse events were numerically lower in patients treated with molnupiravir.

More common adverse events associated with molnupiravir include dizziness, headache, diarrhoea, nausea and vomiting.

Insufficient data are available to ascertain how high the barrier to resistance is with SARS-CoV-2 for molnupiravir. Based on experiences with other nucleoside antiviral drugs, molnupiravir will place a selective pressure for viral resistance mutations within an individual, with the potential to spread at a population level.

It has been proposed that random mutagenesis arising from the molnupiravir mechanism of action might increase diversity in the viral sequences that may result in more rapid emergence of new variants (*3*). Unlike in the considerations for resistance, no conceptual basis exists for molnupiravir placing a selective pressure on emergence of new variants. Sequence variation is lower as molnupiravir is only incorporated in place of two of the four nucleotide bases in the genome rather than in place of any nucleotide. No direct evidence is available to support or refute the variants hypothesis; as such the risk is currently unquantifiable.

The rate of resistance emergence and the risk of additional diversity in the viral genome leading to new variants were acknowledged by the Guideline Development Group to be higher with a higher number of patients receiving the intervention.

Non-clinical safety

The Guideline Development Group reviewed publicly available data on non-clinical safety of molnupiravir from the United States Food and Drug Administration (*4*), highlighting the following safety concerns.

- Genetic toxicology data demonstrated that molnupiravir is mutagenic in vitro, but there was no evidence of mutagenicity in animal models. The Guideline Development Group acknowledged uncertainties in the existing data and concluded that based on the available information, molnupiravir may or may not be carcinogenic in humans.

- An increase in thickness of growth plate associated with decreased bone formation was observed in rapidly growing rats but not in mice, rats or dogs. The Guideline Development Group determined that molnupiravir should not therefore be administered to paediatric patients.

- Importantly, low concentrations of β-D-N4-hydroxycytidine (0.09% maternal exposures) were detectable in 10-day-old rat pups suggesting that NHC is present in breast milk. The Guideline Development Group determined molnupiravir should not be administered to breastfeeding women.

- In developmental and reproductive toxicology assessments, reduced fetal body weights were observed in rats and rabbits, with higher exposures also being associated with embryo-fetal lethality and teratogenicity in rats. Accordingly, molnupiravir should not be administered during pregnancy.

- No data on spermatogenesis were available, which may be particularly prone to the effect of a mutagen in adult males. No data are available to quantify the consequences of this effect on an embryo/fetus conceived by fathers who were receiving or had recently received molnupiravir.

WHO guidelines

The WHO Therapeutics and COVID-19 Living Guideline includes a conditional recommendation for use of molnupiravir for treatment of patients with non-severe COVID-19 at highest risk of hospitalization, excluding pregnant and breastfeeding women, and children (*1*).

The Guideline Development Group noted that the absolute benefits of molnupiravir on hospital admission depend on the prognosis. The group defined a threshold of a 6% absolute reduction in hospital admission to represent what

most patients would value as an important benefit. Molnupiravir would exert such a benefit in patients at highest risk of hospitalization (above 10% baseline risk), such as people without COVID-19 vaccination, older people or those with immunodeficiencies and/or chronic diseases. The conditional recommendation for the use of molnupiravir in people at highest risk reflects this threshold: 60 fewer hospitalizations per 1000 patients, and a greater anticipated absolute survival benefit, although this was not possible to quantify in the absence of data.

The guideline states that molnupiravir should not be given to pregnant or breastfeeding women or to children. In case of doubt about pregnancy, a pregnancy test should be performed before starting treatment. If a woman of childbearing age is considered for treatment, counselling on birth control during treatment and for 4 days after the last dose of molnupiravir should be facilitated. Men planning to conceive should be advised on the potential for temporary genotoxic effect on sperm cell production, and those who are sexually active with females should be counselled to use birth control during treatment and for at least 3 months after the last dose of molnupiravir. The unknown long-term risk of genotoxicity is likely to be higher in younger patients than older patients; thus use in younger adults who are not at high risk should be limited.

Costs/cost–effectiveness

No formal cost–effectiveness analysis was conducted as part of the WHO guideline development process, nor presented in the application.

The application cited non-peer-reviewed estimates from Harvard University, which estimate generic costs of molnupiravir to be US$ 14.16 for a treatment course, compared with the price per course of US$ 700 in the United States (*5*).

Availability

Molnupiravir is under patent by Merck Sharp & Dohme. Two generic brands of molnupiravir 200 mg capsules were prequalified by WHO in late 2022.

The Medicines Patent Pool and Merck Sharp & Dohme signed a voluntary licensing agreement in October 2021 to facilitate global access to generic molnupiravir. To date, the Medicines Patent Pool has signed agreements with 27 generic manufacturers to provide molnupiravir in 105 low- and middle-income countries (*6*).

Committee recommendations

See beginning of section 6.8 Medicines for COVID-19.

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Nirmatrelvir and ritonavir – addition – EML and EMLc

Nirmatrelvir and ritonavir	**ATC code: J05AE30**

Proposal

Addition of nirmatrelvir and ritonavir to the core list of the EML and EMLc for the treatment of patients aged 12 years and older with non-severe COVID-19 at highest risk of hospitalization.

Individuals at highest risk of hospitalization are those older than 60 years, those with immunosuppression and/or chronic disease, and those unvaccinated against COVID-19.

Applicant

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WHO technical department

Country Readiness Strengthening

EML/EMLc

EML and EMLc

Section

6.8 Medicines for COVID-19

Dose form(s) & strengths(s)

Tablet: 150 mg + 100 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Nirmatrelvir and ritonavir have not previously been evaluated for inclusion on the Model Lists.

Summary of evidence: benefits

Evidene for the benefits of nirmatrelvir and ritonavir for non-severe COVID-19 is derived from a living network meta-analysis considered by the WHO Guideline

Development Group for COVID-19 therapeutics (*1*). The meta-analysis included data from two randomized trials (EPIC-SR and EPIC-HR (unpublished)) comparing nirmatrelvir and ritonavir with placebo in 3100 non-hospitalized patients with non-severe COVID-19.

For the outcome of hospital admission at 28 days, there was moderate-certainty evidence that nirmatrelvir and ritonavir reduced hospitalization compared with placebo (odds ratio (OR) 0.15, 95% confidence interval (CI) 0.06 to 0.38), or 30 fewer hospital admissions per 1000 patients (95% CI 33 to 21 fewer) in absolute terms, using the baseline risk in the trials. Subgroup analyses of patients with higher baseline risk were performed which showed moderate-certainty evidence of greater absolute benefits for nirmatrelvir and ritonavir: 51 fewer hospital admissions per 1000 (95% CI 56 to 36 fewer) for patients with higher baseline risk and 84 fewer hospital admissions per 1000 (95% CI 93 to 59 fewer) for patients with the highest risk. There was low-certainty evidence that nirmatrelvir and ritonavir had little or no effect on mortality at day 28 (OR 0.04, CI 95% 0 to 0.67).

Summary of evidence: harms

From the living network meta-analysis, there was high-certainty evidence that nirmatrelvir and ritonavir had little or no risk of adverse effects leading to drug discontinuation compared with placebo (2.1% versus 4.2%; OR 0.48, 95% CI 0.29 to 0.80) (*1*). Subsequent real-world data have shown higher rates of adverse effects for nirmatrelvir and ritonavir of 17.5% in very small (*n* = 50) cohorts (*2*).

The combination of nirmatrelvir and ritonavir is associated with multiple possible dangerous drug interactions, especially through CYP3A inhibition. The use of nirmatrelvir and ritonavir may lead to the development of resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection (*3*).

A 2022 Cochrane systematic review (one randomized controlled trial (*4*), 2246 participants) assessed the safety of nirmatrelvir and ritonavir (*5*). The review found moderate-certainty evidence of little or no effect of nirmatrelvir and ritonavir compared with standard of care plus placebo on treatment-emergent adverse events (any grade) (risk ratio (RR) 0.95, 95% CI 0.82 to 1.10), and moderate-certainty evidence that nirmatrelvir and ritonavir increased treatment-related adverse events (mainly dysgeusia and diarrhoea) compared with standard of care plus placebo (RR 2.06, 95% CI 1.44 to 2.95). Compared with placebo, there was moderate-certainty evidence that nirmatrelvir and ritonavir decreased discontinuation of the study drug due to adverse events (RR 0.49, 95% CI 0.30 to 0.80). No study results were identified for improvement of clinical status, quality of life or viral clearance.

The combination of nirmatrelvir and ritonavir is contraindicated in patients with a history of clinically significant hypersensitivity to the active ingredients and in patients with severe hepatic and renal impairment.

WHO guidelines

The WHO Therapeutics and COVID-19 Living Guideline includes a strong recommendation for the use of nirmatrelvir and ritonavir for treatment of patients with non-severe COVID-19 at highest risk of hospitalization (excluding pregnant and breastfeeding women, and children) (*6*).

The Guideline Development Group considered that the combination of nirmatrelvir and ritonavir was a superior choice to alternatives because it may have greater efficacy in preventing hospitalization. Additionally, it is associated with fewer harms than molnupiravir and does not require intravenous administration as do remdesivir and monoclonal antibodies.

Costs/cost–effectiveness

No formal cost–effectiveness analysis was conducted as part of the WHO guideline development process, nor presented in the application.

The application cited non-peer-reviewed estimates from Harvard University which estimate costs for generic nirmatrelvir and ritonavir to be US$ 73.15 per treatment course, compared with the price per course of US$ 530 in the United States (*7*).

Availability

Nirmatrelvir + ritonavir manufactured by Pfizer Limited (the patent holder) was prequalified by WHO in April 2022. A generic brand manufactured by Hereto Labs Ltd was prequalified by WHO in December 2022.

The Medicines Patent Pool and Pfizer signed a voluntary licensing agreement in November 2021 to facilitate affordable access of nirmatrelvir and ritonavir in 95 countries through 35 sublicensed generic manufacturers worldwide (*8*). Under this agreement, Pfizer will not receive royalties from sales of nirmatrelvir from the Medicines Patent Pool sublicensees while COVID-19 remains classified as a Public Health Emergency of International Concern by WHO. After the pandemic period, sales to low-income countries will remain royalty-free, while lower middle-income countries and upper middle-income countries will be subject to a 5% royalty for sales to the public sector and a 10% royalty for sales to the private sector.

Committee recommendations

See beginning of section 6.8 Medicines for COVID-19.

References

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Remdesivir – addition – EML and EMLc

Remdesivir	ATC code: J05AB16

Proposal

Addition of remdesivir to the complementary list of the EML and EMLc for the treatment of patients with non-severe COVID-19 at highest risk of hospitalization, or with severe COVID-19.

Individuals at highest risk of hospitalization are those older than 60 years, those with immunosuppression and/or chronic disease, and those unvaccinated against COVID-19.

Applicant

Clinical Management Unit, WHO Department of Country Readiness Strengthening, Geneva, Switzerland

WHO technical department

Country Readiness Strengthening

EML/EMLc

EML and EMLc

Section

6.8 Medicines for COVID-19

Dose form(s) & strengths(s)

Powder for injection: 100 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Remdesivir has not previously been evaluated for inclusion on the Model Lists.

Summary of evidence: benefits

Evidence for the benefits of remdesivir for non-severe and severe COVID-19 is derived from a living network meta-analysis considered by the WHO Guideline Development Group for COVID-19 therapeutics (*2*).

Non-severe COVID-19

The meta-analysis included data from five randomized trials (2709 participants) comparing remdesivir with usual care in non-hospitalized patients with non-severe COVID-19.

For the outcome of hospital admission at 28 days, there was moderate-certainty evidence that treatment with remdesivir reduced hospitalization compared with the usual care (odds ratio (OR) 0.25, 95% confidence interval (CI) 0.06 to 0.88; one randomized control trial, 5632 participants) or 26 fewer hospital admissions per 1000 patients (95% CI 33 to 4 fewer), using the baseline risk in the trials. Subgroup analyses for patients with higher baseline risk were performed which showed moderate-certainty evidence of greater absolute benefits for remdesivir – 44 fewer hospital admissions per 1000 (95% CI 56 to 7 fewer) for patients with higher baseline risk and 73 fewer hospital admissions per 1000 (95% CI 93 to 11 fewer) for highest risk. There was low-certainty evidence of no important difference between remdesivir and usual care for the outcome of mortality at day 28 (OR 0.68, CI 95% 0.39 to 1.21; five randomized control trials, 2709 participants). The effect of remdesivir on mechanical ventilation and time to symptom resolution was very uncertain.

Severe COVID-19

The meta-analysis included data from five randomized trials (6631 participants) comparing remdesivir with usual care in patients with severe COVID-19.

For the outcome of mechanical ventilation, there was moderate-certainty evidence that remdesivir reduced mechanical ventilation compared with usual care (OR 0.87, 95% CI 0.77 to 0.99; five randomized control trials, 6620 participants), or 14 fewer mechanical ventilation events per 1000 patients (95% CI 24 to 1 fewer) in absolute terms. For the outcome of mortality, there was low-certainty evidence that remdesivir reduced mortality (OR 0.89, 95% CI 0.78 to 1.02) with 13 fewer deaths (95% CI 26 fewer to 2 more) in absolute terms. There was moderate-certainty evidence of there being no important difference between treatment groups for the outcome of time to symptom improvement.

A 2021 Cochrane systematic review (five randomized control trials, 7452 participants) evaluated remdesivir in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (3). The review found moderate-certainty evidence of little or no effect of remdesivir on all-cause mortality up to day 28 – risk ratio (RR) 0.93, 95% CI 0.81 to 1.06; risk difference (RD) 8 fewer deaths per 1000 patients, 95% CI 21 fewer to 7 more; four studies, 7142 participants. There was limited evidence of a beneficial effect of remdesivir on mortality in a subset of 435 participants who received low flow oxygen at baseline in one study (RR 0.32, 95% CI 0.15 to 0.66), but no corroborative data in other studies. There was low-certainty evidence that

remdesivir reduced the need for invasive mechanical ventilation (RR 0.56, 95% CI 0.41 to 0.77; 67 fewer events per 1000 participants; two studies, 1159 participants).

Summary of evidence: harms

A 2022 systematic review and meta-analysis evaluating adverse effects of remdesivir, hydroxychloroquine and lopinavir/ritonavir for COVID-19 included two studies (1281 participants) (*4*). The review found low-certainty evidence that compared with placebo or standard care, remdesivir had no important effect on the risk of acute renal injury (OR 0.85, 95% CI 0.51 to 1.41) or cognitive dysfunction/delirium (OR 1.22, 95% CI 0.48 to 3.11).

The 2021 Cochrane systematic review found moderate-certainty evidence from three randomized control trials (1674 participants) that remdesivir decreased the rate of serious adverse events at up to 28 days (RR 0.75, 95% CI 0.63 to 0.90; RD 63 fewer events per 1000 patients, 95% CI 94 to 25 fewer). There was low-certainty evidence of any adverse events – RR 1.05, 95% CI 0.86 to 1.27; RD 29 more events per 1000 participants, 95% CI 82 fewer to 158 more) (*3*).

WHO guidelines

The WHO Therapeutics and COVID-19 Living Guideline (*5*) includes:

- a conditional recommendation for use of remdesivir for treatment of patients with non-severe COVID-19 at highest risk of hospitalization, and
- a conditional recommendation for use of remdesivir for treatment of patients with severe COVID-19.

With regard to the recommendation for patients with non-severe COVID-19, the Guideline Development Group considered that nirmatrelvir + ritonavir was a superior choice to alternatives because it may have greater efficacy in preventing hospitalization. Additionally, it is associated with fewer harms than molnupiravir and does not require intravenous administration as do remdesivir and monoclonal antibodies.

The guidelines also note that none of the included remdesivir randomized controlled trials enrolled children or pregnant women, therefore the applicability of the recommendations to these groups is uncertain.

Costs/cost–effectiveness

No formal cost–effectiveness analysis was conducted as part of the WHO guideline development process, nor presented in the application.

The application reported that the commercial costs of a 10-day course of remdesivir in 2020 was US$ 4680.

Availability

Remdesivir manufactured by Gilead Sciences (the patent holder) was prequalified by WHO in April 2022. Other patent applications have been made by other entities in various regions including China (*6*).

Remdesivir is not currently the subject of licensing agreements between the patent holder and the Medicines Patent Pool.

Committee recommendations

See beginning of section 6.8 Medicines for COVID-19.

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Tocilizumab – addition – EML and EMLc

Tocilizumab	ATC code: L04AC07

Proposal

Addition of tocilizumab to the complementary list of the EML and EMLc for the treatment of patients with severe or critical COVID-19, with a square box to indicate sarilumab as a therapeutic alternative.

Applicant

Clinical Management Unit, WHO Department of Country Readiness Strengthening, Geneva, Switzerland

WHO technical department

Country Readiness Strengthening

EML/EMLc

EML and EMLc

Section

6.8 Medicines for COVID-19

Dose form(s) & strengths(s)

Injection: 80 mg/4 mL in 4 mL vial, 200 mg/10 mL in 10 mL vial, 400 mg/20 mL in 20 mL vial

Core/complementary

Complementary

Individual/square box listing

Square box listing for tocilizumab as the representative interleukin-6 (IL-6) receptor blocker, with sarilumab as a therapeutic alternative.

Background

Tocilizumab and sarilumab have not previously been evaluated for inclusion on the Model Lists for treatment of COVID-19.

Summary of evidence: benefits

A prospective meta-analysis of 27 randomized trials (10 930 participants) comparing IL-6 receptor blockers with standard care in hospitalized adult patients with COVID-19 showed high-certainty evidence that treatment with

IL-6 inhibitors reduced mortality (odds ratio (OR) 0.86, 95% confidence interval (CI) 0.79 to 0.95). In absolute terms, this represents 16 fewer deaths per 1000 people (95% CI 24 to 6 fewer) (*1*).

A living network meta-analysis of 30 randomized controlled trials (10 618 participants) considered by the WHO Guideline Development Group for COVID-19 therapeutics that compared IL-6 receptor blockers with standard care provided estimates of benefit for other important outcomes for patients (*2*). This included high-certainty evidence of a reduction in the need for mechanical ventilation in patients receiving IL-6 receptor blockers (OR 0.72, 95% CI 0.57 to 0.90) and low-certainty evidence that IL-6 receptor blockers reduced duration of mechanical ventilation (mean difference (MD) 1.2 lower, 95% CI 2.3 to 0.1 lower), and duration of hospitalization (MD 4.5 lower, 95% CI 6.7 to 2.3 lower).

The Guideline Development Group found that subgroup analyses indicated no effect modification based on choice of IL-6 receptor blocker (sarilumab or tocilizumab), nor disease severity (critical or severe). Subgroup analyses evaluating baseline corticosteroid use indicated that benefits were greater in patients also receiving corticosteroids compared with patients not receiving corticosteroids (*2*).

A 2021 Cochrane systematic review of nine randomized controlled trials (6428 participants) evaluating tocilizumab and two randomized controlled trials (880 participants) evaluating sarilumab compared with standard care in people with COVID-19 of any severity (*3*). The authors concluded that there was high-certainty evidence that tocilizumab reduced all-cause mortality at day 28 compared with standard care or placebo (risk ratio (RR) 0.89, 95% CI 0.82 to 0.97). The effect of sarilumab for this outcome was uncertain (RR 0.77, 95% CI 0.43 to 1.36).

Summary of evidence: harms

From the meta-analysis considered by the WHO Guideline Development Group, the occurrence of adverse events from IL-6 receptor blockers that led to treatment discontinuation was uncertain, while there was low-certainty evidence that IL-6 receptor blockers were not associated with an increase in secondary bacterial infections (*2*).

The Cochrane review found the effect of tocilizumab on (any) adverse events to be highly uncertain (RR 1.23, 95% CI 0.87 to 1.72; seven randomized controlled trials, 1534 participants). There was moderate-certainty evidence that tocilizumab resulted in slightly fewer serious adverse events than standard care or placebo (RR 0.89, 95% CI 0.75 to 1.06; eight randomized controlled trials, 2312 participants) (*3*). For sarilumab, the occurrence of serious adverse events was uncertain (RR 1.17, 95% CI 0.77 to 1.77; two randomized controlled trials, 2312 participants). The authors concluded that it is unlikely that sarilumab causes

an important increase in (any) adverse events (RR 1.05, 95% CI 0.88 to 1.25; one randomized controlled trials, 420 participants), however the possibility could not be excluded.

WHO guidelines

The WHO Therapeutics and COVID-19 Living Guideline includes a strong recommendation for the use of IL-6 receptor blockers tocilizumab and sarilumab for patients with severe and critical COVID-19 (*2*). The applicability of this recommendation to children is currently uncertain, as none of the randomized controlled trials considered by the WHO Guideline Development Group enrolled children. However, the Guideline Development Group had no reason to think that children with COVID-19 would respond any differently to treatment with IL-6 receptor blockers. It was noted that tocilizumab is safely used in children for other indications including polyarticular juvenile rheumatoid arthritis, systemic onset of juvenile chronic arthritis and chimeric antigen receptor T-cell induced cytokine release syndrome. If an IL-6 receptor blocker is used in children, tocilizumab is preferred.

Costs/cost–effectiveness

No formal cost–effectiveness analysis was conducted as part of the WHO guideline development process.

A United States analysis modelled the incremental cost–effectiveness ratio of adding tocilizumab to dexamethasone compared with dexamethasone alone as US$ 16 520 per quality-adjusted life-year (QALY) (95% credible interval (CrI) US$ 10 760 to 51 350) using trial-based probability of mortality. A sensitivity analysis using a lower absolute mortality rate without treatment produced an incremental cost–effectiveness ratio of US$ 26 840 per QALY (95% CrI 14 800 to 101 030). The authors concluded tocilizumab to be cost-effective (*4*).

Cost–effectiveness data for IL-6 receptor blockers for COVID-19 in low- and middle-income countries are lacking. Willingness-to-pay thresholds in these settings are lower than in the United States and other high-income countries.

Availability

Currently, tocilizumab is prequalified by WHO for use in COVID-19 and is provided commercially by the patent holder Roche. Roche has committed to provide up to 250 000 doses of tocilizumab at cost for distribution to low- and middle-income countries through the ACT-Accelerator programme (*5*).

Sarilumab is under patent by Sanofi Genzyme. It is included on the eighth expression of interest for prequalification of COVID-19 therapeutics. As of April 2023, no sarilumab products are prequalified by WHO.

Neither tocilizumab nor sarilumab are currently subjects of licensing agreements between the patent holders and the Medicines Patent Pool.

Committee recommendations

See beginning of section 6.8 Medicines for COVID-19.

References

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Section 8: Immunomodulators and antineoplastics
8.1 Immunomodulators for non-malignant disease
Methotrexate – new formulation – EML and EMLc

Methotrexate	ATC code: L04AX03

Proposal

Addition of subcutaneous injection formulations of methotrexate to the complementary list of the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate.

Applicant

Laboratorios Gebro Pharma, S.A., Barcelona, Spain

WHO technical department

Noncommunicable Diseases

EML/EMLc

EML and EMLc

Section

8.1 Immunomodulators for non-malignant disease

Dose form(s) & strengths(s)

Injection: 50 mg/mL in prefilled syringe or prefilled pen (various sizes)

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Methotrexate, in oral and parenteral formulations, is included in the EML and EMLc for use in the treatment of various cancers. Oral methotrexate is included as a disease-modifying anti-rheumatic medicine for use in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis.

Biological disease-modifying medicines (adalimumab, representative of the pharmacological class of tumour necrosis factor alfa (TNFa) inhibitors) are

included on the Model Lists for use in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and Crohn disease.

A separate application to the 2023 Expert Committee meeting requests inclusion of oral methotrexate on the EML and EMLc for the treatment of severe psoriasis.

Public health relevance

Between 1986 and 2014, the mean global point prevalence of rheumatoid arthritis was reported to be 0.56%, with regional differences in prevalence: 1.46% in north America, 0.80% in Africa, 0.53% in Europe, 0.46% in South America and 0.34% in Asia (*1*).

In the case of psoriasis, global prevalence varies widely. Prevalence in the overall population has been reported as 0.11% in east Asia, 1.58% in Australasia and 1.52% in western Europe. The estimated prevalence of psoriasis in Asian countries was reported to be much lower. Psoriasis occurs more frequently in adults than in children (*2*). The Global Burden of Disease study reported more than 4.6 million incident cases of psoriasis worldwide in 2019 (*3*). About 30% of psoriatic patients develop psoriatic arthritis (*4*).

No information was provided in the application on the prevalence of juvenile idiopathic arthritis, psoriatic arthritis or Crohn disease.

The Global Burden of Disease study reported about 4.9 million cases of inflammatory bowel disease worldwide, without differentiation between Crohn disease and ulcerative colitis (*5*).

Summary of evidence: benefits

Rheumatoid arthritis

The application presented only brief summaries of the findings of publications identified through a literature search. The following information has been elaborated by the Secretariat.

A 2016 systematic review and meta-analysis (seven studies, 1335 participants) compared subcutaneous versus oral methotrexate in the treatment of rheumatoid arthritis (*6*). Subcutaneous methotrexate was associated with greater improvements at 24 weeks in the American College of Rheumatology 20% (ACR20) and 70% (ACR70) responses: ACR20 odds ratio (OR) 1.68, 95% confidence interval (CI) 1.09 to 2.61; ACR70 OR 1.52, 95% CI 1.02 to 2.26; two randomized controlled trials, 467 participants). No significant difference was found in ACR50 response between treatment groups (OR 1.68, 95% CI 0.64 to 4.44). Two studies (535 participants) evaluated pain using visual analogue scale scores. Results showed that participants treated with subcutaneous methotrexate had better pain control (mean difference (MD) –0.65, 95% CI –0.93 to –0.37). Three studies (1163 participants) reported clinical failure and found no significant

difference between the subcutaneous and oral methotrexate treatment groups (OR 1.20, 95% CI 0.85 to 1.71).

A randomized crossover study (47 participants) compared the relative bioavailability, safety and tolerability of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis (*7*). Patients were assigned to receive methotrexate 10 mg, 15 mg, 20 mg and 25 mg a week in a random sequence of three treatments: orally, subcutaneous injection into the abdomen and subcutaneous injection into the thigh. Blood samples were collected for pharmacokinetic analysis and injection sites were assessed for 24 hours after administration. Systemic exposure of oral methotrexate plateaued at doses ≥ 15 mg/week, whereas systemic exposure of subcutaneous methotrexate increased linearly and was greater than oral methotrexate at each dose. Higher systemic methotrexate exposure with subcutaneous treatment was not associated with an increase in adverse events.

A randomized trial evaluated efficacy and tolerability of subcutaneous methotrexate for the treatment of rheumatoid arthritis in Japanese patients (*8*). Patients were randomized to receive 7.5 mg subcutaneous methotrexate (*n* = 52) or 8 mg oral methotrexate (*n* = 50) weekly for 12 weeks (part 1). Long-term (52 weeks) efficacy and safety of subcutaneous methotrexate (up to a maximum dose of 15 mg/week) was assessed in a second part of the trial. The primary efficacy endpoint was the ACR20 response rate at week 12, which was not significantly different between subcutaneous and oral treatment groups (59.6% versus 51.0%, respectively; difference 8.6, 95% CI −11.3 to 27.8).

A single 6-month prospective, randomized, phase IV trial compared the efficacy and safety of subcutaneous versus oral methotrexate in 284 patients with rheumatoid arthritis (*9*). Patients were randomized to receive 15 mg/week orally (*n* = 187) or subcutaneously (*n* = 188) for 24 weeks. The primary outcome was ACR20 response at 24 weeks. Subcutaneous methotrexate was associated with a significantly greater proportion of patients achieving ACR20 response (78% versus 70%) and ACR70 response (41% versus 33%) than oral methotrexate. No significant difference was observed between treatment groups for ACR50 response. Treatment was well tolerated, with a similar rate of adverse events in both treatment groups.

A 2016 narrative literature review identified 23 publications on the use of oral and subcutaneous methotrexate in the treatment of rheumatoid arthritis (*10*). Included publications were 10 systematic reviews/guidelines, six randomized trials, one prospective cohort study, four retrospective studies, one cost-minimization analysis and one expert opinion/editorial. The review authors reported that subcutaneous methotrexate had higher and less variable bioavailability than oral methotrexate, especially at medium-to-high dosages (> 15 mg/week). Clinical response, evaluated through Disease Activity Score-28 and American College of Rheumatology Criteria, was greater with subcutaneous

versus oral methotrexate, in both treatment-naïve patients and those switching from oral methotrexate because of treatment failure. Subcutaneous methotrexate was associated with fewer gastrointestinal side-effects, however other adverse effects were similar for the oral and subcutaneous routes. Evidence on the cost–effectiveness of subcutaneous versus oral methotrexate was not available, however, the review authors postulated that delaying the use of more aggressive and expensive therapies (e.g. biological disease-modifying anti-rheumatic medicines) might provide cost savings.

Another 2016 narrative literature review provided an overview of a change in patient preference from oral to subcutaneous methotrexate and benefits of subcutaneous over oral therapy in patients with arthritis (*11*). Several studies reported better clinical response in patients treated with subcutaneous versus oral methotrexate, which has been attributed to the more stable pharmacokinetics of subcutaneous treatment. Subcutaneous methotrexate was well tolerated and caused minimal gastrointestinal disturbances at higher doses. The authors of the review acknowledged that subcutaneous methotrexate may impose a greater financial burden on patients but concluded that switching patients unresponsive to oral methotrexate to subcutaneous methotrexate might avoid the need for biologicals or other treatments, and hence result in cost savings. Furthermore, the authors concluded that most patients would prefer subcutaneous methotrexate to oral methotrexate.

A 2015 narrative literature review evaluated outcomes related to methotrexate dose and route of administration in patients with rheumatoid arthritis. Six studies (two systematic reviews, two randomized controlled trials, one longitudinal study and one retrospective cohort study) were included in a qualitative synthesis (*12*). The efficacy and toxicity of methotrexate appeared to be related to the absorbed dose rather than the route of administration. While bioavailability was greater for parenteral methotrexate, evidence was lacking that dividing oral doses was less advantageous, safer or more tolerable. The authors conceded that there may be modest benefits associated with starting patients with higher doses of methotrexate, and switching from oral to parenteral treatment when clinical response was inadequate.

Additional, older literature reviews identified in the application reported findings similar to those described above (*13–16*).

Juvenile idiopathic arthritis

The application did not present any evidence for subcutaneous methotrexate for treatment of juvenile idiopathic arthritis.

Psoriasis

The application stated that very few data were available on the use of subcutaneous methotrexate in psoriasis. The METOP study was a prospective, randomized,

double-blind, placebo-controlled, multicentre, phase III trial that examined subcutaneous methotrexate in 120 patients with moderate-to-severe plaque-type psoriasis (*17*). The primary efficacy endpoint (75% reduction in psoriasis area and severity index score (PASI 75) from baseline to week 16) was achieved in 37/91 (41%) patients in the methotrexate group versus 3/29 (10%) patients in the placebo group (relative risk (RR) 3.93, 95% CI 1.31 to 11.81). Subcutaneous methotrexate was reported to be generally well tolerated.

The application identified other prospective (*18,19*) and retrospective (*20*) studies of subcutaneous methotrexate in chronic plaque psoriasis but did not provide any information of the evidence.

Psoriatic arthritis

The application did not present any evidence on subcutaneous methotrexate for psoriatic arthritis, as very limited evidence exists on the use of subcutaneous methotrexate for this condition.

Crohn disease

The application identified four studies that included subcutaneous methotrexate in the treatment of Crohn disease but did not provide any information of the evidence (*21–24*).

Summary of evidence: harms

The application stated that comparative safety data for subcutaneous versus oral or intramuscular methotrexate were lacking.

A 2016 systematic review and meta-analysis that compared subcutaneous versus oral methotrexate in the treatment of rheumatoid arthritis reported no significant difference between treatment groups for headache (OR 0.69, 95% CI 0.39 to 1.24), vomiting (OR 0.55, 95% CI 0.26 to 1.18) or dyspepsia (OR 0.67, 95% CI 0.37 to 1.19). Nausea was reported significantly less frequently in the subcutaneous group (OR 0.53, 95% CI 0.28 to 0.97), as was diarrhoea (OR 0.43, 95% CI 0.20 to 0.95) (*6*).

A randomized trial that evaluated the tolerability of subcutaneous methotrexate for the treatment of rheumatoid arthritis in Japanese patients reported that any adverse events occurred 57.7% and 72.0% of patients in the subcutaneous and oral treatment groups, respectively. A trend to fewer gastrointestinal disorders, in particular nausea, was observed in the subcutaneous group. With long-term treatment, the most commonly reported adverse reactions were nausea (13.8%), stomatitis (11.9%) and increased alanine aminotransferase levels (9.2%) (*8*).

In the METOP study in patients with psoriasis, the drop-out rate with subcutaneous methotrexate was 39% over 52 weeks, primarily due to poor efficacy and adverse events. During the placebo-controlled phase, methotrexate led to

more gastrointestinal adverse events and increased liver enzyme levels compared with placebo. Gastrointestinal adverse events were usually mild to moderate, and led to permanent drug discontinuation in 3% of patients. Elevated liver enzymes occurred in 23% of patients receiving methotrexate, leading to permanent drug discontinuation in 12% of patients (*17*).

WHO guidelines

WHO guidelines for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis or Crohn disease are not currently available.

Costs/cost–effectiveness

The application did not present information on the comparative cost or cost–effectiveness of subcutaneous methotrexate compared with oral, intramuscular or intravenous methotrexate.

In general, subcutaneous formulations of methotrexate appear to be more highly priced than oral or other parenteral forms.

Availability

The application reported that subcutaneous methotrexate has regulatory approval and market availability in most middle- and high-income countries.

Committee recommendations

The Expert Committee acknowledged that methotrexate is one of the mainstays of treatment for chronic inflammatory autoimmune conditions. Oral methotrexate is included on the Model Lists for rheumatoid arthritis and juvenile idiopathic arthritis, and a positive recommendation for oral methotrexate for treatment of severe psoriasis has been made at this meeting.

The Committee noted that data on the clinical efficacy and safety of subcutaneous methotrexate compared with oral or intramuscular formulations are limited and are based mostly on studies in patients with rheumatoid arthritis. Bioavailability data suggest higher concentration following subcutaneous administration, but only a modest effect on response or side-effects.

The Committee noted that the application did not include data on discontinuation/drug survival or compliance, nor on whether subcutaneous methotrexate can delay the need for biological medicines.

The Committee considered that access and affordability of methotrexate is generally acceptable, with generics available. However, the Committee noted that subcutaneous methotrexate is generally more expensive than oral formulations and prefilled syringe/autoinjector delivery systems may substantially increase the cost of treatment. The Committee noted a lack of evidence on cost–effectiveness compared with oral formulations.

The Committee acknowledged that subcutaneous methotrexate may have a role only in a small subgroup of patients in whom oral treatment is suboptimal or not tolerated, however evidence supporting its use in this population is limited.

Overall, the Committee considered the possible benefits of subcutaneous compared with oral methotrexate were unclear, with limited evidence suggesting only modest benefits in a small proportion of patients, at a considerably higher price. Therefore, the Expert Committee did not recommend inclusion of subcutaneous formulations of methotrexate on the EML and EMLc for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, and Crohn disease in patients not responding to maximum tolerable doses of oral methotrexate.

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8.2 Antineoplastics and supportive medicines
CAR T-cell therapy – addition – EML

Axicabtagene ciloleucel	ATC code: L01XL03
Lisocabtagene maraleucel	ATC code: not available
Tisagenlecleucel	ATC code: L01XL04

Proposal

Addition of CD-19-directed antigen receptor (CAR) T-cells (axicabtagene ciloleucel, lisocabtagene maraleucel and tisagenlecleucel) on the complementary list of the EML for treatment of adults with large B-cell lymphoma, including diffuse large B-cell lymphoma, high-grade B-cell lymphoma and primary mediastinal B-cell lymphoma.

Applicant

Evidence-based Medicine Research Group, University Hospital of Cologne, Cologne, Germany

Cochrane Haematology

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical team commented that there were insufficient mature data on the efficacy (as measured by overall survival) and safety of CAR T-cell therapies to justify inclusion on the EML at this time, and that future consideration could be made as more studies are reported and a greater understanding of feasibility is gained. The technical team highlighted the need to monitor the evidence on these therapies and to consider a broader context for access.

EML/EMLc

EML

Section

8.2 Antineoplastic and supportive medicines

Dose form(s) & strengths(s)

Axicabtagene ciloleucel – intravenous infusion: suspension of 2×10^6 CAR-positive T-cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T-cells in about 68 mL

Tisagenlecleucel – intravenous infusion: suspension of 0.6 to 6.0×10^8 CAR-positive viable T-cells

Lisocabtagene maraleucel – intravenous infusion: suspension of $\geq 1.5 \times 10^6$ to 70×10^6 CAR-positive viable T cells per mL

Core/complementary

Complementary

Individual/square box listing

Square box, with axicabtagene ciloleucel and lisocabtagene maraleucel as the main pharmacological class representatives for the second-line treatment of early relapsing or refractory aggressive large B-cell lymphoma and tisagenlecleucel as an alternative in a later treatment line.

Background

In CAR T-cell treatment, T cells are sampled from a patient's blood, modified and multiplied ex vivo before being readministered to the patient. By adding a gene for an engineered receptor (chimeric antigen receptor or CAR) in the laboratory, T cells are enabled to recognize specific cancer cell antigens (in the case of the current application CD-19, a transmembrane glycoprotein expressed by B-cells). The exact design and specificities of the CAR-T receptor varies in different products. As of the date of submission of the application, several different CAR-T treatments had been approved by United States Food and Drug Administration, all for haematological cancers.

In 2021, the Expert Committee reviewed the evidence for axicabtagene ciloleucel and tisagenlecleucel for relapsed or refractory diffuse large B-cell lymphoma. The purpose of the application was only to review the evidence and addition of CAR T-cell therapy to the Model List was not proposed.

The Committee noted that CAR T-cell therapy was highly specialized, requiring dedicated health system resources well beyond those currently available in most settings. Current treatment and management costs were also prohibitively high and exceeded affordability thresholds in almost all countries.

The Committee considered that CAR T-cell therapies were an area of great interest and therapeutic relevance in the treatment of diffuse large B-cell lymphoma, and potentially other diseases. At the time, the Committee acknowledged that the available evidence was limited and of very low certainty. Nevertheless, it was noted that the immature data from multiple studies indicated that CAR T-cell therapy could induce durable complete responses, which may lead to clinical cure in some patients. The main uncertainties about the clinical benefits of CAR T-cell therapy related to the proportion of patients achieving long-term disease-free survival, and when CAR T-cell therapy is best used in the overall treatment algorithm. Safety concerns included cytokine release syndrome and neurological toxicity, both of which occur in a high proportion of patients,

may be life-threatening and require highly specialized medical management. Data on long-term safety were limited.

The Committee acknowledged that the field of CAR T-cell therapy was rapidly evolving, with many ongoing studies that might address the existing clinical uncertainties. The application of this treatment could be advantageous in low- and middle-income settings: a potential curative treatment for haematological malignancies with a single infusion of CAR T-cells might be a competitive therapeutic option when compared with multiple chemotherapy regimens administered in hospital over longer periods of time.

The Committee considered that WHO should continue to monitor evidence on these therapies. The Committee advised that it would welcome an updated review of the evidence for CAR T-cell therapy for consideration at a future meeting. The Committee advised that WHO would need to have a strong leadership and advocacy role in facilitating affordable and equitable access to these treatments (*1*).

Public health relevance

Non-Hodgkin lymphomas are the seventh most common type of cancer and the most common haematological malignancy in the world, accounting for 4.3% of all cancers in the United States in 2015 (*2*). The most common type of malignant lymphomas worldwide are diffuse large B-cell lymphomas with 40% of all non-Hodgkin lymphomas (*3*) and 80% of all aggressive lymphomas (*4*). Based on morphological features and their genetic make-up, other subtypes and related entities, albeit less common, are defined and included with diffuse large B-cell lymphoma under the broader, more heterogeneous group of aggressive large B-cell lymphomas. These include high-grade B-cell lymphomas, primary mediastinal B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, and others (*5*).

Global data on the incidence and mortality of diffuse large B-cell lymphoma are limited. However, the age-adjusted incidence rate of diffuse large B-cell lymphomas in the United States was 5.5 per 100 000 in 2015 (*6*). Between 1970 and 2010, a steady increase of these incidence rates has been reported. In all sexes, racial categories and age groups (except young adults), the increase was reported to be about 3–4% in the United States (*4,7*). Males are at a 1.5 times higher risk of being diagnosed with diffuse large B-cell lymphomas (*4,7*). Mortality was 1.8 per 100 000 in the United States in 2015 (*6*).

Untreated, diffuse large B-cell lymphomas are associated with a median survival of less than 1 year. With first-line chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, most patients have good outcomes (*7*). However, 30–40% of patients relapse or are refractory to first-line treatment. The treatment of relapsed or refractory large B-cell

lymphoma is complex and depends on many factors, of which time to relapse is the most critical one. Even with the second-line treatments, which consist of salvage chemoimmunotherapy followed by autologous haematopoietic stem-cell transplantation, about 60% of patients experience a further relapse (*8,9*). In patients with primary progressive disease or relapse within 1 year after first-line therapy, progression-free survival is about 25% at 2 years (*10*). Accordingly, the prognosis for relapsed or refractory large B-cell lymphomas is still poor.

Summary of evidence: benefits

The application presented the results of a systematic review and meta-analysis of three randomized trials (865 participants) which evaluated the efficacy and safety of CAR T-cell therapy in people with relapsed or refractory aggressive large B-cell lymphoma as second-line treatment, comparing them with the established standard of care of platinum-containing chemotherapy regimens followed by high-dose chemotherapy and autologous stem-cell transplantation.

All three trials were multicentre, phase III open-label studies that recruited participants from Europe, Asia, North and South America, and the Pacific region. The BELINDA trial evaluated tisagenlecleucel (*11*), the ZUMA-7 trial evaluated axicabtagene ciloleucel (*12*) and the TRANSFORM trial evaluated lisocabtagene maraleucel (*13*). The intervention in each trial was a one-time infusion of CD19-directed CAR T-cells after the administration of lymphodepleting chemotherapy with fludarabine and cyclophosphamide over 2–3 days. Co-interventions were not permitted.

Trial designs varied slightly. While leukapheresis (the collection and separation of white blood cells from blood to obtain T-cells) was performed before randomization in BELINDA and TRANSFORM (i.e. independent of group allocation), it was performed after randomization in ZUMA-7. The time from randomization and leukapheresis to CAR T-cell infusion was different across trials, being shortest in ZUMA-7 with a median time of around 4 weeks, to a median of 5 weeks in TRANSFORM and 7 weeks in BELINDA. The timing of leukapheresis may affect T-cell count recovery and quality.

Bridging therapy (chemoimmunotherapy protocols) which were also used in the control arms were permitted in BELINDA and TRANSFORM. In ZUMA-7, only the administration of corticosteroids was permitted as a bridging to CAR T-cell therapy.

Treatment regimes in the control arms were similar across trials. They consisted of three to four prespecified platinum-based chemoimmunotherapy regimens based on investigator's choice. Changes in treatment regimens were permitted in BELINDA and TRANSFORM in case of efficacy concerns. In TRANSFORM, a change of the chemoimmunotherapy regimen was allowed within the first three cycles and in BELINDA after the positron emission

tomography at week six. The proportion of participants in the control arms receiving high-dose chemotherapy and autologous stem-cell transplantation was 33% in BELINDA, 35% in ZUMA-7 and 47% in TRANSFORM.

Crossover from standard of care to CAR T-cell therapy was allowed as a third-line treatment option in BELINDA and TRANSFORM. In ZUMA-7, crossover was not planned, but cellular immunotherapy was permitted outside the protocol. In BELINDA and TRANSFORM, 50–51% of participants allocated to the standard of care arm received third-line CAR T-cell therapy without receiving autologous stem-cell transplantation. In ZUMA-7, 56% of participants in the control arm subsequently received CAR T-cells outside the trial.

Using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach, the overall certainty of the evidence was low to moderate. Risk of bias was deemed low for survival and response assessment, unclear for safety assessment and high for quality of life, which for quality of life was due to the risk of performance and detection bias and the subjective nature of the outcome, as well as attrition bias.

The median age of participants in the trials was 59 years and the proportion of female patients was between 34% and 43% reflecting the higher incidence of large B-cell lymphoma in males. The predominant large B-cell lymphoma subtype in all studies was diffuse large B-cell lymphoma diagnosed in 64% to 69% of patients, followed by high-grade B-cell lymphoma subtypes in 16% to 23%. Eligibility criteria across trials were similar. Trial participants were eligible if they were: diagnosed with aggressive large B-cell lymphoma, refractory or relapsing early (within 1 year) after an anti-CD20 monoclonal antibody and anthracycline-containing immunochemotherapy; had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1; and were eligible for high-dose chemotherapy and autologous stem-cell transplantation. Lymphoma in the central nervous system was an exclusion criterion in BELINDA and ZUMA-7.

Overall survival

The results on overall survival were reported in the three trials. In each trial, data on overall survival were immature at the data cut-off and were presented as interim analyses.

In BELINDA, data on overall survival were immature at the data cut-off. Median overall survival was 16.9 months (95% confidence interval (CI) 11.14 to not estimable) in the CAR T-cell group and 15.3 months (95% CI 12.32 months to not estimable) in the control group (stratified unadjusted hazard ratio (HR) for death 1.24, 95% CI 0.83 to 1.85) (*11*).

In ZUMA-7, median overall survival was evaluated as an interim analysis. Overall survival was not reached in the CAR T-cell group (95% CI 28.3 months to not estimable) and 35.1 months (95% CI 18.5 months to not estimable) in the control group (HR for death 0.73, 95% CI 0.53 to 1.01) (*12*).

In TRANSFORM, overall survival data were immature at the time of the interim analysis. Median overall survival was not reached in the CAR T-cell group (95% CI 15.8 months to not reached) and 16.4 months (95% CI 11.0 months to not reached) in the control group (stratified HR for death 0.51, 95% CI 0.26 to 1.01) (*13*).

Overall survival data from the three trials were not pooled and meta-analysed. The applicants observed that overall survival in TRANSFORM and ZUMA-7 favoured CAR T-cell therapy, however no evidence of a difference between CAR T-cell therapy and standard of care was observed in BELINDA. The applicants concluded that the evidence suggested that CAR T-cell therapy may improve overall survival when compared with second line standard of care treatment. However, it was also noted that the evidence was uncertain, with follow-up still ongoing. Furthermore, considering that more than half of the participants in the control arms received CAR T-cells after treatment failure, the beneficial effect of CAR T-cells might be underestimated and inadequately represented by the overall survival estimates. The applicants proposed that surrogate survival endpoints such as progression-free and event-free survival might be more informative.

Progression-free survival

The ZUMA-7 and TRANSFORM trials reported progression-free survival outcomes (543 participants). In BELINDA, progression-free survival assessment was not included in the trial protocol. The evidence from TRANSFORM and ZUMA-7 suggests that CAR T-cell therapy might improve progression-free survival when compared with standard of care treatment.

In ZUMA-7, median progression-free survival was 14.7 months (95% CI 5.4 months to not estimable) in the CAR T-cell group and 3.7 months (95% CI 0.37 to 0.65 months) in the control group (stratified HR for disease progression or death 0.49, 95% CI 0.37 to 0.65) (*12*).

In TRANSFORM, median progression-free survival was 14.8 months (95% CI 6.6 months to not reached) in the CAR T-cell group and 5.7 months (95% CI 3.9 to 9.4 months) in the control group (stratified HR for disease progression or death 0.41, 95% CI 0.25 to 0.66) (*13*).

Meta-analysis of pooled data from these trials performed by the applicants found moderate-certainty evidence that CAR T-cell therapy improved progression-free survival compared with standard of care (HR 0.47, 95% CI 0.37 to 0.60). In absolute terms, progression-free survival was 601 per 1000 patients with CAR T-cell therapy and 339 per 1000 patients with standard of care.

Event-free survival

Event-free survival was the primary outcome in all three trials. However, event-free survival was defined differently and the timing of assessment differed across the trials.

In BELINDA, median event-free survival was similar between treatment groups: 3 months (95% CI 2.9 to 4.2 months) in the intervention group and 3 months (95% CI 3.0 to 3.5 months) in the control group (HR 1.07, 95% CI 0.82 to 1.40) (*11*).

In ZUMA-7, median event-free survival was 8.3 months (95% CI 4.5 to 15.8 months) in the CAR T-cell group and 2.0 months (95% CI 1.6 to 2.8 months) in the control group (HR 0.40, 95% CI 0.31 to 0.51) (*12*).

In TRANSFORM, median event-free survival was 10.1 months (95% CI 6.1 months to not reached) in the CAR T-cell group and 2.3 months (95% CI 2.2 to 4.3 months) in the control group (HR 0.35, 95% CI 0.23 to 0.53) (*13*).

Event-free survival data from the three trials were not pooled and meta-analysed. The applicants concluded that the evidence suggested that CAR T-cell therapy might lead to an increase in event-free survival compared with standard of care. Additionally, the applicants proposed that differences in the effect estimates might be due to varying interventions and trial designs, with outcome definitions reducing the certainty in the evidence.

Overall response rates

Overall response rates were reported for all three trials.

In BELINDA, the overall response rate was 46% (75/162) of patients in the CAR T-cell group and for 42% (68/160) of patients in the control group (risk ratio (RR) 1.09, 95% CI 0.85 to 1.39) (*11*).

In ZUMA-7, the overall response rate was 83% (150/180) of patients in the CAR T-cell group and 50% (90/179) of patients in the control group (RR 1.66, 95% CI 1.41 to 1.94) (*12*).

In TRANSFORM, the overall response rate was 86% (79/92) of patients in the CAR T-cell group and 48% (44/92) of patients in the control group (RR 1.80, 95% CI 1.43 to 2.26) (*13*).

Meta-analysis of pooled data from these trials performed by the applicants found low-certainty evidence that CAR T-cell therapy leads to a higher overall response rate when compared with second-line standard of care chemoimmunotherapy and autologous stem-cell transplantation (RR 1.49, 95% CI 1.13 to 1.97). In absolute terms, overall response was seen in 698 per 1000 patients with CAR T-cell therapy and 469 per 1000 patients with standard of care.

Quality of life

The ZUMA-7 and TRANSFORM trials reported quality of life outcomes (385 participants) using multiple validated tools for several time points. The application reported results for EuroQoL 5-Dimension 5-Level (EQ-5D-5L) index and the general health/QoL subscale of the EORTC QLQ-C30, for all time points that were reported.

EQ-5D-5L index

In ZUMA-7, mean EQ-5D-5L index scores at baseline were 0.803 (95% CI 0.771 to 0.835) for the CAR T-cell group (n = 165), and 0.799 (95% CI 0.756 to 0.842) for the control group (n = 131). By day 50, there was evidence of a statistically significant decrease in mean EQ-5D-5L index scores in the CAR T-cell group (–0.049, 95% CI –0.081 to –0.017; n = 163), but no evidence of a statistically significant decrease in the control group (–0.003, 95% CI –0.038 to 0.033; n = 123). Based on mixed-effect models with repeated measures analyses controlled for response to first-line therapy and age-adjusted International Prognostic Index at time of screening, there was evidence of a statistically significant difference in the mean changes from baseline to day 100 in favour of the CAR T-cell group (0.081, 95% CI 0.024 to 0.138). No further evidence of statistically significant between-group differences in the estimated mean changes from baseline were observed at day 150 (0.028, 95% CI –0.034 to 0.091), at 9 months (0.020, 95% CI –0.044 to 0.084), at 12 months (–0.029, 95% CI –0.109 to 0.052) and 15 months (–0.066, 95% CI –0.138 to 0.007). Descriptively, the proportion of patients who experienced clinically meaningful improvement (defined by the authors as 0.06 points) was higher in the CAR T-cell arm (15%; 25/166) compared with the control arm (12%; 16/133), but according to time to definitive improvement analyses, there was no evidence of a statistically significant difference (HR 1.15, 95% CI, 0.61 to 2.15) (*14*).

EORTC QLQ-C30 – general health/QoL subscale

In ZUMA-7, the mean European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 – general health/QoL scores at baseline were 68.6 (95% CI 65.6 to 71.7) for the CAR T-call group (n = 165), and 70.1 (95% CI 66.1 to 74.1) for the control group (n = 130). By day 50, mean scores decreased in both groups: changes from baseline –7.4 (95% CI –10.5 to –4.3) in the CAR-T group and –8.5 (95% CI –12.6 to –4.5) in the control group. Based on mixed-effect models with repeated measures analyses controlled for response to first-line therapy and age-adjusted International Prognostic Index at time of screening, there was evidence of a statistically significant and clinically meaningful (defined by the authors as 10 points) difference in the mean changes from baseline to day 100 in favour of the CAR T-cell group (18.1, 95% CI 12.3 to 23.9). Estimated mean changes from baseline at day 150 also favoured the CAR T-cell group (9.8, 95% CI 2.6 to 17.0). No further evidence of statistically significant between-group differences in the estimated mean changes from baseline were observed at 9 months (4.4, 95% CI –3.3 to 12.0), 12 months (–1.5, 95% CI –9.6 to 6.6) and 15 months (–4.9, 95% CI –13.0 to 3.1). Descriptively, the proportion of patients who experienced clinically meaningful improvement were higher in the CAR T-cell arm (19%) compared to the control arm (14%), but according to

time to definitive improvement analyses, there was no evidence of a statistically significant difference (HR 1.25, 95% CI 0.7 to 2.22) (*14*).

In TRANSFORM, mean (standard deviation) EORTC QLQ-C30 – general health/QoL scores at baseline were 67.7 (21.5) for the CAR T-cell group (*n* = 47) and 68.2 (22.1) for the control group (*n* = 43). Based on mixed-effect models with repeated measures analyses which considered all data points through day 126 and controlled for relevant baseline covariates, there was no evidence of a statistically significant difference in the overall least square mean changes from baseline through day 126 between the CAR T-cell group (mean difference 3.0, 95% CI –3.6 to 9.7). Across timings of assessment (days 29, 64 and 126), there was no evidence of statistically significant between-group differences. At 6 months, the observed mean EORTC QLQ-C30 – general health/QoL change scores in the control arm showed clinically meaningful worsening (i.e. mean changes exceeded the authors' prespecified within-group minimally important difference of 10 points). In the CAR T-cell arm, observed mean change scores improved descriptively, but remained lower than the limit of the within-group minimally important difference. Descriptively, from day 126 to month 6, the proportion of patients with meaningful improvement in general health/QoL (using the authors' responder definition of a minimal change threshold (i.e. smallest incremental change) of 5 points) was higher, while deterioration was lower, in the CAR T-cell arm compared with the control arm. That means the proportions of patients with improvement/deterioration at day 126 were 62%/23% (*n* = 26) in the CAR T-cell arm and 30%/60% (*n* = 10) in the control arm. At month 6, the proportions of patients with improvement/deterioration were 53%/18% (*n* = 17) in the CAR T-cell arm and 14%/57% (*n* = 7) in the control arm (*15*).

Quality of life data from the two trials were not pooled and meta-analysed. The applicants concluded that the evidence suggested that quality of life might be increased for CAR T-cell therapy compared with standard of care at some points during the treatment sequence. The evidence was judged to be uncertain and may be limited to patients who respond to or tolerate treatments well.

Summary of evidence: harms

Patients treated with CAR T-cells can experience potentially life-threatening adverse events such as cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome. However, in the evaluated trials there was little to no difference in the occurrence of serious adverse events compared with second-line standard of care.

The BELINDA trial included 162 participants in the intervention group and 160 patients in the control group in the reporting of any (serious) adverse events, but only 155 participants in the intervention group and 81 in the control group for further safety analysis (*11*). In ZUMA-7, 170 participants in

the intervention group and 168 in the control group were included in the safety analysis (*12*). The TRANSFORM trial included 92 participants in the intervention group and 91 participants in the control group in the reporting of any (serious) adverse events. However, further safety analyses were conducted with data from 47 participants in the control group, who crossed over and received CAR T-cell therapy as third-line treatment (*13*).

Any adverse event

Overall, 99–100% of participants in both the intervention and control groups in the BELINDA and ZUMA-7 trials experienced any adverse event (*11,12*). Across all trials, between 84% and 92% of participants in the intervention group and 83% and 90% in the control group experienced any adverse event of grade 3 or higher (*11–13*). The BELINDA trial reported 99% of participants in both the intervention and control group experiencing any adverse event. In the intervention and control groups, respectively, 84% and 90% of participants experienced an adverse event of grade 3 or higher (*11*). In ZUMA-7, 100% of participants in the intervention and control groups experienced any adverse event. In the intervention and control groups, respectively, 91% and 83% of participants experienced an adverse event of grade 3 or higher (*12*). The TRANSFORM trial did not report the number of patients with any adverse event. However, 92% and 87% of participants in the intervention and control groups, respectively, experienced an adverse event of grade 3 or higher (*13*).

Any serious adverse events

In the intervention groups of BELINDA and ZUMA-7, 47% to 50% of participants experienced any serious adverse event, versus 46% to 51% of participants in the control groups. Between 34% and 42% in the intervention groups and 40% and 43% in the control groups experienced serious adverse events of grade 3 or higher (*11,12*). In BELINDA, any serious adverse event was reported in 47% and 51% of participants in the intervention and control groups, respectively. Serious adverse events of grade 3 or higher were reported in 36% and 43% of participants in the intervention and control groups, respectively (*11*). In ZUMA-7, 50% of participants in the intervention group and 46% of participants in the control group experienced any serious adverse event. Serious adverse events of grade 3 or higher were experienced by 42% and 40% of participants in the intervention group and control group, respectively (*12*). The TRANSFORM trial reported serious adverse events of grade 3 or higher in 34% of participants in the intervention group and 43% of participants in the control group. The number of participants with any serious adverse event was not reported (*13*).

Cytokine release syndrome

All trials reported the number of participants with cytokine release syndrome (*11–13*). The number of participants with cytokine release syndrome in the

intervention groups ranged between 49% and 92%, with between 1% and 6% of participants experiencing cytokine release syndrome of grade 3 or higher. In the control groups, between 49% and 75% of participants had cytokine release syndrome of any grade. The BELINDA trial reported cytokine release syndrome in 61% and 75% of participants in the intervention and control groups, respectively, with cytokine release syndrome of grade 3 or higher reported in 5.2% and 4.9% of participants in the intervention and control groups, respectively. Tocilizumab for management of cytokine release syndrome was reported for 51.6% of participants in the intervention group and 55.7% in the control group (*11*). In ZUMA-7, for the intervention group, cytokine release syndrome was reported in 92% of participants and cytokine release syndrome of grade 3 or higher was reported for 6% of participants. The number of participants with cytokine release syndrome in the control group was not reported. Tocilizumab for was administered to 65% of participants, however, it was not reported how many participants per group received tocilizumab, nor if it was administered for cytokine release syndrome or any neurological event (*12*). In TRANSFORM, cytokine release syndrome was reported for 49% of participants in both the intervention and control groups. Cytokine release syndrome of grade 3 or higher was only reported in one participant (1%) in the intervention group. For 10% of participants in the intervention group, and 19% of participants in the control group, tocilizumab was used for management of cytokine release syndrome (*13*).

Neurological events

All trials reported the number of participants with neurological events, however the numbers in the ZUMA-7 control group did not include the number of patients with immune effector cell-associated neurotoxicity syndrome (*12*). The number of participants with neurological events including immune effector cell-associated neurotoxicity syndrome of any grade ranged between 10% and 60% in the intervention group, and between 15% and 17% in the control group. The number of participants with neurological events of grade 3 or higher ranged between 2% and 21% in the intervention group and 3% and 4% in the control group (*11*, *12*). In BELINDA, any neurological event was reported for 10.3% of participants in the intervention group and 14.8% in the control group, both including immune effector cell-associated neurotoxicity syndrome. Additionally, 1.9% in the intervention group and 2.5% in the control group experienced neurological events of grade 3 or higher, including immune effector cell-associated neurotoxicity syndrome. The number of participants receiving tocilizumab for neurological events was not reported (*11*). In ZUMA-7, 60% of participants in the intervention group experienced any neurological event, including immune effector cell-associated neurotoxicity syndrome, and 20% of participants in the control group experienced any neurological event, excluding immune effector

cell-associated neurotoxicity syndrome. Additionally, 21% in the intervention group experienced neurological events of grade 3 or higher, including immune effector cell-associated neurotoxicity syndrome, and 0.6% in the control group experienced neurological events of grade 3 or higher, excluding immune effector cell-associated neurotoxicity syndrome (*12*). The TRANSFORM trial reported any neurological event including immune effector cell-associated neurotoxicity syndrome in 12% of the intervention group and 17% of the control group. Neurological events of grade 3 or higher were reported in 4% of participants in both the intervention and control groups. One patient in the intervention group received tocilizumab for dizziness (*13*).

Any infections

Infections were reported in all three trials. The number of participants with infections ranged between 3% and 41% in the intervention groups, and between 3% and 30% in the control groups (*11–13*). The BELINDA trial reported any infections and infestations in 3.1% of participants in each group (*11*). In the ZUMA-7 trial, infections of any grade were reported in 41% of participants in the intervention group and 30% in the control group. Infections of grade 3 or higher were reported in 14% of participants in the intervention group and 11% in the control group (*12*). In the TRANSFORM trial, infections of grade 3 or higher were reported in 15% of participants in the intervention group and 21% in the control group (*13*).

WHO guidelines

WHO guidelines for treatment of relapsed or refractory large B-cell lymphoma are not currently available.

Costs/cost–effectiveness

The applicants conducted a targeted search for references related to the costs of the medicines included in this application. In addition, health technology assessment reports by the National Institute for Health and Care Excellence (United Kingdom) and the Institute for Quality and Efficiency in Health Care (Germany) were included in the application.

Treatment with CAR T-cells is technologically demanding and resource intensive. It requires well equipped facilities for its production as well as trained physicians and nurses to administer the treatment. Global availability of CAR T-cell therapy is limited. It has not been introduced in low- or middle-income countries (*16,17*). Therefore, data on its comparative cost and cost–effectiveness are limited to high-income countries. Moreover, these data often do not account for costs arising from the need for additional treatment and hospitalization. Since CAR T-cell therapy has been approved by various agencies for the indication of diffuse large B-cell lymphoma, most available evidence is on the treatment of this condition.

Treatment with all three therapies consists of a single use per patient. Cost–effectiveness for all three CAR T-cell therapies depends on the payer's perspective, the applied time horizon and the inclusion of additional treatment costs. In some cases, the therapies can be considered cost-effective compared with other treatment options, especially if incremental cost–effectiveness ratios per life year gained are taken into consideration.

The manufacturers of axicabtagene ciloleucel and tisagenlecleucel have signed outcome-based agreements with several German health insurers. These agreements state that the manufacturer will partially reimburse the treatments cost to the German health care fund if the patient dies within a defined period (*18*).

Cost per case

Axicabtagene ciloleucel

The price for axicabtagene ciloleucel in the United States was reported by the manufacturer to be US$ 373 000 (*19*), with total drug acquisition cost reported to be US$ 399 000 (*20*, *21*). In Germany, the wholesale price was €282 000 (*22*), whereas total drug acquisition cost in Spain was reported at €313 920 (*23*).

The estimated costs per case for axicabtagene ciloleucel varied between US$ 586 313 and US$ 637 129, depending on the indication and the use of additional treatments (*20*, *21*, *24*). Yearly therapy costs in Germany were estimated at €283 227 (excluding costs for the use of additional treatment that are part of other reimbursement processes) (*22*).

Tisagenlecleucel

The acquisition cost for tisagenlecleucel was reported to be US$ 373 000 in the United States (*20*, *24*), Sw.fr. 403 470 in Switzerland (*25*) and €307 200 in Spain (*23*). The wholesale price for tisagenlecleucel in Germany was reported to be €275 000, with yearly therapy estimated at about €283 000 (*26*), depending on the additional treatments needed. However, because of reimbursement processes in Germany, not all additional treatment costs are covered by this figure so the overall treatment costs may be higher (*18*).

Lisocabtagene maraleucel

The acquisition cost for lisocabtagene maraleucel was reported to be US$ 410 300 in the United States (*20*, *21*). The total costs per patient were estimated to be between US$ 597 174 and US$ 620 962, depending on additional treatment costs. Health technology assessment reports from Germany or the United Kingdom are not yet available for lisocabtagene maraleucel.

For overall CAR T-cell therapy, independent of the substance, budget impact calculations estimated US$ 10–21 billion over 5 years for the United States health care systems if these treatments were given to eligible patients. This figure varies because of variation in the indications considered in the estimations (*17,27*).

Cost–effectiveness

The cost–effectiveness of CAR T-cell therapies varied between studies and reports, depending on the time-horizon and the perspective of the analyses, and on the inclusion of additional treatment costs.

Axicabtagene ciloleucel

The January 2019 NICE technology appraisal guidance on axicabtagene ciloleucel reported an incremental cost–effectiveness ratio more than £50 000 per quality-adjusted life year (QALY) gained (*28*). Updated NICE guidance from February 2023 reported an incremental cost–effectiveness ratio of lower than £50 000 per QALY (*29*). An analysis from an Italian payer perspective reported an incremental cost–effectiveness ratio of €44 746 per QALY gained (*30*), whereas an analysis from a United States payer perspective over a lifetime horizon reported an incremental cost–effectiveness ratio of US$ 66 318 per QALY gained (*31*). A Canadian analysis with a societal and public health care payer perspective reported an incremental cost–effectiveness ratio of Can$ 132 747 per QALY gained (*32*). A cost–effectiveness analysis from the perspective of the Chinese health care system reported an incremental cost–effectiveness ratio of US$ 67 250 per QALY gained, above the willingness-to-pay threshold applied of US$ 31 320 per QALY gained, which is three times the gross domestic product per capita (*33*). All the analyses compared axicabtagene ciloleucel with standard of care (i.e. salvage chemotherapy).

Tisagenlecleucel

The highest incremental cost–effectiveness ratio for tisagenlecleucel was US$ 508 530 per QALY gained reported from a Singapore health care payer perspective over a time horizon of 15 years (*34*). From a Canadian societal perspective and over a time horizon of 20 years, the reported incremental cost–effectiveness ratio was Can$ 103 122 per QALY gained (*19*). An analysis using a United States third-party payer perspective with a lifetime horizon reported an incremental cost–effectiveness ratio of US$ 78 652 per QALY gained (*35*). An analysis using a Japanese perspective over a lifetime horizon reported an incremental cost–effectiveness ratio of 5 476 496 Japanese yen per QALY gained (*36*). The NICE technology appraisal guidance on tisagenlecleucel reported an incremental cost–effectiveness ratio between £42 991 and £55 403 per QALY gained (*37*). Incremental cost–effectiveness ratios per life year gained were reported to be US$ 320 200 from the Singapore perspective (*34*) and 5 389 446 Japanese yen from the Japanese perspective (*36*). All analyses compared tisagenlecleucel with salvage chemotherapy.

An analysis from a German payer perspective compared CAR T-cell therapy (axicabtagene ciloleucel and tisagenlecleucel), allogenic stem-cell transplantation and best supportive care and applied the efficiency frontier concept. In this analysis, allogenic stem-cell transplantation and axicabtagene ciloleucel were the most efficient interventions (*38*).

Lisocabtagene maraleucel

Cost–effectiveness analyses of lisocabtagene maraleucel versus salvage chemotherapy were not identified.

A comparison of the three CAR T-cell therapies from a United States payer perspective over a lifetime horizon found that incremental cost–effectiveness ratios for axicabtagene ciloleucel versus its comparators were substantially lower than the threshold of US$ 150 000 used to evaluate its relative cost–effectiveness – US$ 8946 per QALY gained versus lisocabtagene maraleucel and US$ 24 506 per QALY gained versus tisagenlecleucel (*20*).

Availability

Axicabtagene ciloleucel, lisocabtagene maraleucel and tisagenlecleucel have been approved by several regulatory agencies worldwide for various indications including treatment of adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. At the time of the Expert Committee meeting (April 2023), there were no existing or planned licencing agreements with generic manufacturers and/or the Medicines Patent Pool.

Other considerations

The EML Cancer Medicines Working Group reviewed the application and advised that it did not support the inclusion of CD19-directed CAR T-cell immunotherapy as a therapeutic class or as individual medicines on the EML. The Working Group acknowledged that CAR T-cell therapy is superior to salvage chemoimmunotherapy in terms of progression free-survival, without evidence of heterogeneity across trials. However, for all medicines proposed, the Working Group noted that long-term trial follow-up is limited, and that the survival benefit observed is currently uncertain, with one study potentially associated with a detrimental effect of CAR T-cell therapy. In addition, the current costs of the administration of these medicines are very high, with cost–effectiveness analyses finding these treatments not to be cost-effective in most settings at the current prices. Further concerns were raised about the feasibility of administering these treatments and managing adverse effects in resource-constrained settings. It was noted that CAR T-cell therapy is a rapidly evolving field with a high likelihood that the currently available products will be replaced by more advanced products in the future.

The Working Group agreed that CAR T-cell therapies for large B-cell lymphoma, and probably other cancer indications (e.g. acute lymphoblastic leukaemia), are an area of considerable interest and therapeutic relevance. The Working Group considered that the evidence on these therapies should continue to be monitored on an ongoing basis. Costimulatory signalling domains should be also considered as they might have implications for clinical efficacy and in prioritizing one CAR T-cell immunotherapy over others.

The Working Group noted that T-cell production methods, other than industry-scaled centralized manufacturing by companies, are now being explored. The Working Group considered that decentralized production in academic medical centres and hospitals has the potential to facilitate widespread patient access to CAR T-cell therapy.

Committee recommendations

The Expert Committee recalled the review of available evidence for CD19-directed CAR T-cell therapy submitted for consideration in 2021 and appreciated the updated evidence presented by the applicants for the current meeting, proposing inclusion of these therapies on the EML for the treatment of adults with relapsed or refractory large B-cell lymphoma. The Committee noted that the field of CAR T-cell therapy continues to evolve rapidly, with several ongoing clinical trials.

Based on the evidence presented in the application, the Committee acknowledged that CAR T-cell therapy appears to outperform standard care with salvage chemoimmunotherapy in terms of progression-free survival, although with variability across trials for other survival outcomes. The Committee noted in particular the results of the BELINDA trial, in which the point estimate for event-free survival favoured the control arm, and the point estimate for overall survival suggested no difference between treatment groups. However, the Committee also noted that long-term trial follow-up is currently limited for the three CAR T-cell therapies proposed for listing in the EML, and that overall survival data are still immature. Therefore, the Committee considered that the actual survival benefit remained uncertain. Furthermore, the Committee noted significant safety concerns including cytokine release syndrome and neurological toxicity, both of which occur in a high proportion of patients receiving CAR T-cell therapy. These may be life-threatening and require highly specialized medical management. Data on long-term safety are not currently available.

The Committee noted that the application proposed listing CAR T-cell therapies as a therapeutic group but considered that the three therapies proposed were very different in terms of starting material (i.e. type of T-lymphocytes), vector, costimulatory domain and manufacturing; therefore, they may have important differences in both toxicity and efficacy.

The Committee noted that acquisition costs for CAR T-cell therapies are very high, and that cost–effectiveness analyses are generally limited to high-income settings. These analyses report high incremental cost–effectiveness ratios, often greater than the willingness-to-pay thresholds of the settings in which they were conducted. The Committee recognized that treatment of patients using CAR T-cell therapy requires dedicated health system resources and infrastructure well beyond those available in most settings and would have a substantial effect on

budgets due to prohibitively high production costs, as well as costs for specialized administration and management of toxicities. However, the Committee noted with interest that these therapies are becoming increasingly available in academic settings and that closed and semi-automated manufacturing processes are becoming available which may substantially reduce prices and likely increase availability.

Based on these considerations, the Expert Committee did not recommend the inclusion of axicabtagene ciloleucel, lisocabtagene maraleucel or tisagenlecleucel on the complementary list of the EML for treatment of adults with relapsed or refractory large B-cell lymphoma.

Recognizing the promising role of CAR T-cell therapies for large B-cell lymphoma and potentially also other cancers, the Committee recommended that WHO continue to monitor the evidence on these therapies, as well as their growing availability and affordability.

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8.2.1 Cytotoxic medicines

Cancer medicines for children – new indication for anaplastic large cell lymphoma – EML and EMLc

Cancer medicines for children – anaplastic large cell lymphoma	ATC code: various

Proposal

Extension of the indications for cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, methotrexate, prednisolone and vinblastine, and addition of crizotinib on the complementary list of the EML and EMLc to include treatment of anaplastic large cell lymphoma (ALCL) in children and adolescents.

Applicant

European Society for Paediatric Oncology

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department advised that it supported extending the listings of the currently included medicines for the new indication of ALCL, given that it is a highly curable disease, and that EMLc listing can contribute to improving access and quality of care for children and adolescents diagnosed with ALCL, in alignment with the objectives of WHO's global initiative for childhood cancer. The technical department did not support the addition of crizotinib at this time, and preferred to prioritize access to first-line chemotherapy.

EML/EMLc

EML and EMLc

Section

8.2.1 Cytotoxic medicines

8.2.2 Targeted therapies

8.2.4 Hormones and antihormones

Dose form(s) & strengths(s)

Crizotinib – Capsule: 200 mg, 250 mg

Other medicines – dose forms and strengths currently in the EMLc

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Chemotherapy for the treatment of ALCL has not previously been considered by the Expert Committee. With the exception of crizotinib, all the other medicines proposed in the application are already included in the EML and EMLc for other cancer indications.

Public health relevance

Non-Hodgkin lymphoma is the fourth most common cancer in children and adolescents, with an annual incidence of 0.7–1.5 per 100 000 in Europe. Around 10–15% of these cases are ALCL (*1*). ALCL can be classified into four main types: anaplastic lymphoma kinase (ALK)-positive primary systemic ALCL; ALK-negative primary systemic ALCL; cutaneous ALCL; and breast implant-associated ALCL (*2*). ALK-positive ALCL is the most common type in children and adolescents, with almost all cases showing a translocation involving the ALK gene, leading to activation of the ALK kinase and tumour development (*3*).

The incidence of ALCL varies, with about 1.2 cases per million in children younger than 15 years and around 2 cases per million in young adults aged 25–34 years (*4*). This results in about 80 newly diagnosed cases of ALCL in children each year in Europe. Many children with ALCL are diagnosed at an advanced stage. Although relapse occurs in about 30% of patients, the overall survival rate is high at 90% due to various second-line treatment approaches (*3*).

Summary of evidence: benefits

The standard treatment for paediatric ALCL in Europe is the ALCL99-protocol, which consists of a prephase of dexamethasone, cyclophosphamide and intrathecal treatment (with cytarabine, methotrexate and prednisone), followed by three to six cycles of alternating multiagent chemotherapy (course A: cytarabine, dexamethasone, etoposide, ifosfamide, methotrexate, and intrathecal treatment; course B: cyclophosphamide, dexamethasone, doxorubicin methotrexate, and intrathecal treatment), depending on the stage of the disease (*5*).

For some patients with completely resected stage I disease, three cycles of chemotherapy are given. The treatment duration is 10 weeks. For patients in the standard risk and high-risk group, six cycles of chemotherapy are administered over 4–5 months. With this treatment approach, the 2-year event-free survival

rate has been reported to range from 70% to 75% (*3,6*). Most children and adolescents with recurrence can be cured with second-line therapy, which may involve vinblastine monotherapy for late relapse, reinduction chemotherapy or targeted therapy (such as crizotinib) followed by allogeneic haematopoietic stem-cell transplantation for early relapse.

The ALCL99 protocol is based on the non-Hodgkin lymphoma-Berlin-Frankfurt-Münster (NHL-BFM) treatment strategy (*7*). The NHL-BFM 83 and 86 trials used a prephase followed by two alternating courses of treatment. The medicines used in these trials included cyclophosphamide, cytarabine, doxorubicin, ifosfamide, methotrexate, prednisone, and teniposide. In the NHL-BFM 90 protocol, teniposide was replaced with etoposide, both of which are topoisomerase II inhibitors. The NHL-BFM 90 trial demonstrated a favourable event-free survival rate of 76%. The ALCL99 trial built upon the previous NHL-BFM protocols and showed that the 24-hour infusion of methotrexate with additional intrathecal methotrexate can be safely replaced by a schedule of 3 g/m² intravenous methotrexate administered over 3 hours; this was associated with 2-year overall survival of 94.9% (*3*). After 10 years of follow up, progression-free survival was 70% and overall survival was 90% in the ALCL99 trial (*8*).

Vinblastine has a role in the second-line treatment of paediatric ALCL. A retrospective analysis of 41 patients with relapsed ALCL included 12 patients who received weekly vinblastine for 6 to 18 months for relapsed disease. Ten patients achieved complete remission, defined as the complete disappearance of all lesions for at least 4 weeks (*9*). In a prospective ALCL relapse trial, vinblastine monotherapy was effective for patients experiencing a relapse after the first year of initial diagnosis, with an observed long-term remission rate of 81% reported in patients who received vinblastine monotherapy (*10*).

Crizotinib, an ALK-specific tyrosine kinase inhibitor, has been effective in treating relapsed ALK-positive ALCL in both adults and children (*11–14*). Retrospective and prospective studies have shown an unfavourable prognosis for patients who experience progression during first-line treatment, with a high risk of treatment failure during conventional re-induction chemotherapy (*15*). Treatment strategies for re-induction therapy often involve the use of ALK inhibitors, either alone or in combination with other treatments.

A phase I/II trial evaluated the efficacy of crizotinib in 26 paediatric patients with relapsed or refractory ALK-positive ALCL and 14 paediatric patients with metastatic or inoperable ALK-positive inflammatory myofibroblastic tumour. The children with ALCL received crizotinib at doses of either 165 mg/m² or 280 mg/m². The overall response rates were 83% (5/6 patients achieving a complete response) for the lower-dose group and 90% (16/20 patients achieving a complete response and two with a partial response) for the higher-dose group (*14*).

Another phase II trial evaluated the efficacy of crizotinib in 17 paediatric and adult patients with ALCL (15 who could be evaluated, 13 with progression

and two front-line). Children and adults received crizotinib 165 mg/m^2 twice daily and 250 mg/m^2 twice daily, respectively. The overall response rate for the 15 patients was 67% (95% confidence interval (CI), 42% to 85%) – 10 patients achieved an objective response, of whom nine achieved a complete response and one achieved a partial response. Response rates were similar in children and adults (*13*).

Summary of evidence: harms

In the ALCL99 protocol, the most frequently reported adverse reaction was haematological toxicity, including with grade 4 neutropenia occurring after 70% of treatment courses. Other frequent adverse reactions reported were infections (after 41% of courses), elevated liver transaminase and stomatitis (both after 39% of courses). Significant weight gain was reported in 20% of patients (*16*).

The most frequently reported adverse event for crizotinib, regardless of grade, in the ALCL groups was neutropenia, occurring in 33% of patients receiving the lower dose and 70% of patients receiving the higher dose (*14*).

Other reported adverse events associated with crizotinib include thromboembolic events, elevated liver transaminases, visual disorders, nausea and vomiting, and bradycardia (*13*).

WHO guidelines

WHO guidelines for the treatment of ALCL are not available.

Costs/cost–effectiveness

Comparative cost–effectiveness data were not presented in the application.

Based on vial prices from the Kingdom of the Netherlands, for a child with a body surface area of 1 m^2 receiving one course of induction and three (or six) courses of consolidation according to the ALCL99 protocol, the estimated cost of chemotherapy would be about €1126 (or €3292).

The costs per dose for vinblastine and crizotinib were reported in the application as about €76 and €86, respectively.

Availability

Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, methotrexate, and prednisolone and vinblastine are already included on the EML and EMLc for other indications and are available globally in branded and generic versions.

Crizotinib has regulatory approval for use in ALCL from the United States Food and Drug Administration and the European Medicines Agency. No information on the availability of crizotinib in low- and middle-income settings was presented in the application.

Other considerations

The EML Cancer Medicines Working Group reviewed the application and advised that it supported expansion of the listings of existing medicines for the new indication of ALCL but did not unanimously support inclusion of crizotinib.

The Working Group noted that crizotinib is associated with benefits as other first-line chemotherapies, and it is considered a therapeutic option for relapsed or refractory ALK-positive disease. However, crizotinib is associated with potentially severe toxicities. The Working Group commented that brentuximab-based chemotherapy was a new standard of care in adults with ALCL. Brentuximab-based chemotherapy is now studied also in children as it may be a favourable first-line option based on its benefit to harm ratio. The application did not cover brentuximab-based chemotherapy.

Committee recommendations

The Expert Committee noted that ALCL is an important disease in paediatric oncology, accounting for 10–15% of cases of non-Hodgkin lymphoma in paediatric and adolescent patients.

Despite limited evidence presented in the application, the Committee acknowledged that the ALCL99 treatment protocol, involving the use of cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide ifosfamide, methotrexate and prednisolone, is internationally recognized as the standard of care in the first-line treatment of ALCL. The Committee also acknowledged the accepted role of vinblastine in second-line treatment in relapsed/refractory disease. Based on the evidence available, the Committee noted that treatment is associated with clinically meaningful responses in a high proportion of patients. The benefits and harms of all medicines mentioned above were well established from their use in other indications in children and in adults.

The Committee therefore recommended the extension of the current listings of these medicines of the complementary list of the EML and EMLc to include the indication of ALCL.

However, because of insufficient evidence and important toxicity concerns for the use of crizotinib in the treatment of refractory/relapsed ALCL, the Committee did not recommended inclusion of crizotinib on the EML and EMLc.

The Committee considered that the evidence on ALK-inhibitor therapies should continue to be monitored, since more potent and less toxic ALK-inhibitors than crizotinib are currently being tested in clinical trials.

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Cancer medicines for children – new indication for Langerhans cell histiocytosis – EML and EMLc

Cancer medicines for children – Langerhans cell histiocytosis	ATC code: various

Proposal

Extension of the indications for cytarabine, intravenous immunoglobulin, 6-mercaptopurine, methotrexate, prednisone, vincristine, and vinblastine, and inclusion of cladribine on the complementary list of the EML and EMLc for treatment of Langerhans cell histiocytosis (LCH) in children and adolescents.

Applicant

European Society for Paediatric Oncology

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department advised that it supported extending the listings of the currently included medicines to include the new indication of LCH, given that systemic chemotherapy according to international protocols had demonstrated high response rates and overall survival > 80% in patients with LCH with high-risk characteristics. The technical department advised that it did not support the inclusion of cladribine on the EML and EMLc for LCH for feasibility and safety reasons, namely capacity for histopathological diagnosis, and identification and management of immune-related toxicity.

EML/EMLc

EML and EMLc

Section

8.2.1 Cytotoxic medicines

8.2.4 Hormones and antihormones

Dose form(s) & strengths(s)

Cladribine – Injection: 1 mg/mL in 10 mL vial, 2 mg/mL in 5 mL vial

Other medicines – dose forms and strengths currently in the EMLc

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Chemotherapy for the treatment of LCH has not previously been considered by the Expert Committee. With the exception of cladribine, all the other medicines proposed in the application are already included in the EML and EMLc for other oncological indications.

Public health relevance

LCH is a rare clonal disease of the immune system with a myeloid origin. It can affect single or multiple organ systems and hence the range of clinical symptoms is wide. It has an annual incidence of 4.6 cases per 1 million children younger than 15 years. It can affect people of any age group but is most common in children aged 1–3 years. Single-system disease, where only one organ is involved, has a survival rate of nearly 100% with (or without) treatment. In multisystem disease, the outcome is more variable but overall survival is still relatively high. Historically, patients with multisystem disease involving so-called risk organs such as the liver, spleen and haematopoietic system and who did not respond to induction therapy had a poorer prognosis. However, the use of intensive therapy or inhibitors targeting the mitogen-activated protein kinase pathway has improved outcomes (*1*, *2*).

About 30–40% of patients with LCH experience permanent sequelae, depending on the organ(s) affected and treatment required. This includes patients who undergo haematopoietic stem cell transplantation. The long-term survival and late effects in LCH depend on the initial location and extent of the disease. For example, single-site and single-system disease involving the bone carries a low risk of late effects and impact on quality of life. However, involvement of the pituitary gland can lead to a lifelong need for hormone substitution.

Summary of evidence: benefits

Chemotherapy is the mainstay of LCH treatment, and the intensity and duration of treatment depend on the site and extent of the disease.

In the 1980s, the l'Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) Group and the DAL-HX group conducted the largest prospective clinical trials for LCH (*3*,*4*). These trials used systemic chemotherapy immediately after diagnosis. In the AIEOP-CNR-HX 83 trial, various chemotherapeutic agents were used based on the patient's prognosis. Vinblastine was used as monotherapy for patients with a good prognosis, while doxorubicin + etoposide was used for non-responders, and doxorubicin + vincristine +

cyclophosphamide + prednisone was used for patients with a poor prognosis. Most of these medicines are still used in LCH treatment today. The overall mortality in both trial series was low, at 8% (*3*) and 9% (*4*), respectively.

The current standard treatment protocol for LCH is the LCH-IV protocol (*5*), based on the findings of previous protocol versions (*6*). The LCH-IV protocol assigns patients to seven strata, with each stratum having specific treatment dependent on features at presentation and on response to treatment. Medicines included in this protocol include vinblastine, prednisone, 6-mercaptopurine, methotrexate, vincristine, cytarabine, cladribine and intravenous immunoglobulin. These medications have demonstrated effectiveness in LCH treatment, and their combinations have been refined over time. Even for relapsed disease, the second-line treatment is relatively mild and has a relatively good prognosis (*7*). Due to the extensive experience with these drug combinations, individual studies examining the efficacy of each medication specifically for LCH treatment have not been conducted.

Two studies investigated the use of cladribine as monotherapy for salvage therapy for refractory high-risk LCH patients. The first was a retrospective multicentre study in which data were collected from a survey among members of the Histiocyte Society and a literature review. The authors reported on 23 paediatric and adult patients who received treatment with cladribine. The results showed that 57% (13/23) of the patients achieved complete response, 13% (3/23) had a partial response, 26% (6/23) showed no response and one early death occurred (*8*). The subsequent LCH-S-98 prospective multicentre clinical trial registered 92 children with refractory LCH who were treated with cladribine monotherapy, 83 of whom were included in the analysis. The primary outcome measure was early response. The study found that 38% (17/45) of high-risk patients and 62% (23/37) of low-risk patients achieved an early response. The 2-year overall survival rates were 48% for high-risk patients and 97% for low-risk patients (*9*).

Another retrospective study focused on granulomatous type of central nervous system LCH, where 12 paediatric and adult patients were treated with cladribine monotherapy. In this study, 67% (8/12) of patients achieved complete response and 33% (4/12) had a partial response based on radiological evaluation (*10*).

Two studies investigated the use of cladribine in combination with cytarabine for the treatment of LCH. A multicentre prospective pilot study evaluated efficacy and safety of cladribine and cytarabine in 10 children with refractory multisystem LCH and haematological dysfunction (*11*). The primary outcome measure was early response. The study reported three deaths, with six of the remaining seven children showing a partial response. A subsequent international open-label, prospective, non-randomized phase II study

(LCH-S-2005), evaluated cladribine and cytarabine in 27 paediatric patients with high-risk refractory LCH (*1*). The primary endpoint was the response after two cycles of chemotherapy. The results showed that 7% (2/27) of patients achieved complete response, 85% (23/27) had a partial response, and 7% (2/27) had stable disease. Overall 5-year survival was 85.0% (95% confidence interval 65.2% to 94.2%).

Summary of evidence: harms

No evidence on the harms and toxicity of the medicines proposed was presented in the application. The application states that as the medicines proposed are considered part of standard care protocols for LCH, their benefits are therefore deemed to outweigh potential harms and toxicity associated with their use. With the exception of cladribine, all of the proposed medicines are already included in the EML and EMLc. Their safety profiles are well known as a result of long-standing experience with their use.

Cladribine is associated with myelotoxicity. In the LCH-S-2005 study, all patients experienced prolonged pancytopenia along with infectious complications, including septicaemia and invasive aspergillosis (*11*).

WHO guidelines

WHO guidelines for the treatment of LCH are not available.

Costs/cost–effectiveness

Comparative cost–effectiveness data were not presented in the application.

LCH has different clinical presentations and courses. Overall, the treatment approach is characterized by relatively low intensity but requires several months of treatment. The LCH-IV protocol assigns patients into seven strata. Different stages and strata may have varying treatment durations according to the protocol.

Based on vial prices from the Kingdom of the Netherlands, the estimated costs of chemotherapy for a child with body surface area of 1 m^2, weighing 15 kg, and with LCH treated according to different strata in the LCH IV protocol ranged from €1410 to €80 932. The costs of cladribine depend on the strata and were estimated to range from €1554 to €9324.

Availability

Cytarabine, IV immunoglobulin, 6-mercaptopurine, methotrexate, prednisone, vinblastine and vincristine are already included on the EML and EMLc for other indications and are available globally in branded and generic versions.

Cladribine has regulatory approval for use in the treatment of patients with hairy cell leukaemia and patients with B-cell chronic lymphocytic leukaemia.

No information on the availability of intravenous cladribine in low- and middle-income settings was presented in the application.

Other considerations

The EML Cancer Medicines Working Group reviewed the application and advised that it supported expansion of the listing of existing medicines for the new indication of LCH but did not support the inclusion of cladribine.

The Working Group highlighted the severe toxicity associated with cladribine and the difficulty of managing these in resource-constrained settings because its use would be limited to tertiary care centres. Cladribine, as a salvage treatment, is associated with high rates of cure in high-risk patients. However, it is also associated with prolonged hospitalization and increased risk of treatment-related death.

The Working Group noted that an international, multicentre, prospective clinical study for paediatric LCH is ongoing (NCT02205762) (*5*). This study plans to recruit 1400 patients and might provide data to guide the clinical care of children and young adults.

Committee recommendations

The Expert Committee noted that while LCH is a relatively rare condition, affecting 4.6 per 1 million children each year, treatment of single-system disease has an excellent prognosis, with survival rates close to 100%. Prognosis for multisystem disease is variable, but treatment is generally associated with high survival rates.

Despite limited evidence presented in the application, the Committee acknowledged that the treatment for LCH involving cytarabine, intravenous immunoglobulin, 6-mercaptopurine, methotrexate, prednisone, vinblastine and vincristine is recognized as the current standard of care and is associated with meaningful survival benefits. The benefits and harms were accepted as well established from use in other indications in children and in adults.

The Committee therefore recommended the extension of the current listings of these medicines on the complementary list of the EML and EMLc to include the indication of LCH.

However, the Committee expressed concern about the use of cladribine in the treatment of refractory high-risk LCH, noting important haematological toxicities that would limit its safe use to tertiary care centres with capacity to deliver supportive treatment to manage toxicities. The Committee therefore did not recommend the inclusion of cladribine on the EML and EMLc for treatment of LCH.

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Doxorubicin, pegylated liposomal – addition – EML and EMLc

Doxorubicin hydrochloride	ATC code: L01DB01

Proposal

Addition of pegylated liposomal formulation of doxorubicin hydrochloride (PLD) to the complementary list of the EML and EMLc for treatment of Kaposi sarcoma.

Applicant

Médecins Sans Frontières Access Campaign

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department commented that while some data supported the clinical value of PLD with reduced toxicity (including cardiotoxicity) compared with non-pegylated doxorubicin, mature overall survival data were insufficient to fully evaluate its candidacy for inclusion on the Model Lists, particularly given that alternative, established regimens were already included.

EML/EMLc

EML and EMLc

Section

8.2.1 Cytotoxic medicines

Dose form(s) & strengths(s)

Injection: 2 mg/mL in 10 mL or 25 mL vial (as pegylated liposomal)

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Currently included medicines for Kaposi sarcoma on the Model Lists include bleomycin, doxorubicin, paclitaxel (EML only), vinblastine and vincristine. Doxorubicin is included only in its non-pegylated liposomal form.

During the comprehensive review of cancer medicines conducted in 2015, pegylated liposomal doxorubicin for Kaposi sarcoma was not proposed for

consideration by the Expert Committee. At that time, the superiority of PLD over the doxorubicin + bleomycin + vincristine (or vinblastine) regimen had not been demonstrated, and its substantially higher cost did not justify its potential benefits in resource-constrained settings (*1*). Since then, additional clinical evidence has been published and lower-cost sources for pegylated liposomal doxorubicin have become available.

Public health relevance

Kaposi sarcoma is a soft tissue cancer arising from lymphatic endothelial cells and caused by human herpesvirus 8. Different types exist: AIDS-related Kaposi sarcoma, iatrogenic Kaposi sarcoma and classical Kaposi sarcoma.

More than 80% of Kaposi sarcoma occurs in low- and middle-income countries, with more than 60% occurring in the WHO African region. A disproportionately large proportion of deaths from Kaposi sarcoma (85%) occurs in Africa (*2*). In some areas with high HIV prevalence, Kaposi sarcoma is the most frequent type of cancer documented in registries (*3*).

The incidence of paediatric Kaposi sarcoma is highly concentrated in Africa (95% of all cases globally), where it is the sixth most common cancer in young people aged 0–19 years, with more than 2000 new cases in 2020 (*2*).

Summary of evidence: benefits

The application presented evidence of the clinical benefit of pegylated liposomal doxorubicin in Kaposi sarcoma from seven randomized and two observational studies, identified through a comprehensive literature search.

A randomized, open-label, multicentre study compared PLD together with highly active antiretroviral therapy (HAART) versus HAART alone in 28 patients with HIV and moderate-advanced Kaposi sarcoma (*4*). At 48 weeks, 10/13 (77%) patients in the PLD+HAART group and 3/15 (20%) in the HAART alone group achieved complete or partial remission (risk ratio (RR) 3.80, 95% confidence interval (CI) 1.34 to 11.00; low-certainty evidence). A cohort study found no significant difference in overall survival at 12 months in patients with T1 (poor risk) Kaposi sarcoma treated with liposomal anthracyclines plus HAART versus HAART alone (*5–7*), however the study was not designed to compare treatment arms, nor was it powered to detect survival differences.

A randomized, phase II study evaluated the efficacy and safety of liposomal doxorubicin alone or in combination with bleomycin plus vincristine in the treatment of AIDS-related Kaposi sarcoma (*8*). No significant differences were observed between treatment arms for overall response (RR 0.97, 95% CI 0.81 to 1.17; moderate-certainty evidence), complete response (RR 1.03, 95% CI 0.31 to 3.99; low-certainty evidence) or partial response (RR 0.96, 95% CI 0.77 to 1.21; moderate-certainty evidence).

Two randomized studies compared PLD with bleomycin and vincristine in patients with AIDS-related Kaposi sarcoma (*9,10*). The first study found moderate- or high-certainty evidence of no significant difference in tumour response measures between treatment groups (*9*). The second study found that at the end of treatment, the PLD group had significantly higher rates of overall response (38.8% versus 14.2%; RR 2.74, 95% CI 1.67 to 4.49; high-certainty evidence) and other response measures compared to bleomycin with vincristine (*10*).

A randomized, phase III clinical trial evaluated PLD versus doxorubicin + bleomycin + vincristine in 258 adults with AIDS-related Kaposi sarcoma (*11*). A partial response to treatment was achieved by 60/133 (45.1%) of patients in the PLD group versus 31/125 (24.8%) in the doxorubicin + bleomycin + vincristine group (RR 1.82, 95% CI 1.27 to 2.60; high-certainty evidence). No significant difference was found in overall survival between treatment groups (RR for death 1.41, 95% CI 0.79 to 2.53; high-certainty evidence), with median survival duration of about 160 days in each group.

An observational study evaluated survival in 29 patients with pulmonary Kaposi sarcoma. Patients received liposomal doxorubicin, bleomycin and vinblastine or vincristine, or no chemotherapy (*12*). Mean survival time for patients who received liposomal doxorubicin was significantly higher (11.8 months versus 4.4 months).

A randomized trial compared the efficacy and toxicity of PLD and paclitaxel in 73 patients with AIDS-related Kaposi sarcoma, with 73% of participants receiving HAART (*13*). No significant differences between treatment groups were observed for overall survival, progression-free survival or tumour response.

A prospective, single-arm, observational study in Mozambique in 116 patients with AIDS-associated Kaposi sarcoma, found that PLD had an overall response rate of 80% (*14*). The authors noted that response with PLD was achieved faster than had been observed with doxorubicin + bleomycin + vincristine in the same treatment centres in an earlier study (eight or fewer cycles with PLD versus 12 cycles with doxorubicin + bleomycin + vincristine).

Summary of evidence: harms

The randomized trial comparing PLD with the doxorubicin + bleomycin + vincristine regimen (*11*) reported that PLD had significantly lower rates of: grade 3 and 4 peripheral neuropathy (6% (8/133) versus 14% (17/125), *P* = 0.002)); nausea or vomiting (15% (20/133) versus 34% (42/125), *P* < 0.001)); and alopecia (1% (1/133) versus 19% (24/125), *P* < 0.001)). The rate of mucositis/stomatitis was significantly higher in patients receiving PLD (5% (6/133) versus 2% (2/125), *P* = 0.026). No significant differences were found between treatment groups in overall grade 3 and 4 adverse events, grade 3 and 4 anaemia or grade 3 and 4

leukopenia. When interpreting these findings, it is important to note that these patients did not receive HAART, and all patients died by 6 months of follow-up. Median CD4 count was 13.0 cells/microlitre in the doxorubicin + bleomycin + vincristine group and 12.5 cells/microlitre in the PLD group.

The randomized trial comparing PLD with bleomycin + vincristine (*10*) reported that PLD had a significantly lower rate of paraesthesia (3.3% versus 14.2%, $P < 0.005$) and constipation (1.7% versus 10.8%, $P < 0.01$), a higher rate of leukopenia (71.9% versus 50.8%, $P < 0.001$) and opportunistic infections (49.6% versus 30.0%, $P < 0.002$). No significant differences were found between treatment groups in the overall rate of adverse events of any severity. When interpreting these findings, it is important to note that these patients did not receive HAART, although 48.8% of patients in the PLD arm and 56.7% in the bleomycin + vincristine arm were taking one or more antiretroviral drug.

The randomized trial comparing PLD with paclitaxel (*13*) reported a higher incidence of grade 3 or higher toxicity in the paclitaxel arm, although the difference was not significant (84% versus 66%, $P = 0.077$). Similarly, grade 3 and 4 neutropenia occurred more frequently in the paclitaxel group (58% versus 41%, $P = 0.184$). The incidence of grade 1 and 2 alopecia was significantly higher in the paclitaxel arm (58% versus 11%, $P < 0.001$) as was the incidence of sensory neuropathy (26% versus 9%, $P = 0.045$). This trial (with 82 patients included in the toxicity comparison) was not powered to detect a clinically significant difference in neutropenia rates.

A 2020 meta-analysis of PLD versus paclitaxel as first-line treatment for ovarian cancer (any stage) found that paclitaxel was associated with significantly higher rates of neurotoxicity (RR 5.59, 95% CI 1.43 to 21.84) and allergy (RR 1.8, 95% CI 1.06 to 3.24), and higher rates of leukopenia (RR 1.55, 95% CI 0.99 to 2.44) (*15*). No significant differences were found in rates of neutropenia (RR 1.03, 95% CI 0.78 to 1.35), cardiotoxicity (RR 0.51, 95% CI 0.06 to 3.99), fatigue (RR 0.84, 95% CI 0.53 to 1.34) or nausea/vomiting (RR 0.66, 95% CI 0.32 to 1.37). Adverse events that were significantly more common with PLD included anaemia and thrombocytopenia (*15*). A 2021 meta-analysis of PLD versus paclitaxel in recurrent ovarian cancer found that, compared with paclitaxel plus carboplatin, PLD plus carboplatin had significantly lower rates of neutropenia, allergic reactions and arthralgia/myalgia. Anaemia and thrombocytopenia were significantly more common in the PLD arm than the paclitaxel arm (*16*).

The most commonly reported adverse events with PLD in the product information documents of the United States Food and Drug Administration and the European Medicines Agency were haematological (thrombocytopenia, anaemia and neutropenia). The most common non-haematological adverse event reported was nausea (*17,18*). The medicine carries a box warning in the United States for infusion reactions, myelosuppression, cardiotoxicity, liver impairment and substitution with non-liposomal doxorubicin (*17*).

WHO guidelines

The 2014 WHO guidelines on the treatment of skin and oral HIV-associated conditions in children and adults recommend immediate initiation of antiretroviral therapy in adults, adolescents and children living with HIV who are diagnosed with mild-to-moderate Kaposi sarcoma and immediate initiation of antiretroviral therapy in combination with systemic chemotherapy in adults, adolescents and children living with HIV who are diagnosed with severe symptomatic Kaposi sarcoma. Recommended chemotherapy regimens in adults, adolescents and children may include: doxorubicin + bleomycin + vincristine; bleomycin + vincristine; and, when available or feasible, liposomal anthracyclines (doxorubicin or daunorubicin), paclitaxel or oral etoposide at sites with the infrastructure, staff and resources to administer chemotherapy drugs and provide appropriate monitoring and supportive care (*19*).

Costs/cost–effectiveness

The application identified six studies that evaluated the cost–effectiveness of PLD versus various comparators including: liposomal daunorubicin; bleomycin + vincristine; doxorubicin + bleomycin + vincristine; paclitaxel; and oral etoposide (*20–25*). In general, these studies suggest that PLD is a cost-effective treatment compared with liposomal daunorubicin but less cost-effective when compared with bleomycin + vincristine or doxorubicin + bleomycin + vincristine or paclitaxel.

The application also presented a comparison of the price per treatment cycle of PLD and paclitaxel in selected countries which showed substantial variation across settings. For example, prices per treatment cycle for PLD ranged from about US$ 150 in India to US$ 709 in Brazil. Prices per treatment cycle for paclitaxel were lower, ranging from US$ 42 in Indonesia and Ukraine to US$ 350 in Brazil and El Salvador.

Availability

PLD has regulatory approval globally for several indications, including Kaposi sarcoma. It is available in innovator and generic brands.

PLD is also available for pooled procurement from the Global Fund, as a strategic medicine used in HIV programmes.

Other considerations

The EML Cancer Medicines Working Group reviewed the application and advised that it supported the inclusion of pegylated liposomal doxorubicin on the Model Lists for the treatment of advanced-stage Kaposi sarcoma in adults and children based on a positive benefit–risk profile. The Working Group noted that PLD was associated with relevant survival benefits for patients and reduced harms

when compared with other chemotherapies (bleomycin, vinblastine, vincristine, vinorelbine and etoposide).

The Working Group reiterated the relevance of paclitaxel for Kaposi sarcoma, as it is associated with benefits similar to PLD in adults and it is likely to be more available than PLD in resource-constrained settings. However, paclitaxel is associated with higher toxicity compared with PLD, particularly neutropenia and sensory neuropathy. While generics of PLD are becoming more available, the Model List must reiterate the relevance of paclitaxel as first-line chemotherapy for adult patients with advanced AIDS-associated Kaposi sarcoma in sub-Saharan Africa.

Committee recommendations

The Expert Committee acknowledged the public health relevance of effective treatments for Kaposi sarcoma, also noting that this disease disproportionately affects people in low- and middle-income countries.

The Committee considered that the evidence presented from several clinical trials suggests that PLD is superior in efficacy to the alternative chemotherapy regimens involving bleomycin, vincristine or vinblastine, with or without non-liposomal doxorubicin or daunorubicin. It is also non-inferior to paclitaxel. In addition, PLD may be associated with reduced harms compared with alternative chemotherapies.

The Committee considered the comments of the Cancer Medicines Working Group that reiterated the relevance of paclitaxel as first-line chemotherapy for Kaposi sarcoma, which is associated with similar clinical benefits as PLD in adults and may be more widely available and affordable. However, the Committee noted that paclitaxel is associated with higher toxicities than PLD, especially neutropenia and sensory neuropathy. Therefore, the Committee considered that the addition of PLD may offer an additional option with a more favourable side-effect profile and dosing schedule. The Committee also noted that PLD may be preferable to paclitaxel for children with Kaposi sarcoma, as experience with paclitaxel in this population is still limited.

The Expert Committee therefore recommended the inclusion of PLD on the complementary list of the EML and EMLc for the treatment of Kaposi sarcoma.

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8.2.2 Targeted therapies

Cyclin-dependent kinase 4/6 inhibitors – addition – EML

Abemaciclib	**ATC code: L01EF03**
Palbociclib	**ATC code: L01EF01**
Ribociclib	**ATC code: L01EF02**

Proposal

Addition of cyclin-dependant kinase (CDK) 4/6 inhibitors (abemaciclib, palbociclib and ribociclib) to the complementary list of the EML for the treatment of hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2−) advanced breast cancer.

Applicant

European Society for Medical Oncology

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department highlighted that there was clinical evidence showing CDK 4/6 inhibitors to be associated with overall survival gains compared with older treatment regimens, but long-term or real-world data were limited. The technical department expressed its preference to focus on the established first-line therapy (e.g. hormone therapies) that was more feasible in settings with weaker health systems.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strengths(s)

Abemaciclib – Tablet: 50 mg, 100 mg, 150 mg

Palbociclib – Tablet: 75 mg, 100 mg, 125 mg

Ribociclib – Tablet: 200 mg

Core/complementary

Complementary

Individual/square box listing

Square box, with palbociclib as the representative medicine and abemaciclib and ribociclib as therapeutic alternatives.

Background

CDK 4/6 inhibitors were considered for inclusion on the EML in 2021. At the time, the Expert Committee noted that the results of the clinical trials in first- and second-line treatment settings suggested a potentially meaningful survival benefit. However, the medicines were not recommended for inclusion given that the survival data were immature, and there was uncertainty whether promising progression-free survival gains would translate to an increase in overall survival.

Other areas of uncertainty identified by the Committee included questions on the optimal dose and duration of treatment, use in early-stage disease, and whether meaningful clinical differences existed between individual medicines within the pharmacological class.

The Committee also noted that CDK 4/6 inhibitors are unlikely to be cost-effective in most settings due to their high prices which would pose serious affordability challenges for most countries (*1*).

Public health relevance

Breast cancer is the leading cause of morbidity, disability and mortality in women worldwide. In 2020, 2.3 million new cases of breast cancer were diagnosed, which accounted for 25% of all malignancies in women. Breast cancer is the most diagnosed malignancy in women worldwide, and the main cause of death in women in 110 countries. Almost 20% of cancer deaths in 2018 were from breast cancer (*2*), and 60% of incident breast cancer cases and two thirds of the related mortality occurred in low- and middle-income countries. The HR+/HER2– breast cancer subtype is the most common type of breast cancer, reported in more than two thirds of all cases (*3*).

In high-income countries, the incidence of breast cancer is high and mortality rates are low, while in low- and middle-income countries, the incidence is lower, but mortality rates are high. The overall 5-year survival rates for high-income countries are estimated to be more than 85%. In comparison, in low- and middle-income countries, 5-year survival rates range between 38% and 60% (*4*). Impaired timely access to cancer services is a barrier for the curative management of the early disease, with most of the patients presenting with locally advanced and/or non-resectable diseases or metastatic cancer (*2*).

Summary of evidence: benefits

Meta-analysis of randomized trials

A systematic review and meta-analysis of six studies (3421 participants, treated with: fulvestrant plus ribociclib, palbociclib or abemaciclib; letrozole plus palbociclib or ribociclib or a non-steroidal aromatase inhibitor; or tamoxifen plus ribociclib) evaluated the efficacy of CDK 4/6 inhibitors for the treatment of metastatic breast cancer (*5*). For overall survival, the pooled analysis showed a significant reduction in the risk of dying in patients receiving CDK 4/6 inhibitors (hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.68 to 0.85).

Randomized trials

The application presented evidence from seven randomized, placebo-controlled, double-blind, phase III clinical trials: MONARCH 2 and 3; PALOMA 2 and 3; and MONALEESA 2, 3, and 7. The schedules for the treatment within the clinical trials were the same as those approved for the clinical use by regulatory authorities. All the studies were designed for patients with HR+/HER2– advanced breast cancer. All the studies had safety and objective response rates as secondary endpoints. Overall survival was a protocol-specified secondary endpoint in all the trials.

First-line therapy

Abemaciclib

The MONARCH 3 trial evaluated abemaciclib in combination with aromatase inhibitors as initial therapy in 493 postmenopausal women with advanced breast cancer (*6*). Participants were randomized 2:1 to receive abemaciclib in combination with anastrozole or letrozole, or placebo in combination with anastrozole or letrozole. The absolute progression-free survival gain for the abemaciclib arm was 13.4 months (HR 0.54, 95% CI 0.42 to 0.70). Interim analysis after median follow-up of 70 months showed a median overall survival gain for abemaciclib of 12.6 months (HR 0.75, 95% CI 0.58 to 0.97) (*7*). Based on this trial, abemaciclib received a score of 3 on the European Society for Medical Oncology magnitude of clinical benefit scale (*8*).

Palbociclib

The PALOMA 2 trial evaluated palbociclib in combination with letrozole as first-line therapy in 666 postmenopausal women with advanced breast cancer (*9*). Participants were randomized 2:1 to palbociclib plus letrozole or placebo plus letrozole. The absolute progression-free survival gain for the palbociclib arm was 10.3 months (HR 0.58, 95% CI 0.46 to 0.72). Interim analysis showed no difference between the intervention and comparator arms in median overall survival. Based on this trial, palbociclib received a score of 3 on the European Society for Medical Oncology magnitude of clinical benefit scale (*8*).

Ribociclib

The MONALEESA 2 trial evaluated ribociclib in combination with letrozole as first-line therapy in 668 postmenopausal women with advanced breast cancer (*10*). Participants were randomized 1:1 to receive either ribociclib plus letrozole or placebo plus letrozole. After median follow-up of 26.4 months, the absolute progression-free survival gain for the ribociclib arm was 9.3 months (HR 0.57, 95% CI 0.46 to 0.70). After a median follow-up of 6.6 years, ribociclib showed an absolute survival gain compared to placebo of 12.5 months (HR for death 0.76, 95% CI 0.63 to 0.93). Based on updated results from MONALEESA 2, ribociclib received a score of 4 on the European Society for Medical Oncology magnitude of clinical benefit scale (*8*).

The MONALEESA 7 trial evaluated ribociclib plus endocrine therapy (anastrozole, letrozole or tamoxifen, each combined with goserelin) as first-line therapy for advanced breast cancer in 672 premenopausal women (*11*). Participants were randomized 1:1 to either endocrine therapy with ribociclib or endocrine therapy with placebo. Median progression-free survival was 23.8 months versus 13.0 months in the ribociclib and placebo arms, respectively, with an absolute progression-free survival gain of 10.8 months (HR 0.55, 95% CI 0.44 to 0.69). An absolute gain in overall survival of 10.7 months (HR 0.76, 95% CI 0.61 to 0.96) was demonstrated for ribociclib. Based on this trial, ribociclib received a score of 5 on the on the European Society for Medical Oncology magnitude of clinical benefit scale (*8*).

Second-line therapy

Abemaciclib

The MONARCH 2 trial evaluated abemaciclib in combination with fulvestrant as second-line therapy for advanced breast cancer in 669 women of any menopausal status (*12*). Participants were randomized 2:1 to receive abemaciclib or placebo each combined with fulvestrant. After median follow-up of 19.5 months, median progression-free survival was 16.4 months in the abemaciclib arm versus 9.3 months in the placebo arm, an absolute progression-free survival gain of 7.1 months (HR 0.55, 95% CI 0.45 to 0.68). After median follow-up of 47.7 months, median overall survival was 46.7 months in the abemaciclib arm versus 37.3 months in the placebo arm, an absolute overall survival gain of 9.4 months (HR 0.76, 95% CI 0.61 to 0.95) (*13*). Based on this trial, abemaciclib received a score of 4 on the European Society for Medical Oncology magnitude of clinical benefit scale (*8*).

Palbociclib

The PALOMA 3 trial evaluated palbociclib in combination with fulvestrant as second-line therapy for advanced breast cancer in 521 women of any menopausal status (*14*). Participants were randomized 2:1 to either palbociclib or placebo,

each combined with fulvestrant. After median follow-up of 8.9 months, median progression-free survival was 9.5 months in the palbociclib arm versus 4.6 months in the placebo arm, an absolute progression-free survival gain of 4.9 months (HR 0.46, 95% CI 0.36 to 0.59). After a median follow-up of 44.8 months, median overall survival was 34.9 months in the palbociclib arm versus 28.0 months in the placebo arm, an absolute gain in overall survival of 6.9 months (HR 0.81, 95% CI 0.64 to 1.03). Based on this trial, palbociclib received a score of 4 on the European Society for Medical Oncology magnitude of clinical benefit scale (*8*).

Ribociclib

The MONALEESA 3 trial evaluated ribociclib plus fulvestrant as first- and second-line therapy for advanced breast cancer in 726 postmenopausal women (*15*). Participants were randomized 2:1 to either ribociclib or placebo, each combined with fulvestrant. Median progression-free survival was 20.5 months in the ribociclib arm versus 12.8 months in the placebo arm, an absolute progression-free survival gain of 7.7 months (HR 0.59, 95% CI 0.48 to 0.73). The estimated overall survival at 42 months was 57.8% in the ribociclib arm versus 45.9% in the placebo arm (HR 0.72, 95% CI 0.57 to 0.92). An absolute gain in overall survival of 12.2 months (HR 0.59, 95% CI 0.59 to 0.90) for ribociclib was calculated. Based on this trial, ribociclib received a score of 4 on the European Society for Medical Oncology magnitude of clinical benefit scale (*8*).

Real-world studies

A real-world study from five European countries (1017 participants) evaluating treatment patterns and clinical outcomes associated with palbociclib combination therapy showed progression-free survival rates at 12 and 24 months of 88.2% and 62.2% in the first-line setting and 81.1% and 55.2% in the second-line setting, respectively (*16*). Overall survival rates at 12 and 24 months were 97.7% and 93.2% in the first-line setting and 96.8% and 85.2% in the second-line setting, respectively. Dose reductions were observed with palbociclib in 11% and 17% of the patients from Europe in the first- and second-line settings, respectively, mostly related to the neutropenia.

The phase IIIb study CompLEEment1 (3246 participants; 38 countries) assessed the benefit of ribociclib and letrozole as first-line treatment in the subgroup of patients less likely to be included in the pivotal trials (*17*). Patients with a poorer performance status, namely the Eastern Cooperative Oncology Group (ECOG) 2, largely under-represented in clinical trials, showed a comparative benefit to patients with better performance status (e.g. ECOG 0 or 1). In particular, the median time to disease progression was 19.5 months (95% CI 13.5 months to not reached) in the ECOG 2 patients. Safety results were consistent with those in the overall CompLEEment1 population. Neutropenia was the most common side-effect in the ECOG 2 patient subgroup, reported in

63.4% of patients. Treatment discontinuation due to adverse events was reported in 11.6% of patients in the ECOG 2 subgroup, mostly because of neutropenia.

The RENATA study presented a prospective analysis of real-world use of palbociclib with endocrine therapy in 128 patients with ER+/HER2– advanced breast cancer between October 2015 and August 2019 in Buenos Aires, Argentina (*18*). Overall progression-free survival was 36.7 months in the first-line setting and 24.2 months in the second-line setting. Treatment was interrupted in 2% of participants due to drug-related toxicity. Neutropenia was the main moderate-to-severe adverse event, of which 7% was febrile neutropenia (higher than in the pivotal trials). Overall, the data on survival were consistent with the pivotal PALOMA trials (*18*).

A study in the Republic of Korea analysed the outcomes of 169 patients with breast cancer receiving letrozole or fulvestrant plus palbociclib (*19*). The median progression-free survival rates with letrozole plus palbociclib and fulvestrant plus palbociclib were 25.6 months (95% CI 19.1 months to not reached) and 6.37 months (95% CI 5.33 months to not reached) in the first- and second-line, respectively. Neutropenia was observed in 88.3% of the patients, most commonly grade 3 and 4.

In Japan, a phase II single-arm, open-label clinical trial investigated the efficacy and safety of palbociclib plus letrozole as first-line treatment in 42 postmenopausal patients with advanced breast cancer (*20*). After median duration of treatment of 33 months, the probability of progression-free survival at 1 year was 75.6% (90% CI 62.4% to 84.7%), with a median progression-free survival of 35.7 months (95% CI 21.7 to 46.7 months). The safety profile in the Japanese population was consistent with the profile reported in non-Asian patients; neutropenia was the most common adverse effect, with grade 3 and 4 neutropenia occurring in 93% of patients; however, only one patient experienced febrile neutropenia.

Summary of evidence: harms

The main adverse effect of the pharmacological class of CDK 4/6 inhibitors is haematological toxicity. Their use is associated with a predictable, reversible and generally non-infection-prone neutropenia – related to cell cycle effects on the haematopoiesis of the cell cycle blockade (*21*).

A systematic review and meta-analysis of the efficacy and safety of CDK 4/6 inhibitors from the phase III clinical trials reported an onset of grade 3 and 4 neutropenia in 65%, 58% and 26% of patients using palbociclib, ribociclib and abemaciclib, respectively (*22*). However, febrile neutropenia occurred in < 1% of the trial population with all of these compounds. In general, the onset of moderate-to-severe neutropenia leads to a delay, temporary interruption or dose reduction in administration of the CDK 4/6 inhibitor but is less likely to require other

interventions. For example, the use of the granulocyte-stimulating factors and/or antibiotic prophylaxis is not usually required, as febrile neutropenia occurs quite rarely (*23*). The only precaution recommended with the use of CDK 4/6 inhibitors is a complete blood count at the beginning of each cycle and after 2 weeks for the first two cycles to check the bone marrow reserve. Moreover, CDK 4/6 inhibitors are associated with molecule-specific safety profiles that inform the clinician's decision to use one compound over another, along with patient preference. The different safety profiles are currently the most important factor considered in the treatment decision for patients with HR+/HER2– advanced breast cancer in first- or second-line therapy, in the absence of direct comparisons. The main differences in the safety profiles of abemaciclib, palbociclib and ribociclib from the phase III trials are summarized in Table 17.

Table 17
Adverse events in patients treated with CDK 4/6 inhibitors

Adverse event	Percentage of patients		
	Abemaciclib	**Palbociclib**	**Ribociclib**
Any grade 3 and 4	58	74	79
Neutropenia (grade 3 or 4)	26	65	58
Neutropenic fever	< 1	< 1	< 1
Anaemia	30 (7 grade 3)	24 (5.5 grade 3 or 4)	19
Increased aspartate aminotransferase or alanine aminotransferase	All grades < 10	All grades < 10	25 (9 grade 3 or 4)
Diarrhoea	87 (13 grade 3)	25	35
Nausea	45 (3 grade 3)	35	52

WHO guidelines

WHO guidelines for the treatment of breast cancer are not available.

Costs/cost–effectiveness

Most cost–effectiveness analyses have found CDK 4/6 inhibitors unlikely to be cost-effective at current prices and usual willingness-to-pay thresholds.

The average cost for 1 month of treatment with CDK 4/6 inhibitors in Europe was estimated in the application as between US$ 2000 and US$ 7000 for

palbociclib, US$ 8900 for ribociclib and between US$ 3500 and US$ 12 000 for abemaciclib (*24*). In comparison, while the total costs per year for letrozole and palbociclib have been estimated at around US$ 52 400, letrozole alone is US$ 252.

Findings from cost–effectiveness studies of CDK 4/6 inhibitors were previously reported in 2021 (*1*). Incremental cost–effectiveness ratios range from US$ 147 000 per quality-adjusted life year gained in Singapore (*25*) to US$ 634 000 per quality-adjusted life year gained in the United States (*26*).

Availability

Abemaciclib, palbociclib and ribociclib all have regulatory approval in multiple countries globally.

Abemaciclib has primary patent protection until 2029.

Palbociclib has primary patent protection until 2023 in both the United States (at the US Securities and Exchange Commission) and Europe (at the European Patent Office); however, in both regions the patents may be extended up to 5 years (in 2028) under the statutes that provide for patent term extensions.

Ribociclib has primary patent protection until 2027–2029.

Generic products are not currently available for any of the three medicines.

Other considerations

While the pivotal clinical trials did not exclude patients of African ancestry, the definition of restrictive enrolment criteria (e.g. an absolute neutrophil count of 1500/mm^3 or more) in these trials may have affected the likelihood of eligibility and screening success of women of African ancestry, who have, on average, lower neutrophil counts than Caucasian women (*27*). This represents a structural barrier as a result of a less inclusive conceptualization and design of the studies. No study has been conducted specifically in women of African ancestry and this gap is a priority area for research. The PALINA study is a phase II clinical trial investigating palbociclib in combination with letrozole or fulvestrant in African–American women with HR+/HER2– advanced breast cancer (*28*).

Committee recommendations

The Expert Committee noted that breast cancer continues to be the leading cause of cancer death in women, and that more than half of women diagnosed with breast cancer have HR+/HER2– disease, making effective treatments for this disease a high priority.

The Committee noted that in several high-income settings, CDK 4/6 inhibitors were emerging as first-line treatment for HR+/HER2– metastatic breast cancer. However, in low- and middle- income countries CDK 4/6 inhibitors are generally not available and aromatase inhibitors, tamoxifen and cytotoxic agents are still the main treatment options, with a relevant overall survival gain (4+ years).

The Committee noted that, overall, the updated results of clinical trials on CDK 4/6 inhibitors for first-line and second-line treatment suggested a meaningful survival benefit when added to endocrine therapy (aromatase inhibitors, tamoxifen or fulvestrant) compared with endocrine therapy alone. In addition to overall survival gains, secondary benefits have been reported in trials, such as delayed time to use of chemotherapy (by about a year) and delayed deterioration in quality of life. However, the Committee noted that the pivotal trials did not include patients with low baseline neutrophil count who may be at greater risk of haematological adverse events, or patients from certain ethnic or age groups, which may influence the generalizability of the findings to the wider population.

The Committee also considered that uncertainties still existed about the optimal, most active and best tolerated dose, noting that many patients had to reduce the dose in the pivotal trials. The Committee also considered that there were uncertainties about the duration of treatment, positioning as first or second line in the metastatic setting, and whether clinically significant differences existed between agents within the pharmacological class.

As was the case when these medicines were considered by the Expert Committee in 2021, the Committee noted the continuing high prices of these medicines, which pose serious affordability challenges, especially in low- and middle-income countries.

The Expert Committee therefore did not recommend the inclusion of abemaciclib, palbociclib, and ribociclib on the EML for the treatment of patients with HR+/HER2– advanced breast cancer. The Committee requested that data for these medicines continue to be evaluated as they evolve, including data on price. The Committee also reiterated the recommendation of the 2021 Expert Committee that this class of medicines be flagged to the Medicines Patent Pool as potential candidates for voluntary licensing agreements.

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Osimertinib – addition – EML

Osimertinib	ATC code: L01EB04

Proposal

Addition of osimertinib to the complementary list of the EML for first-line treatment of epidermal growth factor receptor (EGFR) mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

Applicant

European Society for Medical Oncology

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department advised that it did not support the inclusion of osimertinib on the EML at this time. The technical department acknowledged that osimertinib was associated with clinical benefits when compared with the first-generation tyrosine kinase inhibitors, gefitinib and erlotinib, for overall survival gain, and it had a more favourable toxicity profile. However, first-generation tyrosine kinase inhibitors are already included on the EML and are more cost-effective than osimertinib and have a lower impact on health budgets.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strengths(s)

Tablet: 40 mg, 80 mg (as mesylate)

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor. It was previously considered for inclusion on the EML by the Expert Committee in

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2021 but was not recommended because of concerns about the clinical benefit and comparative cost–effectiveness. The Expert Committee noted that the application to list osimertinib was based on the results of a single randomized control trial (FLAURA) in which overall survival data were immature. Therefore, the efficacy of osimertinib compared with erlotinib and gefitinib was uncertain.

Furthermore, the Committee was concerned about the high price of osimertinib and several analyses had concluded that osimertinib was not cost-effective at common willingness-to-pay thresholds. At the time, the Committee considered listing osimertinib as a therapeutic alternative to the EGFR tyrosine kinase inhibitors included on the EML. However, given the difference in prices between the medicines, the Committee decided against this option because of the considerable additional expenditure it would impose at the country level (*1*).

Public health relevance

Lung cancer is the most diagnosed and leading cause of death from cancer worldwide, with more than 2 million new cases and almost 1.8 million deaths in 2020 (*2*). Lung cancer is a highly lethal malignancy, with an economic burden estimated at around US$ 8 billion in productivity loss in the BRICS countries – Brazil, Russia, India, China and South Africa (*3*).

More than 80% of lung cancers are classified as non-small cell (*4*), and about 70% are diagnosed at advanced or metastatic stages, with large regional variation (*3*, *5*, *6*). Targeted therapies have changed the therapeutic landscape for patients with NSCLC that is molecularly druggable (e.g. EGFR mutations, anaplastic lymphoma kinase rearrangements, ROS proto-oncogene 1 (*ROS1*) rearrangements and *BRAF* mutations) in metastatic disease. However, these therapies are ineffective in most patients with NSCLC who have tumours that lack such genetic alterations (*7*).

The overall prevalence of EGFR mutations has been reported as about 30%, although this varies by world region, risk factors and population phenotype. For instance, the Asian-Pacific region has the highest prevalence of EGFR mutations (47%), followed by South America (36%), North America (22%), Africa (21%), Europe (15%) and Oceania (12%) (*8–10*).

Summary of evidence: benefits

The FLAURA trial was a phase III, double-blind, clinical trial (556 participants) that compared osimertinib with gefitinib and erlotinib for first-line treatment of EGFR-mutated locally advanced or metastatic NSCLC (*11*, *12*). Participants were randomized in a 1:1 ratio to receive osimertinib 80 mg once daily, or standard treatment (gefitinib 250 mg once daily or erlotinib 150 mg once daily) until disease progression, unacceptable toxicity or withdrawal of consent.

At the time of the primary analysis for the primary endpoint of progression-free survival, osimertinib was associated with a statistically significant improvement

compared with standard treatment (median progression-free survival 18.9 months versus 10.2 months; hazard ratio (HR) for disease progression or death 0.46, 95% confidence interval (CI) 0.37 to 0.57). Osimertinib also demonstrated a significant progression-free survival benefit for participants with central nervous system metastasis, a common site of progression of NSCLC and frequently responsible for deterioration in quality of life (median progression-free survival 15.2 months versus 9.6 months; HR for disease progression or death 0.47, 95% CI 0.30 to 0.74) (*11*).

A final analysis was performed for the secondary endpoint of overall survival with a median duration of follow-up for overall survival of 35.8 months in the osimertinib group and 27.0 months in the comparator group. Median overall survival favoured the osimertinib group over the standard treatment group (median overall survival 38.6 months versus 31.8 months; HR 0.80, 95% CI 0.64 to 1.00), that is, a 6.8-month survival gain in absolute terms. At 36 months, 54% of participants in the osimertinib group were alive compared with 44% in the comparator group (*12*).

Based on the FLAURA trial, osimertinib received a score of 4 on the magnitude of clinical benefit scale of the European Society for Medical Oncology (*13*).

A 2022 systematic review and meta-analysis of seven randomized controlled trials (3335 participants) evaluated the efficacy and safety of osimertinib in patients with EGFR-mutated NSCLC (*14*). Pooled efficacy comparisons showed that osimertinib was associated with higher overall response rate (relative risk (RR) 2.42, 95% CI 0.92 to 6.39; three studies), significantly longer progression-free survival (HR 0.28, 95% CI 0.18 to 0.44; four studies) and significantly longer overall survival (HR 0.78, 95% CI 0.68 to 0.97; four studies) versus the comparators (chemotherapy, other EGFR-tyrosine kinase inhibitors, docetaxel plus bevacizumab, and placebo).

Given the public health relevance of elderly populations in the treatment of NSCLC, a network meta-analysis of 12 randomized controlled trials (3779 participants) assessed the efficacy of different first-line treatments for EGFR-mutated NSCLC in elderly and non-elderly patients (*15*). In patients older than 65 years, 12 studies reported progression-free survival and seven studies reported overall survival. For the comparison of osimertinib versus standard of care (first-generation tyrosine kinase inhibitors) plus chemotherapy, no significant differences were seen between treatment arms for progression-free survival (HR 0.87, 95% credible interval (CrI) 0.13 to 7.52; favouring osimertinib) or overall survival (HR 0.95, 95% CrI 0.34 to 2.54; favouring standard of care plus chemotherapy).

As central nervous system progression is a special concern due to its frequency and associated morbidity and mortality in metastatic NSCLC patients, a prespecified analysis was conducted in 128 patients from FLAURA trial. The

results showed a 2.5 times higher central nervous system overall response rate (66% versus 43%), and a lower central nervous system progression rate of 20% versus 39% in favour of osimertinib compared with first-generation tyrosine kinase inhibitors (*16*).

Summary of evidence: harms

From evidence presented previously from the FLAURA trial (*12*), adverse events of grade 3 or higher were reported in 42% and 47% of participants in the osimertinib group and standard treatment group, respectively. The most reported adverse events (any grade) possibly related to osimertinib treatment (investigator assessed) were diarrhoea, rash or acne, paronychia, dry skin, and stomatitis. Serious adverse events were reported in 27% of the participants in each treatment arm. Decreased ejection fraction was reported in a greater proportion of participants in the osimertinib group than the standard treatment group (5% versus 2%). Similarly, QT prolongation was also reported in a greater proportion of participants in the osimertinib group than the standard treatment group (10% versus 4%). Compared with the primary analysis, there were no new reports of interstitial lung disease or pneumonitis, which were both reported in 2% and 1% of participants in the osimertinib and standard treatment groups, respectively.

An analysis of patient-reported outcomes of FLAURA trial patients showed similar outcomes for both arms for the safety, toxicity and quality-of-life domains analysed (*17*). According to FLAURA data, grade 3 or higher adverse event rates were 34% in the osimertinib group and 45% in the comparator group, indicating a better toxicity profile for osimertinib.

WHO guidelines

WHO guidelines for treatment of NSCLC are not available.

Costs/cost–effectiveness

No new cost–effectiveness data were presented in the application beyond those considered in 2021 (*18*, *19*). Osimertinib is generally considered not to be cost-effective in most health care systems at current prices and common willingness-to-pay thresholds.

In a 2019 study that compared the cost–effectiveness of treatment strategies for NSCLC, costs per day for osimertinib in China and the United States were US$ 259 (US$ 129–259) and US$ 568 (US$ 284–568), respectively (*20*).

Availability

Osimertinib (manufactured by Astra Zeneca) has primary patent and secondary patent protection until 2032 and 2035, respectively. A generic version is available in Bangladesh.

Other considerations

The EML Cancer Medicines Working Group reviewed the application and advised that it did not support the inclusion of osimertinib on the EML for first-line treatment of EGFR-mutated locally advanced or metastatic NSCLC. The Working Group noted that the evidence indicated that osimertinib had meaningful overall survival benefit compared with the earlier generation tyrosine kinase inhibitors currently listed on the EML (erlotinib, gefitinib and afatinib) when used as monotherapy. However, the Working Group noted evidence from a randomized, phase III trial comparing gefitinib monotherapy versus gefitinib in combination with chemotherapy (*21*) in which the addition of chemotherapy to gefitinib significantly prolonged overall survival: not reached versus 17 months (95% CI 13.5 to 20.5 months); HR for death 0.45 (95% CI 0.31 to 0.65). Other trials have shown similar results. The Working Group therefore considered that the benefit of first-generation tyrosine kinase inhibitors in combination with chemotherapies might provide similar benefits to those associated with the use of osimertinib, albeit at a higher risk of toxicity. At the current high price, osimertinib has not been found to be cost-effective and would pose serious affordability challenges, especially in resource-constrained settings.

The Working Group also noted the availability of aumolertinib, which received regulatory approval from the Chinese National Medical Products Administration for the treatment of NSCLC patients with EGFR T790M mutations who had progressed on or after other EGFR tyrosine kinase inhibitor therapy. The approval was based on findings from the open-label phase II APOLLO study (*22*). Additional support for the efficacy of aumolertinib comes from the phase III AENEAS trial, in which progression-free survival was significantly longer with aumolertinib than gefitinib (HR 0.46, 95% CI 0.36 to 0.60) (*23*).

Committee recommendations

The Expert Committee once again recognized the public health importance of effective and safe treatments for lung cancer, a disease that has a high global burden. The Committee recalled that osimertinib was not recommended for inclusion on the EML in 2021, despite promising data from the FLAURA trial showing osimertinib to be associated with extended overall survival compared with earlier generation EGFR tyrosine kinase inhibitors already included on the EML. The 2021 Committee considered the data at the time were still immature and had serious concerns about the high price of osimertinib and lack of cost–effectiveness compared with older generation tyrosine kinase inhibitors listed on the EML for NSCLC, which are more affordable because of the availability of generic products.

The Committee noted that the current data, after a median of 35.8- and 27.0-month follow-up in the osimertinib and comparator arms, respectively,

showed a median overall survival gain of 6.8 months for osimertinib, which met the established threshold for EML consideration. However, the Committee noted again the high price of osimertinib compared with older generation tyrosine kinase inhibitors in most countries, but particularly in low- and middle-income countries. Consequently, the Committee was concerned that recommending the inclusion of osimertinib on the EML could worsen health inequity by diverting limited resources away from less expensive medicines already listed on the EML for this indication.

Furthermore, the Committee noted the input from the EML Cancer Medicines Working Group on a phase III trial comparing gefitinib in combination with chemotherapy to gefitinib monotherapy. The trial found that the addition of chemotherapy to the first-generation tyrosine kinase inhibitor significantly improved overall survival, to a magnitude similar to that associated with the use of osimertinib, albeit with a higher risk of toxicity. The Committee considered that this approach to treatment, using medicines already included on the EML, may be a more feasible, affordable and equitable option at this time, particularly in resource-constrained settings.

The Expert Committee therefore did not recommend addition of osimertinib to the complementary list of the EML for the first-line treatment of EGFR-mutated locally advanced or metastatic NSCLC. The Committee recommended that data for osimertinib continue to be evaluated as they evolve and encouraged efforts to facilitate affordable access to osimertinib in low- and middle-income settings, for example, by negotiating public health licensing agreements through the Medicines Patent Pool.

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Rituximab – new indication – EML and EMLc

Rituximab	ATC code: L01FA01

Proposal

Extension of the indications for the listing of rituximab on the complementary list of the EML and EMLc to include treatment of Burkitt lymphoma.

Applicant

European Society of Paediatric Oncology

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department commented that there was strong merit to extend the listed indications for rituximab to include the treatment of Burkitt lymphoma based on its clinical effect in decreasing early death and improving survival for advanced disease. It also highlighted that feasibility must also be considered in terms of diagnostic capacity, management of side-effects and affordability. The Global Platform for Access to Childhood Cancer Medicines, established by WHO and St Jude Children's Research Hospital in Memphis, Tennessee, will play an important role in increasing access to rituximab in low- and middle-income settings. In this context, the technical unit advised that it generally favoured the inclusion of rituximab on the Model Lists for treatment of Burkitt lymphoma.

EML/EMLc

EML and EMLc

Section

8.2.2 Targeted therapies

Dose form(s) & strengths(s)

Injection (intravenous): 100 mg/10 mL in 10 mL vial, 500 mg/50 mL in 50 mL vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Rituximab has not previously been evaluated for inclusion on the Model Lists for the treatment of Burkitt lymphoma. It is listed on the EML and/or EMLc for follicular lymphoma, chronic lymphocytic leukaemia and diffuse large B-cell lymphomas. There are a variety of chemotherapies listed on the EML and EMLc for use in the treatment of Burkitt lymphoma.

Public health relevance

Non-Hodgkin lymphomas are the fourth most common group of malignancies in children and adolescents. In 2019, the global incidence of non-Hodgkin lymphoma in people younger than 20 years was 0.98 (range 0.82 to 1.18) per 100 000 (*1*). Among non-Hodgkin lymphomas, the three main subtypes are mature aggressive B-cell lymphoma (58%), lymphoblastic lymphoma (21%), and anaplastic large cell lymphoma (13%) (*2*,*3*). Burkitt lymphoma (and leukaemia) is the most common subtype of mature aggressive B-cell lymphoma and accounts for 80% of cases (*4*).

It is estimated that 90% of children diagnosed with non-Hodgkin lymphoma live in low- and middle-income countries (*5*). Burkitt lymphoma is endemic in the area known as the Burkitt belt in sub-Saharan Africa, where it represents more than 50% of childhood cancers.

Summary of evidence: benefits

A randomized, open-label, international, phase III trial evaluated rituximab in 328 patients younger than 18 years with high-risk, mature B-cell non-Hodgkin lymphoma, 85.7% of whom had Burkitt lymphoma (*6*). After median follow-up of 39.9 months, event-free survival at 3 years was 93.9% the rituximab-chemotherapy group and 82.3% in the chemotherapy group (hazard ratio (HR) for primary refractory disease or first occurrence of progression, relapse after response, death from any cause, or second cancer: 0.32, 95% confidence interval (CI) 0.15 to 0.66). Overall survival at 3 years was 95.1% and 87.3% in the rituximab + chemotherapy and chemotherapy groups, respectively (HR for death 0.36, 95% CI 0.16 to 0.82).

A phase II window of opportunity study evaluated the activity of rituximab in 136 patients younger than 19 years with newly diagnosed paediatric mature B-cell non-Hodgkin lymphoma (*7*). The study design allowed evaluation of the activity of a single dose of rituximab (375 mg/m^2) as monotherapy in a 5-day upfront window before starting chemotherapy. Response criterion was defined as the product of the two largest perpendicular diameters of one to three lesions and/or the percentage of blasts in bone marrow or peripheral blood within 24 hours before rituximab and on day 5. In view of a possible subsequent phase III trial testing whether rituximab can be a substitute for chemotherapy drugs, a high response rate for favourable activity was set at 65%. A total of 87 participants

could be evaluated, giving a response rate of 41% (95% CI 31% to 52%), including 27 (of 67) participants with Burkitt lymphoma. The study found that single-agent rituximab was active in newly diagnosed paediatric mature B-cell non-Hodgkin lymphoma, despite the response rate being lower than set in the trial plan. The authors considered that the short window of 5 days may not have allowed the full effect of rituximab to be measured, and their findings might be an underestimate of the true response rate.

The Children's Oncology Group ANHL01P1 trial evaluated the efficacy and safety of rituximab in combination with standard chemotherapy in 45 children and young adults (younger than 30 years) with intermediate-risk mature B-cell lymphoma, of whom 56% had Burkitt lymphoma (8). The 3-year event-free survival for all 45 eligible patients was 93% (95% CI 79% to 98%). For 38 patients who received six doses of rituximab, the 3-year event-free survival was 95% (95% CI 80% to 99%) and 3-year overall survival was 95% (95% CI 83% to 99%).

Summary of evidence: harms

In the randomized, open-label, phase III trial of rituximab plus standard chemotherapy versus standard chemotherapy alone, acute adverse events of grade 4 or higher were reported in 33% and 24% of participants in the rituximab + chemotherapy and chemotherapy groups, respectively. Grade 4 or higher febrile neutropenia was reported in 11.7% and 6.5% of participants in the rituximab + chemotherapy and chemotherapy groups, respectively. The incidence of grade 4 or higher infection was 18.5% and 11.1%, respectively. Low immunoglobulin G levels were significantly higher in the patients treated with rituximab both at the end of therapy (70.3% versus 46.8%, P = 0.002) and 1 year after inclusion (55.9% versus 25.4%, P < 0.001) (6).

WHO guidelines

WHO guidelines for Burkitt Lymphoma (and/or leukaemia) are not available.

Costs/cost–effectiveness

No information on comparative cost–effectiveness of rituximab in Burkitt lymphoma was provided in the application.

The application reported the price of rituximab in the Netherlands as €213.74 for the 10 mL vial and €1068.74 for the 50 mL vial. Prices in other countries were not reported.

Availability

Rituximab intravenous injection is already included on the Model Lists and has regulatory approval and market availability in more than 60 countries globally. Innovator and biosimilar brands of rituximab were prequalified by WHO in 2020.

Other considerations

The EML Cancer Medicines Working Group reviewed the application and advised that it supported the inclusion of rituximab on the EML and EMLc for use in the treatment of Burkitt lymphoma. The Working Group acknowledged the limited availability of clinical evidence but agreed that efficacy and safety could be accepted based on the limited evidence, together with extrapolation of well known benefits and harms from the use of this medicine in adults, and for other indications in children, as part of standard cancer care. The Working Group acknowledged that expanding the indications for rituximab would support the goals of the WHO Global Paediatric Cancer Initiative and contribute to achieving the best possible cancer care for children.

Committee recommendations

The Expert Committee noted that Burkitt lymphoma is the most frequent type of non-Hodgkin lymphoma in children, the majority of children diagnosed lived in low- and middle-income countries and there was a need for safe, effective and affordable treatments.

Despite limitations in the evidence presented in the application, the Committee noted that rituximab, added to standard chemotherapy, was associated with prolonged event-free and overall survival in children and adolescents with high-grade, high-risk mature B-cell non-Hodgkin lymphoma, including Burkitt lymphoma. The Committee considered that the safety profile of rituximab was well established. The most common adverse events were febrile neutropenia, infections, hypogammaglobulinaemia and anaphylactic reactions, and these required careful monitoring and management.

The Committee noted that rituximab was available globally as originator and biosimilar brands, both of which were prequalified by WHO to facilitate greater access and affordability of quality-assured products.

The Expert Committee therefore recommended that the listing for rituximab on the complementary list of the EML and EMLc be extended to include the new indication of Burkitt lymphoma.

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Zanubrutinib – addition – EML

Zanubrutinib	**ATC code: L01EL03**

Proposal

Addition of zanubrutinib to the complementary list of the EML for the treatment of adults with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).

Applicant

Constantine S. Tam, Lymphoma Service, Alfred Hospital, and Monash University, Melbourne, Australia

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department commented that there was insufficient mature overall survival data currently available to justify inclusion of zanubrutinib on the Model List. In addition, the technical department noted the need for additional data about toxicity and feasibility of use in settings with weaker health systems without specialized clinical services.

EML/EMLc

EML

Section

8.2.2 Targeted therapies

Dose form(s) & strengths(s)

Capsule: 80 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

An application for inclusion of the Bruton tyrosine kinase inhibitor zanubrutinib on the EML for the treatment of relapsed or refractory CLL/SLL was considered by the Expert Committee in 2021 (*1*). The Expert Committee noted that

targeted therapy with Bruton tyrosine kinase inhibitors was emerging as the cornerstone of treatment for CLL/SLL in high-income countries, replacing chemoimmunotherapy as the accepted standard of care because these inhibitors were more effective, had less acute toxicity and had minimal risk of the development of secondary leukaemias.

The 2021 Committee considered that the application for inclusion of zanubrutinib on the EML for the proposed indication was premature. The available data on efficacy and safety were limited to one phase II single-arm trial, with a small number of participants. Comparative evidence of efficacy and safety versus other treatments, for example ibrutinib, was also lacking. The available data were therefore considered insufficient to evaluate the clinical benefit and safety of zanubrutinib at that time.

The 2021 Committee also noted that zanubrutinib was expensive, had unknown cost–effectiveness and had very limited global regulatory approval and availability. Therefore, the Committee did not recommend its inclusion on the EML. However, recognizing the emerging importance of Bruton tyrosine kinase inhibitors as a therapeutic class in the treatment of CLL for both first- and second-line treatment, the Committee advised that it would welcome an application including zanubrutinib and other Bruton tyrosine kinase inhibitors for inclusion on the EML in the future when mature data are available.

At the same meeting, the Expert Committee recommended the addition of ibrutinib, another Bruton tyrosine kinase inhibitor, to the complementary list of the EML for treatment of relapsed/refractory CLL. The Committee considered that the data in this case were compelling for an important sustained benefit and improved tolerability for all patients with CLL (i.e. with or without 17p deletion). The Committee acknowledged the potential of ibrutinib as a first-line treatment, particularly in the subgroup of patients with 17p deletion, but considered that the available evidence, while promising, was currently immature, unlike the evidence for relapsed/refractory disease. The Committee therefore did not recommend listing ibrutinib for first-line treatment (*1*).

The EML currently also includes bendamustine and rituximab as chemoimmunotherapy for CLL.

Public health relevance

CLL/SLL is the main non-Hodgkin lymphoma (NHL) subtype occurring mainly in middle-aged and elderly people. CLL and SLL are indolent B-cell malignancies that are often considered to be different clinical presentations of one disease, the major difference being whether a patient presents with adenopathy alone (SLL) or with an elevated lymphocyte count (CLL).

In many high-income countries, CLL is the most common leukaemia in adults and accounts for 5–11% of non-Hodgkin lymphoma with an annual

incidence of 4.2 per 100 000 people (*2*). The annual incidence increases to more than 30 per 100 000 people in those aged 80 years and older. The median age at diagnosis is 72 years (*3*). CLL is much less prevalent in Asian countries, where it accounts for 1–3% of non-Hodgkin lymphoma and has an age-adjusted incidence of 0.2–0.3 per 100 000 people (*4*). During 2010–2016, the 5-year relative survival of CLL/SLL patients in the United States was 85.7% with lower survival in older age groups. The 5-year relative survival of CLL/SLL patients aged 0–19 years, 20–64 years and 65 years and older was 93.0%, 92.4% and 81.1%, respectively (*5*).

Although mostly considered an indolent disease, clinical presentations vary widely, and CLL/SLL is still a life-limiting and incurable illness. All patients who require therapy will relapse at some point. The prognosis of patients with CLL/SLL is highly heterogeneous with median overall survival of about 10 years. Some patients can survive for many years while about 20% have a very aggressive presentation and a median overall survival of 1.5–3.0 years (*6*). The presence of a deletion of the short arm of chromosome 17p is associated with more rapid disease progression and poor response to treatment.

Summary of evidence: benefits

The SEQUOIA trial was a randomized, phase III trial comparing zanubrutinib and bendamustine–rituximab in 590 patients with previously untreated CLL/SLL (*7*). Patients without 17p deletion (del(17p13·1)) were randomly assigned to receive zanubrutinib (group A) or bendamustine–rituximab (group B). Patients with 17p deletion (del(17p13·1)) were enrolled in group C and received zanubrutinib. The primary endpoint was progression-free survival assessed by an independent review committee in the intention-to-treat population in groups A and B. At median follow-up of 26.2 months, median progression-free survival had not been reached in either group. The estimated rate of progression-free survival at 24 months was 85.5% (95% confidence interval (CI) 80.1% to 89.6%) in group A, compared with 69.5% (95% CI 62.4% to 75.5%) in group B (hazard ratio (HR) 0.42, 95% CI 0.28 to 0.63). The progression-free survival benefit was consistently observed across key patient subgroups. Estimated overall survival at 24 months was similar between the two arms: 94.3% (95% CI 90.4% to 96.7%) in group A and 94.6% (95% CI 90.6% to 96.9%) in group B. Median overall survival had not yet been reached in either group. In group C, with a median follow-up of 30.5 months, median progression-free survival was not reached, estimated 24-month progression-free survival was 88.9% (95% CI 81.3% to 93.6%) and estimated 24-month overall survival was 93.6% (95% CI 87.1% to 96.9%).

An interim analysis of health-related quality of life outcomes was assessed using patient reported outcomes using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L VAS (*8*). Patients who were treated with zanubrutinib showed greater improvements in health-

related quality of life at weeks 12 and 24 compared with patients treated with bendamustine–rituximab. At 24 weeks, these differences were significantly higher for zanubrutinib in global health status, physical functioning, role functioning, and reduction in diarrhoea, fatigue and nausea/vomiting.

The ALPINE study was a randomized, phase III trial comparing the efficacy and safety of zanubrutinib versus ibrutinib in patients with relapsed/ refractory CLL/SLL (9). Patients were randomized 1:1 to zanubrutinib 160 mg orally twice daily or ibrutinib 420 mg orally once daily. After a median follow up of 29.6 months, zanubrutinib was superior to ibrutinib for progression-free survival among 652 patients (HR for disease progression or death, 0.65, 95% CI 0.49 to 0.86), as assessed by the investigators; the results were similar to those as assessed by an independent review committee. At 24 months, the investigator-assessed rates of progression-free survival were 78.4% in the zanubrutinib group and 65.9% in the ibrutinib group. Median progression-free survival was not reached in the zanubrutinib group and was 34.2 months (95% CI 33.3 months to not estimable) in the ibrutinib group. Among patients with a 17p deletion, a TP53 mutation or both, those who received zanubrutinib had longer progression-free survival than those who received ibrutinib (HR for disease progression or death 0.53, 95% CI 0.31 to 0.88). Progression-free survival across other major subgroups consistently favoured zanubrutinib. In the intention-to-treat population, zanubrutinib had a higher overall response rate (assessed by an independent review committee) than ibrutinib (86.2% versus 75.7%), with a rate of partial response with lymphocytosis or better of 91.7% versus 83.1%.

An interim analysis of health-related quality of life outcomes was done for patient-reported outcomes using EORTC QLQ-C30 and EQ-5D-5L VAS. Compared with baseline, the positive improvements in health-related quality of life, as assessed by disease-related symptoms and treatment-related effects and functioning, were greater in cycle seven (6 months after the start of therapy), which suggests that treatment with zanubrutinib could potentially alleviate disease burden earlier than ibrutinib in this patient population. The health-related quality of life results align with results from the interim analysis of ALPINE showing that rates of adverse events such as atrial fibrillation, major bleeding and adverse events leading to discontinuation or death were lower in patients treated with zanubrutinib than ibrutinib (10).

Study BGB-3111-205 was a single-arm, open-label phase II study evaluating safety and efficacy of zanubrutinib in relapsed/refractory CLL/SLL (11). After a median follow up of almost 34 months, investigator-assessed overall response rate was 87.9%, with 6.6% of patients achieving a complete response, 69.2% achieving a partial response (PR), and 12.1% achieving a PR with lymphocytosis. Overall response rate was generally consistent across all subgroups analysed, including patients with high-risk cytogenetics (12).

Study BGB-3111-AU-003 was a phase I/II open-label, multiple dose, dose escalation and expansion study to investigate the safety and pharmacokinetics of zanubrutinib in 123 patients with treatment naïve or relapsed/refractory CLL/SLL (*13*). After a median follow-up of 47.2 months, the overall response rate was 95.9% % (treatment naïve, 100%; relapsed/refractory 95%), with 18.7% achieving complete response. Ongoing response at 3 years was reported in 85.7% of patients. The overall response rate in patients with the del(17p)/tumour protein p53 mutation was 87.5%. The 2- and 3-year estimated progression-free survival was 90% and 83%, respectively.

Summary of evidence: harms

In the phase III SEQUOIA study of zanubrutinib versus bendamustine–rituximab, grade 3 or higher adverse events were reported in 126 (52.5%) and 181 (79.7%) participants in the zanubrutinib and brentuximab–rituximab arms, respectively. Serious adverse events were reported in 88 (36.7%) and 113 (49.8%) participants, respectively. The most frequently reported adverse events ≥ grade 3 in the zanubrutinib arm were infections (16.3%), neutropenia (11.7%), other cancers (7.1%), hypertension (6.3%) and bleeding and major bleeding (both 3.8%). The most frequently reported adverse events ≥ grade 3 in the brentuximab–rituximab arm were neutropenia (51.1%), infections (18.9%), thrombocytopenia (7.9%) and hypertension (4.8%) (*7*).

In the phase III ALPINE study of zanubrutinib versus ibrutinib, treatment discontinuation was lower with zanubrutinib (26.3%) versus ibrutinib (41.2%), with most discontinuations due to adverse events (16.2% versus 22.8%) or progressive disease (7.3% versus 12.9%). Discontinuation due to cardiac disorders occurred in 0.3% versus 4.3% of participants. Rates of ≥ grade 3 adverse events, serious adverse events, dose interruptions and dose reductions were also lower with zanubrutinib compared with ibrutinib. The proportion of participants with new-onset atrial fibrillation/flutter was lower with zanubrutinib than ibrutinib (5.2% versus 13.3%); rates of other adverse events of special interest were similar between treatments. No grade 5 adverse events due to cardiac disorders occurred with zanubrutinib, whereas these occurred in six (1.9%) participants treated with ibrutinib (*9*).

The ASPEN trial was a pivotal, randomized, open-label, phase III, study comparing zanubrutinib with ibrutinib in patients with Waldenström macroglobulinaemia (*14*). In the long-term follow up of ASPEN, zanubrutinib was associated with fewer adverse events leading to death, treatment discontinuation, and dose reduction compared with ibrutinib. The prevalence of atrial fibrillation, hypertension and bleeding were lower in the zanubrutinib arm at all time intervals (*15*).

Safety data from the phase II BGB-3111-205 study (*11*) were the same as those reported in the 2021 application (*1*).

In the phase I/II BGB-3111-AU-003 study, 76 (61.8%) participants experienced at least one grade 3 or higher adverse event. Five (4.1%) participants discontinued zanubrutinib therapy due to an adverse event; three were deemed unrelated and two related to zanubrutinib therapy. One person experienced an adverse event leading to death, which was deemed unrelated by investigators (*13*).

WHO guidelines

WHO guidelines for treatment of CLL/SLL are not currently available.

Costs/cost–effectiveness

Comparative cost–effectiveness studies for zanubrutinib in the treatment of CLL/SLL are lacking.

The application presented a comparison of the costs per day of zanubrutinib (all indications) and ibrutinib (two groups of indications: CLL/SLL/Waldenström macroglobulinaemia and mantle cell lymphoma/marginal zone lymphoma) in 19 upper middle- and high-income countries. The average price difference for zanubrutinib compared with ibrutinib was –0.3% for CLL/SLL/Waldenström macroglobulinaemia indications and –24.1% for mantle cell lymphoma/marginal zone lymphoma indications. The application asserted that substitution of ibrutinib with zanubrutinib would be associated with health budget savings, based on the assumption that zanubrutinib had clinical advantages and a cheaper price than ibrutinib.

Availability

As of 30 November 2022, zanubrutinib was approved for selected indications (other than CLL/SLL) in 61 markets including Australia, Canada, China, European Union, Republic of Korea, Switzerland, the United Kingdom, and the United States. Additional regulatory submissions are under review around the world.

Zanubrutinib is currently approved for use in the treatment of CLL/SLL only in China (relapsed/refractory disease only) and the European Union. Regulatory approval in other jurisdictions is ongoing.

Other considerations

The EML Cancer Medicines Working Group reviewed the application and advised that did not support the inclusion of zanubrutinib on the EML for the treatment of CLL/SLL at this time. The working Group noted that while data supported progression-free survival gains with zanubrutinib compared to ibrutinib, it considered that the magnitude of these gains might be limited. The Working Group also noted that few long-term and real-world data were available. Furthermore, the Group acknowledged the following limitations for zanubrutinib: high rates of toxicity (particularly neutropenia); remaining uncertainty on a better safety

profile compared with ibrutinib for bleeding, hypertension and atrial fibrillation; and limited information on prices with uncertain cost–effectiveness (given that lower doses can be used with ibrutinib compared with those proposed in the application).

Committee recommendations

The Expert Committee acknowledged the role of targeted therapy with Bruton tyrosine kinase inhibitors in the treatment of CLL/SLL, especially in high-income countries, and recalled the recommendation of the 2021 Committee to include ibrutinib on the EML for patients with relapsed/refractory disease as there was compelling evidence of relevant benefit and improved tolerability compared with chemoimmunotherapy.

The Committee noted the results of clinical trials comparing zanubrutinib with bendamustine–rituximab in previously untreated patients, and with ibrutinib in patients with relapsed/refractory disease, which showed promising survival gains. However, the Committee considered that the magnitude of these gains may be limited and noted that few long-term data were currently available. The Committee also noted the toxicity concerns highlighted by the Cancer Medicines Working Group and considered longer-term data would be informative to confirm the safety profile of zanubrutinib.

The Committee also noted the high price of zanubrutinib and considered that at this price, it was unlikely to be cost-effective or affordable in most low- and middle-income settings. The Committee also considered that the substitution of ibrutinib with zanubrutinib would not necessarily be associated with savings in health budgets as proposed in the application, because lower ibrutinib doses than those described in the application could be used in clinical practice.

The Expert Committee therefore did not recommend the addition of zanubrutinib to the complementary list of the EML for the treatment of CLL/SLL. However, recognizing the role of Burton tyrosine kinase inhibitors in the treatment of CLL/SLL, the Committee recommended that the data continue to be evaluated as the evidence evolves and matures.

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8.2.3 Immunomodulators

PD-1/PD-L1 immune checkpoint inhibitors – addition – EML

Atezolizumab	**ATC code: L01FF05**
Cemiplimab	**ATC code: L01FF06**
Durvalumab	**ATC code: L01FF03**
Pembrolizumab	**ATC code: L01FF02**

Proposal

Addition of programmed cell death protein 1 (PD-1) and programmed cell death ligand-1 (PD L1) immune checkpoint inhibitors (atezolizumab, cemiplimab, durvalumab and pembrolizumab) to the complementary list of the EML for the treatment of non-oncogene-addicted locally advanced and metastatic non-small-cell lung cancer (NSCLC).

Applicant

European Society for Medical Oncology

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical team was uncertain about the inclusion of immune checkpoint inhibitors on the EML at this time because, despite established evidence of meaningful clinical benefit of these medicines in NSCLC, there were concerns about the feasibility of introducing these medicines because of limited accessibility, limited availability of diagnostic testing, limited capacity to manage toxicities and overall implications for the budget of health systems. The technical team proposed that data from low- and middle-income countries that could test and validate the effectiveness and feasibility of widespread use of immune checkpoint inhibitors would help stakeholders understand the implications of including this class of medicines in WHO Model List. These data can include evaluating ability to safely delivery these medicines, provide concomitant diagnostic services, manage toxicities and evaluate the effect on health expenditure.

EML/EMLc

EML

Section

8.2.3 Immunomodulators

Dose form(s) & strengths(s)

Atezolizumab – Injection: 840 mg/14 mL, 1200 mg/20 mL in vial

Cemiplimab – Injection: 350 mg/7 mL in vial

Durvalumab – Injection 120 mg/2.4 mL, 500 mg/10 mL in vial

Pembrolizumab – Injection: 100 mg/4 mL in vial

Core/complementary

Complementary

Individual/square box listing

Square box listing for pembrolizumab with atezolizumab and cemiplimab as therapeutic alternatives for treatment of metastatic NSCLC with PD-L1 ≥ 50%.

Individual listing for durvalumab for treatment of locally advanced, non-metastatic NSCLC with PD-L1 ≥ 1%.

Background

Applications for the inclusion of PD-1/PD-L1 immune checkpoint inhibitors on the EML for the treatment of NSCLC were reviewed by the Expert Committee in 2019 and 2021. On each occasion, inclusion was not recommended.

In 2019, inclusion of pembrolizumab, nivolumab and atezolizumab was not recommended as the Committee considered that the precise place of these medicines in the treatment of this condition was still evolving (i.e. immunotherapy alone or in combination with chemotherapy). The Committee noted the evidence of efficacy in the treatment of patients with metastatic NSCLC with these agents. The Committee observed that the duration of follow-up of the single studies for first-line and second-line immunotherapy in trials for lung cancer was generally shorter than 3 years, and considered that data from longer follow-up would better demonstrate the magnitude of benefit. The Committee expressed the hope that by the time of the 2021 Committee meeting, more mature data would be available for metastatic NSCLC and also for use of these agents in locally advanced non-resectable disease, and as adjuvant therapy. Furthermore, the Committee noted that the clinical development of cancer immunotherapy still had some areas of uncertainty about the optimal time for introduction of treatment (first- or second-line), appropriate patient selection (i.e. use of biomarkers) and whether or not the use of immune checkpoint inhibitors in combination with other medicines was superior to monotherapy. The Committee expressed concern about the potential impact of oncology medicines on health budgets, which could be an impediment to access, and the fact that countries may not be able to list these medicines on their national EMLs because of their high price (*1*).

In 2021, the Committee acknowledged that atezolizumab, durvalumab, nivolumab and pembrolizumab were associated with a relevant median overall

survival benefit as first-line treatment, well over the EML threshold of 4 to 6 months, based on evidence from several randomized trials. The Committee also noted that the addition of PD-1/PD-L1 immune checkpoint inhibitors to conventional chemotherapy was associated with modest increases in toxicity which may require specialized management in selected case. Overall, the Committee considered that these medicines had a favourable benefit-to-harm ratio and acknowledged that they had substantially improved outcomes for the treatment of NSCLC in practice. However, inclusion of was not recommended as the Committee considered that at current prices, these medicines were prohibitively expensive in many settings. The issue of treatment costs and appropriate use of these medicines is further complicated by the need for diagnostic testing to identify patients most likely to benefit from treatment, uncertainties about the optimal duration of treatment, the significant disease burden and the likely large eligible patient population. The Committee considered that the financial implications of listing PD-1/PD-L1 immune checkpoint inhibitors for this indication would result in unsustainable expenditures for many patients and health systems (*2*).

The PD-1 immune checkpoint inhibitor nivolumab (with a square box indicating pembrolizumab as a therapeutic alternative) was added to the EML in 2019 for first-line monotherapy in patients with unresectable and metastatic melanoma (*1*).

Public health relevance

Lung cancer is a leading cause of morbidity, disability and death worldwide (*3*). In 2020, 2.2 million people were diagnosed with lung cancer, corresponding to 11.4% of all cancers diagnosed; 1.8 million people died from this disease, constituting 18% of all cancer-related deaths. The economic impact of lung cancer is estimated to be around US$ 8 billion in productivity lost in developing countries (*4*). In the absence of a wide coverage of effective screening programmes globally, more than 60% of lung cancer cases are diagnosed when the disease is locally advanced or metastatic, with some regional variability (*5*).

More than 80% of the lung cancers are classified as NSCLC (*6*). Targeted therapies have redefined treatment for patients with genomic alterations in driver oncogenes including: epidermal growth factor (EGFR) mutations, anaplastic lymphoma kinase rearrangements, ROS1 rearrangements, BRAF mutations, human epidermal growth factor receptor 2 (HER2) mutations, or amplifications, and neurotrophic tyrosine kinase 1-3 fusions. However, the greatest proportion of NSCLC, both squamous and non-squamous histology type, do not have specific pathogenic genomic alterations that can be treated with targeted medicines, including EGFR, anaplastic lymphoma kinase gene or ROS1 (*7*).

Historically, patients with non-oncogene-addicted NSCLC have experienced poor survival outcomes because of a lack of therapeutic options in

advanced disease settings. For non-oncogene-addicted NSCLC, the treatments currently included in the EML are all chemotherapies and are associated with a median overall survival of about 12 months.

Summary of evidence: benefits

Advanced and metastatic NSCLC expressing high levels of PD-L1 (≥ 50%)

Pembrolizumab

The phase III KEYNOTE-024 study evaluated pembrolizumab as first-line treatment in 305 participants with previously untreated, advanced NSCLC with tumour PD-L1 expression ≥ 50% and no sensitizing mutation of the EGFR gene or translocation of the anaplastic lymphoma kinase gene (*8–10*). Participants were randomized to receive 200 mg pembrolizumab every 3 weeks for up to 35 cycles (154 patients) or four to six cycles of standard platinum doublet chemotherapy (151 patients). Patients in the chemotherapy group with progressive disease were permitted to cross over to pembrolizumab. The effective crossover rate was 66% (99/151; 83 on-study and 16 outside the study). At a median follow-up of 5 years, median overall survival was 26.3 months (95% confidence interval (CI) 18.3 to 40.4 months) for pembrolizumab and 13.4 months (95% CI 9.4 to 18.3 months) for chemotherapy (hazard ratio (HR) 0.62, 95% CI 0.48 to 0.81). Progression-free survival was 7.7 versus 5.5 months (HR 0.50, 95% CI 0.39 to 0.65), with 3- and 5-year progression-free survival rates of 22.8% and 12.8% with pembrolizumab and 4.1% and 0.0% with standard chemotherapy (*10*).

The health-related quality of life analysis showed a clinically meaningful and significant improvement favouring patients treated with pembrolizumab (*11*). Fewer participants treated with pembrolizumab had deterioration in the QLQ-LC13 composite endpoint than participants given chemotherapy: 31% (46/151) versus 39% (58/148). Time to deterioration was longer with pembrolizumab than with chemotherapy: median not reached (95% CI 8.5 months to not reached) versus 5.0 months (95% CI 3.6 months to not reached); HR 0.66, 95% CI 0.44 to 0.97). Compliance with quality of life questionnaires was 90% at baseline and about 80% at 15 weeks.

Atezolizumab

The phase III IMpower110 study evaluated atezolizumab as first-line treatment in 554 participants with previously untreated metastatic EGFR or anaplastic lymphoma kinase wild type NSCLC with tumour PD-L1 expression of ≥ 1% (*12*). Patients were randomized to receive atezolizumab 1200 mg every 3 weeks (277 patients) or four to six cycles of platinum-based chemotherapy (277 patients). Crossover from the chemotherapy group to the atezolizumab group was not permitted. At the interim analysis after median follow-up of 15.7 months, atezolizumab monotherapy was associated with longer overall survival and

progression-free survival, compared with chemotherapy. The overall survival for atezolizumab and chemotherapy in the population with high-PD-L1 expression (≥ 50%) was 20.2 months and 13.1 months, respectively (HR 0.59, 95% CI 0.40 to 0.89). Progression-free survival in the population with high-PD-L1 expression was 8.1 and 5 months in the atezolizumab and chemotherapy arms, respectively (stratified HR 0.63, 95% CI 0.45 to 0.88). Investigator-assessed confirmed response was higher with atezolizumab than with chemotherapy (38.3% versus 28.6%) in the population with high-PD-L1 expression. Investigator-assessed confirmed response rates did not differ significantly between treatment arms in the populations with any (≥ 1%) or high or intermediate (≥ 5%) PD-L1 expression.

In an updated analysis with a median follow-up of 31.3 months, the median overall survival for atezolizumab versus chemotherapy in the high or intermediate PD-L1 expression group was 19.9 months versus 16.1 months (stratified HR 0.87, 95% CI 0.66 to 1.14). An exploratory overall survival analysis in the high PD-L1 expression group showed a median overall survival of 20.2 months with atezolizumab and 14.7 months with chemotherapy, consistent with the primary analysis (*13*).

Prespecified analysis of quality-of-life patient-reported outcomes for the high PD-L1 expression population included evaluation of the time to confirmed deterioration as a secondary endpoint and change from baseline in global health status, functioning and lung cancer symptoms. The mean baseline scores for global health status, physical functioning and role functioning were moderate, the symptom burden was low and all were similar in both arms. No differences in time to deterioration were seen between arms for cough (HR 0.98, 95% CI 0.48 to 2.03), chest pain (HR 1.02, 95% CI 0.47 to 2.22), dyspnoea (HR 0.96, 95% CI 0.57 to 1.60) and three-symptom composite score (HR 0.92, 95% CI 0.59 to 1.44). No clinically meaningful worsening in dyspnoea, cough or chest pain was seen with atezolizumab versus chemotherapy. Fatigue and nausea/vomiting scores numerically improved immediately with atezolizumab and were maintained to week 48 (*14*).

Cemiplimab

The open-label phase III EMPOWER-lung 1 study compared cemiplimab monotherapy with platinum doublet chemotherapy in the first-line treatment of 710 patients with advanced NSCLC with tumour PD-L1 expression of ≥ 50% (*15*). Patients were randomized to receive cemiplimab 350 mg every 3 weeks for up to 36 cycles (356 patients) or four to six cycles of platinum-based chemotherapy (354 patients). Crossover from chemotherapy to cemiplimab was allowed following disease progression. Thus, 74% (150/203) of patients who progressed on chemotherapy received cemiplimab as a crossover treatment; 32% (50/158) of patients who progressed on cemiplimab received extended treatment

with the addition of chemotherapy. The primary endpoints were overall survival and progression-free survival; quality of life was a secondary endpoint. At a median follow-up of 10.8 months, median overall survival was not reached (95% CI 17.9 months to not evaluable) with cemiplimab versus 14.2 months (95% CI 11.2 to 17.5 months) with chemotherapy (HR 0.57, 95% CI 0.42 to 0.77). Median progression-free survival was 8.2 months with cemiplimab compared with 5.7 months with chemotherapy (HR 0.54, 95% CI 0.43 to 0.68).

Cemiplimab appeared to improve, or not have a detrimental effect on, quality of life. Clinically meaningful effects (mean difference of scores of more than 5 points) were observed on social functioning and global health status and quality of life: differences in least-square means +5.27 (95% CI 2.41 to 8.13, two-sided nominal $P = 0.0003$) and +5.03 (95% CI 2.11 to 7.96, two-sided nominal $P = 0.0008$), respectively. Fatigue (least-square mean −8.6), appetite loss (−7.52), alopecia (−18.57) and constipation (−5.7) also favoured cemiplimab. For all other symptoms assessed, cemiplimab had similar quality-of-life effects as chemotherapy, with no detrimental effects (*16*).

Locally advanced, unresectable NSCLC with PD-L1 expression ≥ 1%

Durvalumab

The phase III PACIFIC trial evaluated durvalumab versus placebo as consolidation therapy in 713 patients with stage III locally advanced, unresectable NSCLC, irrespective of tumour PD-L1 expression, who did not have disease progression after at least two cycles of platinum-based chemoradiotherapy (*17–19*). Patients were randomized 2:1 to receive durvalumab 10 mg/kg every 2 weeks for up to 12 months (476 patients) or matching placebo (237 patients). At an interim analysis after median follow-up of 14.5 months, median progression-free survival was 16.8 months versus 5.6 months in the durvalumab and placebo groups, respectively (HR 0.52, 95% CI 0.42 to 0.65) (*17*). Analysis after median follow-up of 25.2 months showed the 24-month overall survival rate was 66.3% versus 55.6% in the durvalumab and placebo groups, respectively (HR 0.68, 99.73% CI 0.47 to 0.997) (*18*). Analysis after median follow-up of 34.2 months reported median overall survival rates of 47.5 months with durvalumab versus 29.1 months with placebo (stratified HR 0.68, 95% CI 0.53 to 0.87), corresponding to 5-year overall survival rates of 42.9% with durvalumab versus 33.4% with placebo. Median progression-free survival was 16.9 months with durvalumab versus 5.6 months with placebo (HR 0.52, 95% CI 0.42 to 0.65), corresponding to an estimated 5-year progression-free survival rate of 33.1% with durvalumab versus 19.0% with placebo. An exploratory analysis based on the level of tumour PD-L1 expression showed that patients seemed to derive greater benefit when PD-L1 expression was ≥ 1% (HR for overall survival 0.61, 95% CI 0.44 to 0.85) than when PD-L1 expression was < 1% (HR for overall survival 1.15, 95% CI 0.75 to 1.75) (*19*).

Health-related quality of life was also reported in the PACIFIC trial (*20*, *21*). After median follow-up of 25.2 months, more than 79% of patients given durvalumab and more than 82% of patients given placebo completed questionnaires up to week 48. Between baseline and 12 months, the prespecified longitudinal patient-reported outcomes of interest (cough, dyspnoea, chest pain, fatigue, appetite loss, physical functioning and global health status or quality of life) remained stable with both treatments, with no clinically relevant changes from baseline. Generally, no clinically important between-group differences were found in time to deterioration of prespecified key patient-reported outcome endpoints.

Real-world studies evaluating durvalumab

The PACIFIC-R study was an international, retrospective study of patients who started durvalumab within an early access programme between September 2017 and December 2018 (*22*). Median progression-free survival was 21.7 months; it was longer in patients with PD-L1 expression ≥1% compared with < 1% (22.4 months versus 15.6 months). Overall survival data were not reported.

A cohort study in Germany based on an expanded access programme of durvalumab reported data on 121 patients (*23*). With a median follow-up of 25.1 months, median progression-free survival was 20.1 months and median overall survival was not reached. At 12 and 18 months, rates of progression-free survival were 56% and 53%, while overall survival rates at 12 and 24 months were 79% and 66%. The data were consistent with the PACIFIC trial.

A multicentre real-world cohort study in Canada included 141 patients treated with chemoradiotherapy plus durvalumab consolidation and compared the outcome with a historical cohort of 121 patients treated with chemoradiotherapy and no consolidation. Median follow-up was 15.8 months in the durvalumab cohort and 51.5 months in the historical cohort. Overall survival improved with durvalumab, with a median overall survival not reached versus a median overall survival of 26.9 months in the historical control cohort (HR 0.56, 95% CI 0.37 to 0.85). Overall survival rates at 12-months were 92.5% for the durvalumab group and 78.5% for the historical cohort (HR 0.56, 95% CI 0.37 to 0.85) (*24*).

A cohort study in the Republic of Korea reported data on 61 patients, 21 of whom had received durvalumab consolidation and 40 had received no consolidation treatment after chemoradiotherapy. More than half of the patients did not meet the criteria of the PACIFIC study; however, they still received consolidation durvalumab in real-world practice. Median progression-free survival was not reached in the durvalumab group versus 9.6 months in the observation group. Durvalumab treatment was associated with favourable progression-free survival also in the subgroup of patients who did not meet the criteria of the PACIFIC study (not reached versus 6.4 months). Overall survival data were not reported (*25*).

An observational cohort study across the Veterans Health Administration in the United States included patients with stage III NSCLC who had received concurrent chemoradiotherapy, with or without durvalumab: 1006 patients who had received durvalumab and 989 who had not. The addition of durvalumab was associated with higher progression-free survival (HR 0.62, 95% CI 0.55 to 0.70) and overall survival (HR 0.57, 95% CI 0.50 to 0.66) (*26*).

Another cohort study analysed data from the United States National Cancer Database for patients diagnosed with clinical stage III NSCLC between 2015 and 2017 with follow-up to the end of 2018 who were treated with chemoradiation. The cohort included 23 811 patients, of whom 1297 (5.4%) had received durvalumab. The use of immunotherapy was associated with longer overall survival (HR 0.74, 95% CI 0.67 to 0.82), corresponding to a 3-year overall survival rate of 52% versus 44% (*27*).

Summary of evidence: harms

The safety of pembrolizumab was evaluated in KEYNOTE-024 study (*8–10*). The rate of adverse events among patients in the pembrolizumab arm was 76.6% versus 90.0% among patients in the chemotherapy arm, corresponding to a proportion of moderate-severe adverse events of 31.2% versus 53.3%. Toxicity led to treatment discontinuation in 13.6% and 10.7% in the pembrolizumab and chemotherapy arms, respectively, and resulted in toxic death in 1.3% and 2%, respectively. The most common adverse events with pembrolizumab were diarrhoea, fatigue, pyrexia and pruritus, all reported in 10–15% of the patients, and generally of low-to-moderate grade. Immune-related adverse events were reported in 34.4% of patients, of which 13.6% were moderate to severe and one case of fatal pneumonitis. The most common immune-related events were thyroiditis (11%, but less than 1% were moderate to severe) and pneumonitis.

In the IMpower110 study, the adverse events of any grade with atezolizumab and chemotherapy were reported in 90.2% and 94.7% of participants, respectively. Grade 3 and 4 adverse events were reported in 30.1% and 52.5% of participants in the atezolizumab and chemotherapy arms, respectively, while grade 5 adverse events were reported in 3.8% and 4.2%. The most frequent grade 3 and 4 adverse events were anaemia, neutropenia and thrombocytopenia. Hepatic laboratory abnormalities, rash and hypothyroidism were the most reported immune-mediated adverse events ($\geq$ 5% in each group). Grade 3 or 4 immune-mediated adverse events occurred in 6.6% and 1.5%, with no grade 5 event reported (*12*).

The EMPOWER-lung 1 study assessed the overall safety profile of cemiplimab (*15*). In total, adverse events were reported in 43% and 40% of patients in the cemiplimab and chemotherapy arms, respectively, of which 14% and 39% were moderate-to-severe events and 3% and 2% were fatal events. The most common toxicities observed with cemiplimab were poor appetite,

transaminitis and anaemia, all occurring in 5% of the patients, and generally grade 1–2. Treatment with chemotherapy was associated with anaemia (30%, with 14% grade 3, i.e. haemoglobin < 8 g/dL), nausea (25%), peripheral neuropathy (10%) and hyporexia (14%).

The safety of durvalumab was evaluated in the PACIFIC study (*19*). The most frequent adverse reactions were cough (40.2% versus 30.3% in the placebo arm), upper respiratory tract infections (26.1% versus 11.5% in the placebo arm) and rash (21.7% versus 12.0% in the placebo arm). The most frequent grade 3/4 adverse reaction was pneumonia (6.5% versus 5.6% in the placebo arm). The overall incidence of grade 3/4 adverse reactions was 12.8% in the durvalumab arm versus 9.8% in the placebo arm. Radiation pneumonitis occurred in 33.9% patients in the durvalumab arm and 24.8% patients in the placebo arm, including grade 3 (3.4% versus 3.0%) and grade 5 (1.1% versus 1.7%). Grade 5 (fatal) immune-mediated pneumonitis occurred in 0.8% patients on durvalumab versus 1.3% patients on placebo.

In the combined safety database with durvalumab monotherapy (3006 participants with multiple tumour types), immune-mediated pneumonitis occurred in 92 (3.1%) patients, including grade 3 in 25 (0.8%) patients, grade 4 in two (< 0.1%) patients and grade 5 in six (0.2%) patients. Of the 92 patients with immune-mediated pneumonitis, 69 received high-dose corticosteroid treatment and durvalumab was discontinued in 38 patients. Other immune-related adverse reactions reported in less than 1% of patients treated with durvalumab monotherapy in clinical trials were myasthenia gravis, myocarditis, myositis, polymyositis, meningitis, encephalitis and Guillain–Barre syndrome. No overall differences in safety were reported between older (≥ 65 years) and younger patients (*28*).

The phase II PACIFIC-6 clinical trial was designed to evaluate the safety and benefit of durvalumab after sequential chemoradiotherapy, in a single-arm prospective cohort (*29*). The study enrolled 117 patients. The median progression-free survival was 10.9 months with a 12-month progression-free survival rate of 49.6% and an overall survival rate of 84.1%. Grade 3/4 toxicity occurred in 18.8% of patients. Two patients (1.7%) experienced Grade 5 (fatal) adverse events. Safety and efficacy appeared consistent with findings from the PACIFIC trial.

WHO guidelines

WHO guidelines for treatment of NSCLC are not currently available.

Costs/cost–effectiveness

Pembrolizumab

The application identified six cost–effectiveness studies of first-line pembrolizumab versus chemotherapy for NSCLC with high levels of PD-L1 (*30–35*). All but one

of the studies (*34*) were from high-income country settings. Incremental cost–effectiveness ratios per quality-adjusted life year (QALY) gained were €84 097 in France, Sw.fr. 57 402 in Switzerland, US$ 103 128 in China, US$ 110 922 in China, Hong Kong SAR and US$ 97 621 in the United States. In the United Kingdom, the incremental cost–effectiveness ratio per end-of life adjusted QALY was US$ 52 000.

A systematic review that evaluated the cost–effectiveness of pembrolizumab versus cemiplimab for NSCLC with high levels of PD-L1 in the United States reported an incremental cost–effectiveness ratio for pembrolizumab of US$ 114 246 per QALY gained (*36*).

Atezolizumab

The application identified two cost–effectiveness studies of first-line atezolizumab versus chemotherapy for NSCLC with high levels of PD-L1 (*37*, *38*). Incremental cost–effectiveness ratios varied from US$ 52 415 per QALY gained (using a scenario involving a patient-assistance programme) to US$ 125 779 per QALY gained in China, and from US$ 123 424 to US$ 224 590 per QALY gained in the United States.

Cemiplimab

The application identified two cost–effectiveness studies of first-line cemiplimab versus chemotherapy for NSCLC with high levels of PD-L1, both from the United States perspective (*39*, *40*). Incremental cost–effectiveness ratios ranged from US$ 40 390 to US$ 91 891 per QALY gained.

Another study modelled the cost–effectiveness of cemiplimab, pembrolizumab and atezolizumab, from a United States health-sector perspective (*41*). The results suggested that first-line cemiplimab was a cost-effective option compared with first-line pembrolizumab (incremental cost–effectiveness ratios US$ 52 998 per QALY gained), and a dominant alternative versus first-line atezolizumab at a willingness-to-pay threshold of US$ 100 000 per QALY gained.

Durvalumab

The application identified seven cost–effectiveness studies of durvalumab as consolidation therapy in locally advanced NSCLC, from the perspective of China, Switzerland, United Kingdom and United States (*42–48*). Incremental cost–effectiveness ratios were US$ 55 285 to US$ 138 920 per QALY gained in the United States (depending on the payer perspective), £22 665 per QALY gained in the United Kingdom, Sw.fr. 66 131 to Sw.fr. 88 703 per QALY gained (depending on PD-L1 tumour expression), and ¥46 093 to ¥193 898 per QALY gained in China (depending on use of a patient assistance programme or retail prices).

Availability

Pembrolizumab, atezolizumab and cemiplimab have regulatory approval in multiple countries for the treatment of metastatic NSCLC. They have primary patent protection until 2028, 2029 and 2035, respectively.

Durvalumab has regulatory approval in multiple countries for the treatment of locally advanced, unresectable NSCLC as consolidation therapy after platinum-based chemotherapy. It has primary patent protection until 2030.

No biosimilar products are available.

Other considerations

The EML Cancer Medicines Working Group reviewed the application but was not able reach a consensus to support or not the inclusion of PD-1/PD-L1 immune checkpoint inhibitors on the EML for first-line treatment of selected patients with metastatic NSCLC with PD-L1 expression ≥ 50%, whose tumours do not harbour a targetable oncogene. The Working Group acknowledged a relevant and meaningful survival benefit after long follow-up and a possible improvement of the quality of life associated with the use of pembrolizumab. The Group noted that atezolizumab and cemiplimab for the same indication, and durvalumab for locally advanced non-metastatic lung cancer with PD-L1 expression ≥ 1%, after prior chemotherapy and radiation therapy, provide similar benefits although the available trial data for these medicines have a shorter duration of follow-up duration.

Several members of the Working Group were still uncertain about the implications at the country level of listing immune checkpoint inhibitors on the WHO Model List, including: the financial risks based on the current costs of procurement; the opportunity costs associated with diverting resources from other diseases or treatments; highly limited feasibility of use because of barriers to the timely access to diagnostics; and lack of information about the most cost-effective duration of treatment and dose. Predictive biomarkers, such as PD-L1 expression, are key to selecting patients with tumours that are more likely to respond to immune checkpoint inhibitors. It was also highlighted that, despite the approval of several checkpoint inhibitors, prices for these agents have remained prohibitively high in most settings, discounting is consistently limited by the production companies and biosimilar products cannot be expected to be available in most countries in the near future.

Other Working Group members highlighted that a positive recommendation by WHO on immune checkpoint inhibitors for the treatment of NSCLC could guide countries in prioritizing these medicines for this specific indication, limiting their use for other cancers in which benefits were less relevant. The Model List can support national decision-making and inform national guidelines for clinical practice and guide the procurement and supply of medicines in the public sector. Working Group members also stressed that price

competition should be facilitated for immune checkpoint inhibitors by allowing early utilization of more molecules in national markets. The Working Group also noted that the application did not consider camrelizumab, nivolumab/ipilimumab, sintilimab, sugemalimab or toripalimab. Most of these therapies have shown comparable improvement in disease control compared with other immune checkpoint inhibitors under consideration. However, overall survival data were mature only for nivolumab/ipilimumab, with all other molecules tested in clinical trials with incomplete survival data.

Committee recommendations

The Expert Committee recognized that PD-1/PD-L1 immune checkpoint inhibitor therapy has become part of the standard treatment for patients with NSCLC with tumours that do not express targetable oncogenes based on improvements in overall survival that meet the established thresholds for possible inclusion on the Model List.

The Committee acknowledged possible improvement in quality of life in addition to improved overall survival associated with the use of pembrolizumab, when compared with platinum-based chemotherapy in patients with advanced/metastatic NSCLC expressing high levels of PD-L1. The Committee noted that longer follow-up data were now available, with overall survival benefits maintained over a 5-year period. The Committee also noted that atezolizumab and cemiplimab showed similar benefits, that is, prolonging median overall survival compared with platinum-based chemotherapy in patients with advanced/metastatic NSCLC and high PD-L1 expression, although the available follow-up data were shorter than for pembrolizumab. For durvalumab as consolidation therapy in locally advanced disease, data also suggested a meaningful benefit. However, the Committee considered that the data were less mature and required further evaluation over time.

The Committee acknowledged that individual immune checkpoint inhibitors may differ in their efficacy and safety profiles but considered that an overall net benefit could be assumed for the entire class when compared with platinum-containing chemotherapies. The Committee considered that in principle, the availability of several interchangeable immune checkpoint inhibitors could boost competition and favour access. However, the Committee noted that uncertainty remained about the optimal medicine dose and duration of treatment, with ongoing clinical trials investigating the use of immune checkpoint inhibitors in various cancers at lower doses or for a shorter duration (*49*). The Committee commended these studies and recommended that such trials be promoted and publicly funded to confirm if lower doses and shorter duration of treatment were indeed associated with non-inferior survival outcomes, similar or lower toxicity and lower costs, and offered a pathway to more affordable and widespread access.

The Committee noted that prices of immune checkpoint inhibitors have remained prohibitively high in most settings. In the absence of true competition, the Committee remained concerned that this situation would continue to contribute to serious inequities between rich and poor countries and patients, which would result in negligible availability and unaffordable prices of these medicines for a large proportion of the global population. The Committee also noted the need to select patients that could benefit from immune checkpoint inhibitors based on PD-L1 expression. Affordable access to necessary diagnostics would add an extra burden on countries and listing these medicines without being able to target their use to those patients who would benefit most from them could lead to additional waste of resources, both public and private.

The Committee reiterated the importance for WHO to continue to tackle the high prices of cancer medicines and welcomed the news of progress being made in the establishment of the WHO Technical Advisory Group on Pricing Policies for Medicines to increase affordable access to essential and priority medicines.

The Committee recognized the risks at the country level of listing immune checkpoint inhibitors on the WHO Model List, including financial risks based on the current costs of procurement, opportunity costs associated with diverting resources from other diseases, treatments or preventive programmes (e.g. smoking cessation, clean air), and limited feasibility because of barriers to the timely access to diagnostics. The Committee considered that the potential financial impact associated with procurement and appropriate use of immune checkpoint inhibitors could be a significant risk to the financial sustainability of health budgets in many low- and middle-income countries. This was especially true if these countries aimed to provide universal treatment coverage, given the current high prices of immune checkpoint inhibitors and PD-L1 testing, as well as the high prevalence of NSCLC. The Committee recognized that the opportunity costs of providing immune checkpoint inhibitors at current prices for the treatment of patients with NSCLC would be substantial for many health systems. The Committee considered that an assessment of various scenarios based on different assumptions on procurement price, capacity to administer and proportion of patients eligible for treatment would help foster the development of solutions that facilitated access without bankrupting the health care budget.

The Committee recalled the recommendation made in 2019 to include nivolumab pembrolizumab on the EML for treatment of metastatic melanoma (*1*). The Committee noted that the magnitude of benefit of immune checkpoint inhibitors for melanoma far exceeded the benefit seen in lung cancer. The Committee proposed that countries with access to these medicines for melanoma and with sufficient resources to increase the number of patients that could be treated could consider the use of immune checkpoint inhibitors as first-line

treatment of metastatic, non-oncogene-addicted NSCLC, in patients with high PD-L1 expression, as a high-priority for expansion.

Based on these considerations, the Expert Committee did not recommend the inclusion of PD-1/PD-L1 immune checkpoint inhibitors on the EML for the first-line treatment of metastatic NSCLC with PD-L1 expression ≥ 50% (pembrolizumab, atezolizumab, cemiplimab), nor for locally advanced, unresectable NSCLC with PD-L1 expression ≥ 1% after chemoradiotherapy (durvalumab).

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Pegfilgrastim – addition – EML and EMLc

Pegfilgrastim	ATC code: L03AA13

Proposal

Addition of pegfilgrastim on the complementary list of the EML and EMLc for primary prophylaxis in patients at high risk of developing febrile neutropenia associated with myelotoxic chemotherapy, and for secondary prophylaxis in patients who have experienced neutropenia following prior myelotoxic chemotherapy.

Applicant

Amgen Inc., Zug, Switzerland

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical team advised that it supported the inclusion of pegfilgrastim on the Model Lists, given its similar efficacy and safety compared with filgrastim, and potential indirect cost benefits and quality-of-life benefits.

EML/EMLc

EML and EMLc

Section

8.2.3 Immunomodulators

Dose form(s) & strengths(s)

Injection: 6 mg/0.6 mL in prefilled syringe

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Granulocyte colony-stimulating factors (filgrastim and pegfilgrastim) were previously considered for inclusion on the Model Lists for use as supportive treatment with myelotoxic chemotherapy regimens as part of a comprehensive review of cancer medicines in 2015. The Expert Committee noted that several studies had shown comparability in effectiveness and patient outcomes of daily

filgrastim and once per cycle pegfilgrastim. The Committee considered that the choice between filgrastim and pegfilgrastim was largely determined by individual preference, ease of administration and cost. At that time, pegfilgrastim was considerably more expensive than filgrastim, for which biosimilar products were available. Therefore, the Committee recommended only the inclusion of pegfilgrastim on the EML and EMLc. The Expert Committee acknowledged that avoidance of febrile neutropenia was a meaningful goal of holistic care of patients with cancer undergoing myelotoxic chemotherapy (*1*).

Public health relevance

Chemotherapy-induced myelotoxicity is a common and potentially life-threatening adverse event for cancer patients. The incidence of febrile neutropenia associated with myelotoxic chemotherapy varies depending on the type of cancer, the specific type and number of myelosuppressive chemotherapy agents in use, and other factors such as age and comorbidities (*2,3*). Febrile neutropenia is the most common life-threatening complication of cancer therapy and is an oncologic emergency. Myelosuppression continues to be a major dose-limiting toxicity for many chemotherapy regimens (*4*).

In resource-constrained areas particularly, but also in high-income countries for many cancers, newer targeted and immunological cancer treatments might not be widely available, affordable, or feasible and myelosuppressive treatments are still the standard of care. In such settings, prevention and treatment of febrile neutropenia associated with cancer treatment is a high priority.

Summary of evidence: benefits

Two pivotal randomized, double-blind, multicentre, phase III studies compared the efficacy of pegfilgrastim versus filgrastim in patients with solid tumours receiving chemotherapy.

The first study included 157 patients who were randomized to receive a single fixed 6 mg dose of pegfilgrastim ($n = 80$) or filgrastim 5 micrograms/kg a day ($n = 77$) with each cycle of chemotherapy (doxorubicin and docetaxel) for four cycles. The results showed that a single 6 mg injection of pegfilgrastim was as effective as daily injections of filgrastim for all efficacy measures for all cycles. The mean duration of grade 4 neutropenia in cycle one was 1.8 and 1.6 days for the pegfilgrastim and filgrastim groups, respectively. Results for all efficacy endpoints in cycles two to four were consistent with the results from cycle one. A trend towards a lower incidence of febrile neutropenia was noted across all cycles with pegfilgrastim compared with filgrastim, 13% versus 20% (*5*).

The second study included 310 patients who were randomized to receive single dose pegfilgrastim 100 micrograms/kg or filgrastim 5 micrograms/kg a day with each cycle of chemotherapy (doxorubicin and docetaxel) for four cycles. The results showed that one dose of pegfilgrastim per chemotherapy

cycle was comparable to daily subcutaneous injections of filgrastim for all efficacy endpoints, including the duration of severe neutropenia and depth of the absolute neutrophil count nadir in all cycles. Febrile neutropenia in all cycles occurred less often in patients who received pegfilgrastim. The difference in the mean duration of severe neutropenia between the treatment groups was less than 1 day. Pegfilgrastim and filgrastim were similarly safe and well tolerated (*6*).

A 2011 systematic review and meta-analysis assessed the effectiveness of granulocyte colony-stimulating factors as primary prophylaxis against febrile neutropenia in adults undergoing chemotherapy for solid tumours or lymphoma. Twenty studies compared primary prophylaxis with filgrastim (10 studies), lenograstim (five studies) or pegfilgrastim (five studies) versus no prophylaxis. A further five studies compared filgrastim and pegfilgrastim. The results showed that any primary prophylaxis with granulocyte colony-stimulating factors significantly reduced the incidence of febrile neutropenia (relative risk (RR) 0.51, 95% confidence interval (CI) 0.41 to 0.62). The RRs for each medicine were 0.30 (95% CI 0.14 to 0.65) for pegfilgrastim, 0.57 (95% CI 0.48 to 0.69) for filgrastim and 0.62 (95% CI 0.44 to 0.88) for lenograstim. In the comparison of filgrastim and pegfilgrastim, the incidence of febrile neutropenia was significantly lower for pegfilgrastim (RR 0.66, 95% CI 0.44 to 0.98) (*7*).

A 2007 meta-analysis of five randomized- trials (617 participants) compared the effect pegfilgrastim and filgrastim on the incidence of febrile neutropenia, grade IV neutropenia, time to absolute neutrophil count recovery and bone pain in patients with solid tumours and malignant lymphomas receiving myelosuppressive chemotherapy. Pooled estimates indicated that pegfilgrastim, administered as a single dose per cycle, was associated with a significant reduction in febrile neutropenia compared with daily filgrastim injections (risk ratio 0.64, 95% CI 0.43 to 0.97). Rates of grade IV neutropenia, time to absolute neutrophil count recovery and incidence of bone pain were similar between the treatments (*8*).

A 2021 systematic review of 13 studies (10 non-randomized studies, three randomized trials, 4315 participants) evaluated the effectiveness and safety of pegfilgrastim in preventing febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy regimens. Meta-analyses were not performed because of the heterogeneity of the studies. Six of the studies provided statistical comparisons for pegfilgrastim versus filgrastim or placebo. Three studies found a significant decrease in the incidence of febrile neutropenia with pegfilgrastim compared with filgrastim or placebo. In the remaining three, a non-significantly lower incidence of febrile neutropenia was observed with pegfilgrastim compared with filgrastim. Five of the studies reported dose delays or dose reductions, with two finding significantly lower incidences with pegfilgrastim compared with filgrastim. In one study, the incidence of dose reductions was significantly lower in patients receiving pegfilgrastim with two-weekly chemotherapy regimens compared with three-weekly chemotherapy regimens (*9*).

Summary of evidence: harms

The overall safety profile of single-dose pegfilgrastim was comparable to that of standard daily filgrastim in both pivotal comparative trials (*5,6*).

Safety data in the United States Food and Drug Administration's product information for originator pegfilgrastim were reported from a randomized, placebo-controlled, double-blind study of pegfilgrastim plus docetaxel in 928 patients with breast cancer. Adverse events occurred in similar percentages of patients across treatment arms and were typical of those associated with docetaxel (alopecia, diarrhoea, fever, and nausea and vomiting). Most adverse events were of mild or moderate intensity. Adverse events occurring more frequently in the pegfilgrastim arm than the placebo arm were bone pain (31% versus 26%) and pain in extremities (9% versus 4%) (*10*).

WHO guidelines

WHO guidelines for prophylaxis of febrile neutropenia are not currently available.

Costs/cost–effectiveness

Since the previous consideration of pegfilgrastim by the Expert Committee in 2015, the patent for pegfilgrastim has expired and biosimilar products have become available. As a result, the price of pegfilgrastim has decreased markedly.

The application presented data extracted from the Eversana database (a proprietary aggregator database of public prices) comparing the price of filgrastim and pegfilgrastim, per mg and per cycle, in 21 high-income countries. Pegfilgrastim prices (per mg and per 2-week cycle) were between 5% and 68% lower than filgrastim prices in 20 of the 21 countries investigated.

No information on cost–effectiveness was presented in the application. The application stated that in high-income countries, in general, pegfilgrastim was reimbursed on a cost-minimization basis to filgrastim on the basis that the efficacy and safety of pegfilgrastim and filgrastim were equivalent.

Availability

Pegfilgrastim has regulatory approval and market availability in more than 70 countries worldwide. It is available as the originator product and biosimilar products.

Other considerations

The EML Cancer Medicines Working Group reviewed the application and advised that it supported the inclusion of pegfilgrastim on the EML and EMLc for the prevention of febrile neutropenia in patients receiving myelotoxic chemotherapy.

The Working Group highlighted that pegfilgrastim has been shown to be a safe and effective alternative to daily filgrastim injections, which is of

particular importance in settings with limited resources. Short-acting filgrastim can lead to lower adherence due to its daily administration and cold supply chain limitations in low-income countries. Shorter treatment durations are common because of these constraints, potentially leading to worse outcomes. Despite the cost of pegfilgrastim, lower costs of biosimilar products make it a viable option, which offers a single-dose administration. Pegfilgrastim is preferred for patients on shorter chemotherapy cycles, while caution is advised against routine use of granulocyte colony-stimulating factors unless the risk of neutropenia is substantial.

Committee recommendations

The Expert Committee acknowledged that the prevention of febrile neutropenia is an important aspect of cancer care in people undergoing myelosuppressive chemotherapy regimens.

The Committee noted that a single dose of pegfilgrastim (once every 2 weeks) is an effective and safe alternative to daily injections of filgrastim with most of the available evidence showing no significant difference between treatments in reducing the risk of febrile neutropenia.

The Committee considered that pegfilgrastim may offer advantages over filgrastim in settings where refrigerated storage outside of secondary treatment centres is limited. In these settings, patients being treated with daily injections of filgrastim face longer hospital stays or daily clinic visits and this has been associated with lower adherence to treatment and increased risk of life-threatening infections. The Committee noted that filgrastim is still a relevant treatment option for patients in whom a treatment duration of less than 2 weeks is indicated.

The Committee recalled the 2015 recommendation not to include pegfilgrastim on the Model Lists because of a substantial difference in price compared to filgrastim at the time. The Committee noted that since then the patent for pegfilgrastim had expired and biosimilars had entered the market, resulting in reductions in price, often lower than the price of filgrastim.

The Expert Committee therefore recommended the inclusion of pegfilgrastim (including quality-assured biosimilar products) on the complementary list of the EML and EMLc for primary prophylaxis in patients at high risk of developing febrile neutropenia associated with myelotoxic chemotherapy, and for secondary prophylaxis in patients who have experienced neutropenia following prior myelotoxic chemotherapy.

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Tislelizumab – addition – EML

Tislelizumab	ATC code: L01FF09

Proposal

Addition of the programmed cell death protein 1 (PD-1) immune checkpoint inhibitor tislelizumab to the complementary list of the EML for treatment of locally advanced and metastatic non-small cell lung cancer (NSCLC).

Applicant

Hao Hu, Institute of Chinese Medical Science, University of Macau, Macau, China

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases did not provide comments on the application for tislelizumab.

EML/EMLc

EML

Section

8.2.3 Immunomodulators

Dose form(s) & strengths(s)

Injection: 100 mg/10 mL

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Tislelizumab has not previously been considered for inclusion on the Model List for NSCLC.

In 2021, tislelizumab was considered for treatment of adults with relapsed or refractory Hodgkin lymphoma after at least one second-line chemotherapy. However, it was not recommended due to immature data and unknown cost–effectiveness (*1*).

Currently, the Model List includes cytotoxic medicines (carboplatin, cisplatin, etoposide, gemcitabine, paclitaxel and vinorelbine) and targeted therapies (erlotinib, afatinib and gefitinib) for treatment of NSCLC.

The PD-1 immune checkpoint inhibitor nivolumab (with a square box indicating pembrolizumab as a therapeutic alternative) was added to the EML in 2019 for first-line monotherapy in patients with unresectable and metastatic melanoma (*2*).

Public health relevance

Lung cancer is a leading cause of morbidity, disability and death worldwide (*3*). In 2020, 2.2 million patients received a diagnosis of lung cancer, corresponding to 11.4% of all cancers diagnosed; 1.8 million people died from this disease, constituting 18% of all cancer-related deaths. The economic impact of lung cancer is estimated to be about US$ 8 billion in productivity lost in developing countries (*4*). Moreover, in the absence of wide coverage of effective screening programmes globally, lung cancer diagnoses occur at locally advanced and metastatic stages in more than 60% of cases (*5*). People living in low- and middle-income countries are more likely to be diagnosed with late-stage disease due to poor access to care, lack of awareness, inadequate health care infrastructures and poor referrals to diagnosis and palliative care (*6*,*7*). Most patients diagnosed with lung cancer in an advanced or metastatic stage have a poor 5-year survival rate of 10% to 20% (*3*,*6*). The overall 5-year survival rate in the United States is 24% (*8*). In comparison, the 5-year survival rate in North Africa and the Middle East is only 8% (*9*).

More than 80% of lung cancers are classified as NSCLC (*10*). Targeted therapies have redefined treatment for patients with genomic alterations in driver oncogenes (epidermal growth factor (EGFR) mutations, anaplastic lymphoma kinase rearrangements, *ROS1* rearrangements, *BRAF* mutations, human epidermal growth factor receptor 2 mutations, or amplifications and neurotrophic tyrosine kinase 1-3 fusions) to guide the selection of treatments. However, the greatest proportion of NSCLC, both squamous and non-squamous histology type, do not carry specific pathogenetic genomic alterations that can be treated with targeted medicines, including EGFR, anaplastic lymphoma kinase or *ROS1* (*11*).

Historically, patients with non-oncogene-addicted NSCLC have experienced poor survival outcomes due to a lack of therapeutic options for advanced disease. For non-oncogene-addicted NSCLC, the treatments currently included in the EML are all chemotherapies, associated with a median overall survival of about 12 months.

Summary of evidence: benefits

The application presented evidence from six phase I–III clinical trials in which tislelizumab was used (*12–17*). All studies included patients with histologically confirmed, locally advanced (stage IIIB) or metastatic (stage IV) NSCLC. Patients were treated with tislelizumab 200 mg every 3 weeks. Only the three phase III trials are described below.

First-line chemoimmunotherapy

RATIONALE 304 was a randomized, open-label, multicentre phase III study evaluating tislelizumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone in 332 patients in China (*13*). The primary endpoint was progression-free survival. After 9.8 months of follow-up, progression-free survival was 9.7 months in the tislelizumab arm compared with 7.6 months in the chemotherapy arm (hazard ratio (HR) 0.65, 95% confidence interval (CI) 0.46 to 0.90). Objective response rates in the tislelizumab and chemotherapy arms were 57.4% (95% CI 50.6% to 64.0%) and 36.9% (95% CI 28.0% to 46.6%), respectively. Median overall survival was not reached in either treatment arm. The 6-month overall survival rate was higher in the tislelizumab arm (92.7%, 95% CI 88.3% to 95.5%) compared with the chemotherapy arm (84.6%, 95% CI 76.0% to 90.2%).

RATIONALE 307 was a randomized, open-label, multicentre phase III study evaluating tislelizumab plus chemotherapy (carboplatin plus (nab) paclitaxel) versus chemotherapy alone in 360 patients in China (*14*). The primary endpoint was progression-free survival. After 8.6 months of follow-up, progression-free survival was 7.6 months in the tislelizumab arm compared with 5.5 months in the chemotherapy arm. Overall survival data were immature.

The effect of tislelizumab on health-related quality of life was evaluated in patients enrolled in the RATIONALE 304 and RATIONALE 307 trials (*18,19*). Adding tislelizumab to platinum-based chemotherapy was associated with improvements in global health status/ quality-of-life scores, and reduced scores on symptom-specific subscales for coughing, chest pain, dyspnoea, haemoptysis and peripheral neuropathy.

Second- and third-line monotherapy

RATIONALE 303 was a randomized open-label, phase III study evaluating tislelizumab versus docetaxel in 805 patients with locally advanced or metastatic squamous or non-squamous NSCLC who had disease progression on a prior platinum-containing regimen (*17*). Coprimary endpoints were overall survival in the intention-to-treat population and the population of patients with PD-L1 tumour cell expression ≥ 25%. At the final analysis, in the intention-to-treat population, median overall survival was longer with tislelizumab than docetaxel (16.9 months versus 11.9 months; HR 0.66, 95% CI 0.56 to 0.79). Median overall survival was also longer with tislelizumab than docetaxel in the population with PD-L1 ≥ 25% (19.3 months versus 11.5 months; HR 0.53, 95% CI 0.40 to 0.70). Median progression-free survival was also longer with tislelizumab compared with docetaxel (4.2 months versus 2.6 months; HR 0.63, 95% CI 0.53 to 0.75). Patients receiving tislelizumab also had a greater objective response rate (22.6% versus 7.0%) and a longer duration of response (13.5 months versus 6.0 months) compared with patients in the docetaxel group.

The effect of tislelizumab on health-related quality of life was evaluated in patients enrolled in the RATIONALE 303 trial (*20*). The global health status/ quality-of-life score in the tislelizumab arm improved relative to baseline from cycles five through to 10 while it declined in cycles six through to 10 in the docetaxel arm. The tislelizumab arm showed a reduction from baseline at cycle 12 in the symptom scores of coughing, chest pain and dyspnoea while patients in the docetaxel arm experienced an increase in symptoms.

Summary of evidence: harms

In RATIONALE 304, 222/222 patients (100%) in the tislelizumab arm and 109/110 patients (99.1%) in the chemotherapy arm experienced at least one treatment-emergent adverse event. The most common treatment-emergent adverse events in both treatment arms were haematological (e.g. anaemia, leukopenia and thrombocytopenia), and most were grade 1 or 2 in severity. Serious treatment-emergent adverse events were reported in 97 patients (33.3% in the tislelizumab arm and 20.9% in the chemotherapy arm). Discontinuation of any treatment component because of treatment-emergent adverse events was reported in 25.7% and 9.1% of patients in the tislelizumab and chemotherapy arms, respectively. Treatment-emergent adverse events leading to permanent discontinuation of tislelizumab and dose modifications of tislelizumab occurred in 11.3% (25/222) of patients and 59.9% (133/222) of patients, respectively (*13*).

In RATIONALE 307, 99.6% (237/238) of patients in the tislelizumab arm and 100.0% (117/117) of patients in the chemotherapy arm experienced at least one treatment-emergent adverse event. The most common treatment-emergent adverse event of grade 3 or higher was decreased neutrophil levels. Serious treatment-emergent adverse events were reported in 118 patients: 37.4% (89/238) of patients receiving tislelizumab and 24.8% (29/117) or patients receiving chemotherapy. Discontinuation of any treatment component because of treatment-emergent adverse events was reported in 21.0% (50/238) of patients receiving tislelizumab and in 15.4% (18/117) of patients receiving chemotherapy. Treatment-emergent adverse events leading to permanent discontinuation of tislelizumab occurred in 10.1% (24/238) of patients. Treatment-emergent adverse events leading to death were similar in treatment arms: 3.8% (9/238) for tislelizumab and 4.3% (5/117) for chemotherapy. Treatment-related adverse events occurred in 99.4% (353/355) of patients. The most common treatment-related adverse events were anaemia, alopecia and decreased neutrophil levels. Grade 3 or higher treatment-related adverse events occurred in 296 patients: 85.8% (202/238) of patients receiving tislelizumab and 80.3% (94/117) of patients receiving chemotherapy. Grade 3 or higher treatment-related adverse events were mostly haematological and consistent with known adverse events of chemotherapy. Six patients experienced treatment-related adverse events leading to death (three patients receiving tislelizumab and

three patients receiving chemotherapy), none of which were solely attributed to tislelizumab. Hyperglycaemia, hypothyroidism and pneumonia were the most common immune-mediated adverse events in patients who received tislelizumab therapy. Most potential immune-mediated adverse events were grade 1 and 2 and did not lead to treatment discontinuation (*14*).

In RATIONALE 303, 96.8% (517/534) of patients in the tislelizumab arm and 98.4% (254/258) of patients in the docetaxel arm experienced at least one treatment-emergent adverse event. There were fewer reported treatment-emergent adverse events of grade 3 or higher in the tislelizumab arm than in the docetaxel arm (42.1% versus 74.8%). The most common treatment-emergent adverse events of any grade in the tislelizumab arm were anaemia, cough and increases in liver enzymes. The incidence of immune-mediated treatment-emergent adverse events of all grades in the tislelizumab arm was 18.9%, with hypothyroidism (7.9%) and pneumonitis and immune-mediated lung disease (4.5%) being the most frequently occurring events. Treatment-related adverse events occurred in 74.9% (400/534) of patients in the tislelizumab arm and 93.8% (242/258) of patients in the docetaxel arm. The most common treatment-related adverse events of any grade in the tislelizumab arm were liver enzyme increases, anaemia and hypothyroidism. Grade 3 or higher treatment-related adverse events occurred in 15.7% (84/354) of patients in the tislelizumab arm and 66.3% (171/258) of patients in the docetaxel arm (*17*).

WHO guidelines

WHO guidelines for treatment of NSCLC are not currently available.

Costs/cost–effectiveness

A study using data from the RATIONALE 304 trial assessed the cost–effectiveness of adding tislelizumab to first-line pemetrexed-platinum chemotherapy in locally advanced or metastatic non-squamous NSCLC without known sensitizing EGFR mutations or anaplastic lymphoma kinase rearrangements from the perspective of the Chinese health care system (*21*). For the entire patient population, first-line tislelizumab plus chemotherapy was associated with an incremental cost–effectiveness ratio of US$ 29 132 per quality-adjusted life year (QALY) gained compared with chemotherapy alone. In subgroup analyses based on factors including age, sex, performance status and PD-L1 tumour expression, the incremental cost–effectiveness ratios ranged from US$ 27 018 to US$ 33 074 per QALY gained. These values were below the willingness-to-pay threshold used in the analysis.

Another study assessed the cost–effectiveness of tislelizumab versus docetaxel for patients who were previously treated for advanced NSCLC in China (*22*). Efficacy and safety data were based on the RATIONALE 303 trial. Costs

were calculated from the perspective of Chinese health care system. Tislelizumab was associated with an incremental cost–effectiveness ratio of US$ 18 122 per QALY gained compared with docetaxel. This was lower than the cost-effective threshold of three times the gross domestic product per capita in China used in the analysis. Utility of progression-free survival, followed by the price of tislelizumab had the greatest impact on the incremental cost–effectiveness ratio.

The application reported the current annual cost of tislelizumab as ¥49 300. In comparison, annual costs for pembrolizumab, nivolumab, atezolizumab and durvalumab were reported to range between ¥479 010 and ¥759 696.

Availability

Tislelizumab has regulatory approval from the National Medical Product Administration in China for nine indications, including those requested in the application.

Applications for tislelizumab have been submitted to regulatory agencies in Australia, Europe, the Republic of Korea, New Zealand, Switzerland, United Kingdom and United States and are currently under review.

Committee recommendations

The Committee acknowledged the global burden of lung cancer and noted that most patients are diagnosed with advanced disease with metastasis which results in poor 5-year survival rates. This is especially relevant to patients in low- and middle-income countries where diagnosis at advanced stages occurs frequently.

The Expert Committee recognized that PD-1/PD-L1 immune checkpoint inhibitor therapy has become part of the standard treatment for patients with NSCLC wild-type or non-oncogene-addicted tumours because of improvements in clinical outcomes that meet the established thresholds for overall survival benefit for possible inclusion on the Model List.

The Committee noted the evidence presented from randomized studies and additional single-arm trials comparing tislelizumab with chemotherapy for treatment of locally advanced and metastatic NSCLC which suggested promising clinical benefits. However, the Committee noted that survival data were still immature, with observation not yet reaching 2 years of follow-up, and therefore considered that the overall survival benefit associated with tislelizumab was uncertain.

The Committee also noted that the trials did not include patients based on levels of PD-L1 tumour expression. The Committee considered that preselection of patients based on PD-L1 tumour expression, as seen in other studies on immune checkpoint inhibitors, might have enhanced the patient population that would benefit from tislelizumab.

The Committee acknowledged that the reported price of tislelizumab in China (the only country where tislelizumab is current approved and available for

this indication) was markedly lower than the price of other immune checkpoint inhibitors in this setting.

The Expert Committee did not recommend the inclusion of tislelizumab on the WHO EML at this time because of uncertain survival benefit due to immature data.

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Toripalimab – addition – EML

Toripalimab	ATC code: to be assigned

Proposal

Addition of the programmed cell death protein 1 (PD-1) immune checkpoint inhibitor toripalimab to the complementary list of the EML for treatment of nasopharyngeal carcinoma and oesophageal squamous cell carcinoma in combination with cytotoxic chemotherapy.

Applicant

Shanghai Junshi Biosciences Co. Ltd, Shanghai, China

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. It was the view of the technical department that there were currently insufficient mature data on the efficacy and safety of toripalimab. However, the technical team noted with interest the relevant early findings in nasopharyngeal and oesophageal cancers, and advised that further consideration could be made as additional studies are reported and a greater understanding of feasibility of use was gained.

EML/EMLc

EML

Section

8.2.3 Immunomodulators

Dose form(s) & strengths(s)

Concentrate solution for infusion: 240 mg/6 mL

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Toripalimab has not previously been considered for inclusion on the EML for the proposed indications, or any other indications.

Medicines currently included on the EML for the treatment of nasopharyngeal carcinoma are carboplatin, cisplatin, fluorouracil and paclitaxel.

Medicines for the treatment of oesophageal carcinoma have not previously been evaluated.

The PD-1 immune checkpoint inhibitor nivolumab (with a square box indicating pembrolizumab as a therapeutic alternative) was added to the EML in 2019 for first-line monotherapy in patients with unresectable and metastatic melanoma (*1*).

Public health relevance

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma is a rare and malignant cancer. Substantial geographical variation in incidence exists with the highest incidence in south-eastern Asia, eastern Asia, eastern Africa, and middle Africa (*2*). Overall, Asia accounts for more than 85% of the global incidence, mortality and 5-year prevalence. The geographic pattern is associated with differences in genetic susceptibility and the prevalence of Epstein–Barr virus infection in different regions. In 2020, more than 130 000 new cases and 80 000 deaths were recorded worldwide. The incidence age-standardized rate was 1.5 per 100 000 and the mortality age-standardized rate was 0.88 per 100 000 (*3*).

Oesophageal squamous cell carcinoma

Globally, oesophageal cancer ranks eighth in incidence and sixth in mortality among all cancers. In 2020, more than 600 000 new cases and 544 000 deaths occurred worldwide, corresponding to age-standardized rates for incidence and mortality of 6.3 and 5.3 per 100 000, respectively (*4*). The burden of oesophageal cancer varies greatly across countries and populations. Eastern Asia has the highest regional incidence rates, in part because of the large burden in China, followed by southern Africa, eastern Africa, northern Europe and south-central Asia. Of all cases, 59.2% occurred in eastern Asia, with 53.7% in China alone. As regards deaths related to oesophageal cancer, 58.7% occurred in eastern Asia with 55.3% in China alone (*5*).

Oesophageal cancer can be categorized into two main histological subtypes, adenocarcinoma and squamous cell carcinoma. Globally, squamous cell carcinoma is the most common subtype in both male and female patients, contributing to 85% of all oesophageal cancer cases (*5*). The burden of disease of oesophageal squamous cell carcinoma is greater in low-income countries than in high-income countries. About 90% of all oesophageal cancers in developing countries are squamous cell carcinoma s, compared with 66% in high-income countries, with developing countries representing 82% of all new squamous cell carcinoma cases worldwide (*6*).

Summary of evidence: benefits

Nasopharyngeal carcinoma

JUPITER-02 is a randomized, double-blind, multicentre, phase III trial (289 participants) that compared toripalimab with placebo, in combination with gemcitabine plus cisplatin as first-line treatment of recurrent or metastatic nasopharyngeal carcinoma (7). All enrolled patients in the JUPITER-02 study were Asian and 99% had non-keratinizing nasopharyngeal carcinoma. Patients were randomized (1:1) to receive either toripalimab or placebo in combination with chemotherapy every 3 weeks for up to six cycles, followed by monotherapy with toripalimab or placebo. The primary endpoint was progression-free survival as assessed by a blinded independent review committee. At the prespecified interim progression-free survival analysis, median progression-free survival was 11.7 months in the toripalimab arm compared with 8.0 months in the placebo arm (hazard ratio (HR) 0.52, 95% confidence interval (CI) 0.36 to 0.74). As of 18 February 2021, median survival had not been reached (stratified HR 0.60, 95% CI 0.36 to 1.00). The estimated proportion of patients who were alive at 2 years was 77.8% (95% CI 68.0% to 85.0%) for the toripalimab arm and 63.3% (95% CI 49.8% to 74.1%) for the placebo arm. Patients with PD-L1-positive and -negative tumours had a similar median progression-free survival (11.4 versus 11.0 months) when treated with the toripalimab in combination with gemcitabine plus cisplatin. Improvement in progression-free survival was also observed in other relevant subgroups, stratified by sex, Eastern Cooperative Oncology Group (ECOG) performance score, Epstein–Barr virus baseline copy number and disease stage (recurrent or primary metastatic).

At the final progression-free survival analysis (8 June 2021), median follow-up was 22.1 months for the toripalimab arm and 21.4 months for the placebo arm. Median progression-free survival, assessed by a blinded independent review committee, was 21.4 months in the toripalimab arm versus 8.2 months in the placebo arm (HR 0.52, 95% CI 0.37 to 0.73). The 1-year progression-free survival rates were 59.0% versus 32.9%. The overall response rate was 78.8% in the toripalimab arm versus 67.1% in the placebo arm and the median duration of response was 18.0 versus 6.0 months (HR 0.49, 95% CI 0.33 to 0.72). Investigator-assessed progression-free survival was 17.3 months in the toripalimab arm versus 8.1 months in the placebo arm (HR 0.43, 95% CI 0.31 to 0.58). Median overall survival was not reached in either arm, with interim results favouring toripalimab (HR 0.59, 95% CI 0.37 to 0.94) (8).

Based on the JUPITER-02 trial, toripalimab has a score of 3 on the European Society for Medical Oncology (ESMO) magnitude of clinical benefit scale V1.1.

Oesophageal squamous cell carcinoma

JUPITER-06 is a randomized, double-blind, multicentre, phase III trial (514 participants) that compared toripalimab versus placebo, in combination with

paclitaxel plus cisplatin, as first-line treatment of advanced oesophageal squamous cell carcinoma (*9*). Patients were randomized (1:1) to receive toripalimab or placebo in combination with chemotherapy every 3 weeks for up to six cycles, followed by toripalimab or placebo maintenance. Coprimary endpoints were progression-free survival assessed by a blinded independent central review committee and overall survival in the intention-to-treat population. At the prespecified final analysis, median progression-free survival was 5.7 months in the toripalimab arm versus 5.5 months in the placebo arm (stratified HR for progression or death 0.58, 95% CI 0.46 to 0.74). The 1-year progression-free survival rates were 27.8% in the toripalimab arm and 6.1% in the placebo arm. At the prespecified interim analysis median overall survival was 17 months in the toripalimab arm versus 11 months in the placebo arm (stratified HR for death 0.58, 95% CI 0.43 to 0.78). The 1-year overall survival rates were 66.0% versus 43.7% in the toripalimab and placebo arms, respectively.

A post-hoc analysis of the JUPITER-06 study evaluated efficacy stratified by PD-L1 tumour proportion score < 1% and ≥ 1% (*10*). The results showed significantly greater clinical benefit with PD-1 antibody plus chemotherapy versus chemotherapy alone in both the high and low PD-L1-expressing subgroups.

All enrolled patients in the JUPITER-06 study were Chinese with 100% squamous histology. An ESMO magnitude of clinical benefit scale score for toripalimab in oesophageal squamous cell carcinoma is not available.

A systematic review and network meta-analysis (five randomized controlled trials, 2163 participants) evaluated the efficacy and safety of different PD-1 inhibitors (camrelizumab, nivolumab, pembrolizumab, sintilimab and toripalimab) in combination with chemotherapy as first-line treatment for advanced oesophageal cancer (*11*). Significant improvements in overall survival (HR 0.69, 95% CI 0.62 to 0.76), progression-free survival (HR 0.62, 95% CI 0.55 to 0.70) and objective response rate (risk ratio (RR) 1.41, 95% CI 1.23 to 1.62) were observed when a PD-1 inhibitor was added to chemotherapy. Toripalimab plus chemotherapy achieved greater overall survival benefit relative to chemotherapy alone than the other PD-1 inhibitors plus chemotherapy. Subgroup analyses suggested a significant overall survival advantage in groups with PD-L1 tumour-positive scores ≥ 10% and longer progression-free survival in groups with PD-L1 combined positive scores ≥ 10.

Summary of evidence: harms

Treatment-related adverse events occurring in ≥ 5% of patients from the toripalimab monotherapy safety database or the JUPITER-02 and JUPITER-06 trials were reported in the application. Such treatment-related adverse events that were more common in the toripalimab monotherapy population included increased hyperbilirubinaemia, abnormal thyroid function test, abnormal creatine phosphokinase, abnormal lipids, increased amylase and proteinuria.

Nasopharyngeal carcinoma

In the JUPITER-02 study, the incidence of grade ≥3 adverse events was similar between the toripalimab and placebo arms (89.7% versus 90.2%), as was the incidence of fatal adverse events (2.7% versus 2.8%). Immune-related adverse events were more frequent with toripalimab (53.4% versus 21.7%), including those of grade ≥ 3 (8.9% versus 1.4%) (*7*).

Oesophageal squamous cell carcinoma

In the JUPITER-06 study, treatment-emergent adverse events of grade ≥ 3 occurred in 73.2% of patients in the toripalimab arm and 70.0% of patients in the placebo arm. Fatal treatment-emergent adverse events occurred in 8.2% of patients in each treatment arm, of which 0.4% in the toripalimab arm and 1.2% in the placebo arm were related to the study treatment. The incidence of serious adverse events (36.2% versus 28.8%) and infusion-related reactions (3.5% versus 3.1%) were similar between treatment arms. Treatment emergent adverse events that led to treatment discontinuation occurred in 11.7% and 16.2% of patients in the toripalimab and placebo arms, respectively (*9*).

WHO guidelines

WHO guidelines for treatment of nasopharyngeal and oesophageal carcinomas are not currently available.

Costs/cost–effectiveness

Nasopharyngeal carcinoma

Two cost–effectiveness analyses evaluated toripalimab or camrelizumab combined with chemotherapy and chemotherapy alone for patients with recurrent or metastatic nasopharyngeal carcinoma from the Chinese payers' perspective (*12,13*). Compared with chemotherapy alone, toripalimab plus chemotherapy was associated with incremental cost–effectiveness ratios of US$ 6696 (*12*) and US$ 19 726 (*13*) per quality-adjusted life year. The medicine cost for one cycle of treatment with toripalimab (240 mg) reported in the analyses were US$ 426.02 (*12*) and US$ 659.40 (*13*).

Oesophageal squamous cell carcinoma

Published cost–effectiveness evaluations for toripalimab in treatment-naive advanced oesophageal squamous cell cancer are not available.

Availability

Toripalimab has regulatory approval from the National Medical Product Administration in China for six indications, including those requested in the application.

Regulatory applications have been submitted to the United States Food and Drug Administration, the European Medicines Agency and the United Kingdom Medicines and Healthcare products Regulatory Agency and are currently under review.

Other considerations

The EML Cancer Medicines Working Group did not support the inclusion of toripalimab on the EML for the treatment of nasopharyngeal or oesophageal squamous cell cancer at this time because the absolute benefits are still unclear and data from trials have a short follow-up (22 months). The Working Group considered that toripalimab could have potentially high therapeutic value for the treatment of patients with nasopharyngeal cancer, a cancer which is endemic in some low- and middle-income countries with limited therapeutic options. The Working Group noted that multiple immune checkpoint inhibitors suggesting similar benefits are under development or have been granted approval for the management of advanced oesophageal carcinoma. A comprehensive evaluation of the treatment landscape is appropriate to identify those immune checkpoint inhibitors that provide the best value for health care systems. The Working Group noted that the lower price of toripalimab compared with other immune-checkpoint inhibitors and improvement of the overall survival may result in better cost–effectiveness, although the cost for treatment may still have a large impact on health budgets.

Committee recommendations

The Expert Committee acknowledged the global health burden of nasopharyngeal and oesophageal cancer and noted the endemic nature of nasopharyngeal cancer in low- and middle-income countries. The Committee agreed that better therapeutic options were needed for treatment of these cancers.

The Committee noted that the evidence presented in the application focused on patients with metastatic or recurrent, locally advanced disease and that the patients included in the trials were not selected based on the level of tumour expression of PD-L1, although this aspect was explored in post-hoc analyses based on aggregated data from multiple randomized controlled trials on oesophageal cancer. The Committee considered that more evidence analysing the effect of treatment based on PD-L1 expression or other biomarkers would be informative to understand whether a particular subgroup of patients might benefit more from treatment.

The Committee considered that the benefits observed when toripalimab was added to chemotherapy in first-line treatment for advanced nasopharyngeal cancer were modest, and that toripalimab was assigned a score of 3 on the ESMO magnitude of clinical benefit scale, which is lower than the accepted threshold for EML consideration.

For advanced oesophageal squamous cell cancer, the Committee acknowledged that the addition of toripalimab to chemotherapy might be associated with relevant improvements in survival compared with chemotherapy alone, although the evidence is still immature, with short follow-up. A score on the ESMO magnitude of clinical benefit scale is not available for toripalimab for this indication.

The Committee acknowledged that the reported price of toripalimab was considerably lower than other immune checkpoint inhibitors. However, the price estimates were only available from China, the only country where toripalimab is currently marketed.

The Expert Committee therefore did not recommend inclusion of toripalimab on the complementary list of the EML for the treatment of nasopharyngeal and oesophageal squamous cell carcinomas. The Committee acknowledged the promising role of chemoimmunotherapy in the treatment of these cancers and recommended that the evidence for these treatments continue to be monitored for potential future EML consideration.

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Section 9: Therapeutic foods

Ready-to-use therapeutic food – addition –EMLc

Ready-to-use therapeutic food	ATC code: not available

Proposal

Addition of ready-to-use therapeutic food (RUTF) to the core list of the EMLc for the dietary management of uncomplicated severe acute malnutrition in children aged 6 months to 5 years.

Applicant

Minh Tram Le, United Nations Children's Fund (UNICEF), New York, NY, United States of America

Alison Fleet, UNICEF Supply Division, Copenhagen, Denmark

Jaden Bendabenda, WHO Department of Nutrition and Food Safety, Geneva, Switzerland

WHO technical department

The application was made in collaboration with the WHO Department of Nutrition and Food Safety

EML/EMLc

EML

Section

9 Therapeutic foods (renamed)

Dose form(s) & strengths(s)

Biscuit or paste of nutritional composition as determined by the UN joint statement on the community-based management of severe acute malnutrition and Codex Alimentarius guidelines

Core/complementary

Core

Individual/square box listing

Individual

Background

Applications requesting inclusion of RUTF on the EMLc for prevention of severe acute malnutrition have been considered on two previous occasions by the Expert Committee. On each occasion, listing was not recommended.

In 2017, the Expert Committee acknowledged the effectiveness of RUTF in the outpatient treatment of uncomplicated severe acute malnutrition in children aged 6–59 months. The Committee agreed that improving access to RUTF in health facilities at the country level for the outpatient treatment of severe acute malnutrition is essential. However, at that time, the Committee considered that listing RUTF on the EMLc may have had implications for the availability of alternative products or formulations, including decreasing availability at the country level because of increased regulation and requirements on the production and supply chain. The Committee recommended further analysis of the implications and impacts of including RUTF in the EMLc addressing the following aspects:

- country regulatory requirements if RUTF is included in the national EML (medicine/pharmaceutical versus food) and ability of local and international producers to comply with those requirements;

- cost and access implications if RUTF is listed as a medicine/pharmaceutical rather than a food;

- guidelines on appropriate use of RUTF, that is, only for uncomplicated cases of severe acute malnutrition and not for other children;

- progress by the Codex Committee on Nutrition and Foods for Special Dietary Uses) on the development of RUTF guidelines; and

- outcome of ongoing systematic reviews of the effectiveness and safety of RUTF (*1*).

Following a resubmission in 2019, the Expert Committee acknowledged once again the efficacy of RUTF for the dietary management of uncomplicated severe acute malnutrition in children younger than 5 years, many in non-hospitalized settings. However, a new report prepared in response to the request of the previous Expert Committee accompanying the application highlighted the divided opinions and ongoing uncertainty of the country-level implications of including RUTF as a medicine on the Model List. Some concerns initially raised in 2017 were still valid: the report highlighted that adding RUTF to the Model List could have unknown or unintended consequences such as more restricted access and increased costs and could potentially hinder local production. The Committee noted that, at that time, the work to establish standards and guidelines

for RUTF under the Codex Alimentarius, regarding production, nutritional aspects and labelling to facilitate harmonization of the requirements of RUTF at an international level, was not yet finalized. In the absence of such standards, and without a clear indication of the potential consequences and implications at the country level of including RUTF on the Model List, and without the reassurance of a risk-mitigation plan to address any consequences, the Expert Committee did not recommend the addition of RUTF to the core list of the EMLc. In 2019, the Committee recommended that a comprehensive risk-mitigation plan for potential consequences of the addition of RUTF on the Model List would be highly relevant for any future consideration of the inclusion of this product (*2*).

Public health relevance

Severe acute malnutrition in children aged 6–59 months is defined anthropometrically using any one or combination of the following criteria: a mid-upper arm circumference < 115 mm or a weight-for-height < –3 Z-scores of the WHO growth standards, or bilateral nutritional oedema (*3*). This target population is identified through passive and active screening at health facilities and at the community level and this screening is integrated into national health systems using the community management of acute malnutrition model. Children detected as having severe acute malnutrition and presenting specific and severe medical complications or with complete anorexia are referred for inpatient care treatment. Children detected with severe acute malnutrition but not needing inpatient treatment and with a preserved appetite are admitted into outpatient care and given RUTF alongside the appropriate medical treatment and follow-up.

Rates of severe acute malnutrition in children have remained persistently high and progress towards the Sustainable Development Goal (SDG) target of reducing the prevalence of child wasting to less than 5% by 2025 has been limited (*4*). Severe acute malnutrition affects about 13.6 million children younger than 5 years on an annual basis in low- and lower middle-income countries (*5*). Some of the highest prevalence of the condition is reported in countries in east and west Africa, however, more than half of all children suffering from severe acute malnutrition live in southern Asia. While severe acute malnutrition has typically been linked to humanitarian crises, three out of four children suffering from severe acute malnutrition do not live in areas affected by such crises, demonstrating that this condition is a widespread public health concern (*4*). In the context of climate change, persistent drought, elevated food prices and COVID-19, the rates of severe acute malnutrition are rising in many countries. In 2022, 260 000 additional children suffered from severe acute malnutrition in 15 of the highest burden countries (*6*). In some countries, Afghanistan for example, rates of severe acute malnutrition have doubled in the last 5 years (*7*).

Summary of evidence: benefits

The evidence of benefits presented in the current application remained largely unchanged from the application submitted in 2019. Two systematic reviews on the use of RUTF were published in 2013.

A 2013 Cochrane systematic review included three quasi-randomized trials comparing RUTF with a standard flour porridge diet for the treatment of severe acute malnutrition. The meta-analysis found that RUTF improved recovery (risk ratio (RR) 1.32, 95% confidence interval (CI) 1.16 to 1.50) but the evidence was too limited to draw definitive conclusions on relapse, mortality or weight gain (*8*). This review was updated in 2019 with an additional 11 studies included, bringing the total number of studies to 15. RUTF was associated with improvements in recovery (RR 1.33, 95% CI 1.16 to 1.54; six studies, 1852 participants; moderate-quality evidence) and in weight gain (mean difference (MD) 1.12 g/kg a day, 95% CI 0.27 to 1.96 g/kg a day; four studies, 1450 participants; low-quality evidence). Results were less certain for relapses (RR 0.55, 95% CI 0.30 to 1.01; four studies, 1505 participants; very low-quality evidence) and mortality (RR 1.05, 95% CI 0.51 to 2.16; four studies, 1505 participants; very low-quality evidence). A meta-analysis of two quasi-randomized cluster trials showed that standard RUTF meeting total daily nutritional requirements may improve recovery (RR 1.41, 95% CI 1.19 to 1.68; low-quality evidence) and reduce relapse (RR 0.11, 95% CI 0.01 to 0.85; low-quality evidence) compared with RUTF given as a supplement to the usual diet. The effects were imprecise for mortality (RR 1.36, 95% CI 0.46 to 4.04; very low-quality evidence) and rate of weight gain (MD 1.21 g/kg a day, 95% CI –0.74 to 3.16 g/kg a day; very low-quality evidence). The updated review concluded that RUTF likely contributed to improved recovery and weight gain, however the effects on relapse and mortality were still unknown. Different formulations of RUTF were compared with the current evidence not favouring a particular formulation over another for most outcomes (*9*).

A 2013 systematic review, meta-analysis and Delphi process on the treatment of severe and moderate acute malnutrition compared children who received RUTF with those who received standard care (in-patient treatment with therapeutic milks followed by provision of corn soy blend food for feeding at home). The review included largely the same studies used in the Cochrane review and the evidence was also considered to be of low quality. The meta-analysis found that children given RUTF were 51% more likely to achieve nutritional recovery (weight-for-height Z score ≥ –2) than the standard care group (RR 1.51, 95% CI 1.04 to 2.20). Weight gain in the RUTF group was also higher: this difference was statistically significant but small (MD 1.27 g/kg a day, 95% CI 0.16 to 2.38 g/kg a day). No significant differences were found in mortality between the two groups. Because of the limited number of high-quality comparative trials evaluating community-based treatment using RUTF, the authors complemented

the systematic review and meta-analysis with a Delphi process to gather and synthesize expert opinion on the plausible impact estimates of the intervention. For community-based treatment of uncomplicated severe acute malnutrition using RUTF, the Delphi process estimated a case fatality rate of 4% (range: 2–7%) and a recovery rate of 80% (range: 50–93%). Overall, the review argued that the management of uncomplicated severe acute malnutrition in children aged 6–59 months using RUTF is backed by a wealth of observational and programmatic data, despite the limited number of impact studies (*10*).

The application also summarized the results of additional studies documenting the acceptability of RUTF formulation and programme evaluation. One randomized control trial in India of 26 children with severe acute malnutrition found that children who received RUTF in addition to standard supplementary nutrition (roughly 500 kcal of energy and 12–15 g of protein) had 10 times higher odds of recovery compared the control group (odds ratio (OR) 10.28, 95% CI 1.02 to 103.95) (*11*). Another study was conducted to assess the effects of different types of RUTF (soybean, maize and sorghum RUTF with and without added milk (high iron and vitamin C arms) and peanut and milk standard RUTF (low iron arm)) on anaemia, iron deficiency and recovery. The study was characterized by high attrition, with missing data for about 30% of children in both arms. Soybean, maize and sorghum RUTF with and without added milk was associated with the lowest prevalence of anaemia and iron deficiency, and the highest recovery rate (*12*).

Summary of evidence: harms

The 2019 Cochrane systematic review evaluated the safety of RUTF compared with standard flour porridge diet for mortality, frequency of diarrhoea and adverse outcomes. No difference was seen in mortality between the children who received RUTF and those who received standard diets (RR 0.97, 95% CI 0.46 to 2.05; three studies, 599 participants). Similarly, there was no difference in the frequency of diarrhoea (number of days of diarrhoea in the first 2 weeks of treatment) between the children who received RUTF and those who received the standard diets (MD –0.6, 95% CI –1.30 to 0.10; one study, 352 participants) (*9*).

The other systematic review reported did not include adverse events among considered outcomes (*10*).

Peanuts, chickpeas and soybeans – the main raw foods used in lipid-based RUTF formulations – contain a wide range of naturally occurring microorganisms, some capable of causing human diseases. Therefore, even low-moisture foods with sufficiently low water content to prevent the growth of bacteria can be vehicles for pathogens. Children with acute malnutrition may be more susceptible to foodborne illnesses because changes caused by malnutrition may affect their immune system and their ability to defend against pathogens (*13,14*).

For peanut-based RUTFs, the largest safety concern is contamination by Salmonella spp. Salmonellosis is a health risk even in very low doses in some foods (e.g. foods with high lipid content) and its link to foodborne disease outbreaks is well established (*14*). Aflatoxin, a family of toxins produced by certain mushrooms, may be present in peanuts and milk. Chronic consumption of high levels of aflatoxin in early life can affect children's growth and development, and their immune and hepatic systems (*13*).

Vitamin toxicity is a theoretical concern for fat-soluble vitamins A, D and E as these are present in RUTF in doses higher than the recommended daily intakes because these high doses are necessary to resolve vitamin deficiencies in children with severe acute malnutrition. If RUTF is consumed by a child without malnutrition, they may be at risk of toxicity of fat-soluble vitamins.

The Codex Alimentarius guidelines for RUTF include appropriate food safety guidance on microbiological, chemical and physical hazards associated with RUTF and its production (*15*).

WHO guidelines

The use of RUTF for the outpatient treatment of severe acute malnutrition in children aged 6–59 months has been a recommended treatment approach for more than 15 years. The 2007 Joint Statement issued by the WHO, the World Food Programme, the United Nations System Standing Committee on Nutrition and UNICEF highlighted the importance of community-based treatment of severe acute malnutrition with RUTF and recommended this approach for uncomplicated cases of this condition (*3*). The Joint Statement further advocates the importance of national protocols and provision of RUTF for the management of severe acute malnutrition.

The 2013 WHO guidelines for the management of severe acute malnutrition recommend outpatient treatment for children who have passed an appetite test and are clinically well. Despite the low quality of evidence identified, these guidelines include a strong recommendation for the use of RUTF for outpatient treatment (*16*). More recently, RUTF has been included in the WHO guidelines on the dairy protein content in RUTF for treatment of uncomplicated severe acute malnutrition. This guidance document on the appropriate use of RUTF clarifies which cases of severe acute malnutrition are eligible for RUTF (*17*). It addresses the concerns raised by previous Expert Committees on the lack of recommendations on when and how to use RUTF.

Costs/cost–effectiveness

A 2020 review by Action Against Hunger and Save the Children United Kingdom brought together all the existing literature on cost and cost–effectiveness of treatment of severe acute malnutrition. The review identified 21 studies, of which

20 reported the cost per treated child, and 11 cost–effectiveness data reports. The studies spanned countries in Africa and south Asia and were conducted between 2009 and 2019. Total costs per treated child ranged from US$ 76 in Niger to US$ 805 in Ghana, with a median cost of US$ 196. These costs included RUTF procurement and transportation, as well as costs of delivery (e.g. infrastructure, health worker time, additional drugs delivered with the treatment package and community outreach) (*18*). The wide range in cost per child reflects the varying treatment methods, contexts, scale and models of implementation. For example, in the Ghana study, only 40 children were treated which is likely to have driven up the cost per child treated. Another factor influencing the large variation in costs is linked to the method used and the sources of cost information included, which differed across studies. While total cost of treatment varied significantly, the absolute cost of RUTF was more consistent across programmes. In programmes with higher total costs, RUTF accounts for a smaller portion of the total cost (RUTF was 13% of the total cost of treatment in Ghana) and vice versa (RUTF was 46% of the total cost of treatment in Niger). The total treatment cost is largely driven by the context, scale and characteristics of the programme and, to a lesser extent, by the cost of RUTF.

While the evidence on the cost–effectiveness of treatment of severe acute malnutrition is limited, treatment with RUTF using the community-based model is considered a highly cost-effective intervention. Six studies included in the review assessed the cost per disability-adjusted life year (DALY) averted. The cost per DALY averted ranged from US$ 26 in Bangladesh to US$ 53 in Zambia. Given that these estimates are lower than the gross domestic product per capita in the countries where implemented, the intervention is considered to be cost effective (*18*).

UNICEF, the main procurer of RUTF, reported that the weighted average price per carton of RUTF decreased from US$ 52 in 2006 to US$ 41 in 2021 (*19*). One carton of RUTF includes 150 sachets, sufficient to treat a child for 68 weeks (*20*). The application noted that RUTF price reductions achieved over the past 16 years risk being reversed due to the current global situation (disruption of supply chains due to COVID-19 and armed conflicts) where prices are rising for ingredients, packaging, energy and international freight.

Availability

Over the past decade, UNICEF has been focusing efforts on integrating RUTF in national supply chains and securing domestic funding for this product. Modest gains have been made by governments in high-burden countries, although UNICEF continues to procure 75–80% of RUTF for the treatment of severe acute malnutrition. The availability of recognized international guidelines will support the integration process by providing national governments with

a regulatory framework which can be applied at the country level to ensure quality and standards. These guidelines will be able to orient governments in the procurement process and will also be an essential tool to assist in building regulatory capacity within national governments to establish their own regulatory framework for RUTF.

Other considerations

A recent mapping exercise by UNICEF identified 71 countries with national clinical guidelines on the management of severe acute malnutrition which includes treatment with RUTF. A further 10 countries have draft or interim guidance on the management of severe acute malnutrition using RUTF (*21*). The application reported that, as of November 2021, 25 countries with programmes to treat severe acute malnutrition with RUTF had included RUTF in their country's national EML. The number of countries with RUTF in the national EML was considerably higher in the African region than elsewhere. Only 18% of countries in the region of the Americas and 10% of countries in the western Pacific region included RUTF in the national EML. No countries in the Eastern Mediterranean, European or South-East Asia regions included RUTF in their national EMLs. Of the 25 countries with RUTF in the national EML, 11 classified RUTF as a medicine, seven as a food for special medical purposes and seven as other. In most countries RUTF is regulated by medicines regulatory authorities. The mapping exercise did not find any impediments or issues from regulatory agencies or in procuring RUTF when it was included in the national EML as a medicine instead of a food.

In 2022, the Codex Alimentarius guideline for RUTF was finalized, thus providing the first international reference document detailing the composition and manufacturing standards for RUTF (*15*). This guideline is expected to support procurement processes and provide governments with a regulatory framework which can be applied at the country level to ensure quality and standards of RUTF products. The guideline also clarifies the regulatory status of RUTF as a food for special medical purposes. One of the key concerns in listing RUTF on the EML raised in stakeholder consultations in 2018 was that this listing might lead to the application of pharmaceutical standards to the manufacturing process (*22*). The Codex Alimentarius guideline has determined that RUTF sits within the regulatory framework of food production, with a focus on the fact that this product is for specific medical purposes. Classifying RUTF as a food for special medical purpose will help countries by clarify that these products are specially processed or formulated, highlighting that they are only for use in the treatment of severe acute malnutrition, not for general consumption. The guidelines provide a set of quality standards for suppliers and limiting definitions and nutrient compositions of RUTF. These standards can also be used as importation requirements.

Unlike therapeutic milk products, RUTF formulas are not water-based, thus limiting bacterial growth. They can be transported and stored without refrigeration and in areas where hygiene conditions are suboptimal (*3*), making RUTF an ideal candidate to treat severe acute malnutrition at the community level in areas afflicted by poverty, lack of access to food, disease, and humanitarian emergencies.

Committee recommendations

The Expert Committee noted that severe acute malnutrition in children continues to be a considerable global health burden, affecting about 13.6 million children every year. Severe acute malnutrition is associated with metabolic dysregulation, impaired gluconeogenesis, disrupted amino acid or lipid metabolism, and increased risk of illness and mortality. Low- and middle-income countries are most affected and treatment services are estimated to reach less than 15% of undernourished children. The Committee noted that use of RUTF is currently recommended for use in several WHO guidelines and it is already included in national EMLs of a number of countries.

The Committee also noted that the use of RUTF for the treatment of severe acute malnutrition in children aged 6 months to 5 years is supported by evidence from clinical trials showing benefits in improved recovery from malnutrition and weight gain compared with standard care. The Committee also noted that the effects of RUTF on relapse and mortality were still uncertain, and RUTF treatment was not associated with severe adverse events.

The Committee noted that although data were limited, available cost–effectiveness studies indicate RUTF to be a cost-effective intervention as part of community-based management programmes for severe acute malnutrition, and more cost-effective than inpatient treatment.

The Committee was satisfied with the information provided by the applicants addressing the specific concerns of the 2019 Expert Committee about the potential consequences of including RUTF on the Model List and associated risk-mitigation measures. The Committee was also reassured by the publication of the Codex Alimentarius guidelines which define the nutritional composition, production and labelling standards for RUTF as a food for special medical purposes. Potential risks of contamination are minimized by following good manufacturing processes which are also outlined the Codex Alimentarius guidelines.

Based on these considerations, the Expert Committee recommended the inclusion of RUTF on the core list of the EMLc, in a new section on therapeutic foods, for treatment of severe acute malnutrition in children aged 6 months to 5 years.

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Section 10: Medicines affecting the blood
10.1 Antianaemia medicines

Ferrous salt + folic acid – new formulation – EML

Ferrous salt + folic acid	**ATC code: B03AD**

Proposal

Addition of a new strength formulation of ferrous salt + folic acid (60 mg elemental iron + 2.8 mg folic acid) to the core list of the EML for weekly iron and folic acid supplementation for the prevention of anaemia in menstruating women and adolescent girls, and for reducing the risk of pregnancies affected by neural tube defects.

Applicant

Nutrition International

WHO technical department

The application was made in consultation with and support from the WHO Department of Nutrition and Food Safety.

EML/EMLc

EML

Section

10.1 Antianaemia medicines

Dose form(s) & strengths(s)

Tablet: equivalent to 60 mg elemental iron + 2.8 mg folic acid

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Core/complementary

Core

Individual/square box listing

Individual

Background

Applications requesting inclusion of this formulation of ferrous salt + folic acid for prevention of anaemia have been considered on two previous occasions by the Expert Committee.

In 2013, the Expert Committee recognized the programmatic needs for appropriate supplementation in pregnancy, but did not recommend listing of the

formulation at that time because the available data did not show the intermittent (weekly) regimen to be at least equivalent to the daily regimen of 60 mg elemental iron + 0.4 mg folic acid (the formulation currently included on the EML) (*1*).

Following a resubmission in 2015, the Expert Committee once again did not recommend listing, considering that the evidence presented for efficacy of intermittent supplementation was insufficient. The overall quality of the evidence for outcomes of iron supplementation, intermittent or daily, with or without folic acid, ranged from low to moderate. The Committee also noted that evidence for better adherence with the intermittent regimen had not been adequately reported, and that commercial availability of the proposed fixed-dose combination product was limited to one country (*2*).

Public health relevance

Anaemia is a public health problem widely prevalent in several low- and middle-income countries. Despite a World Health Assembly target (2012–2025) of a 50% reduction in anaemia in adolescent girls and women 15–49 years of age, the most recent data from WHO's Global Health Observatory indicate little progress has been made in reducing the prevalence of anaemia in the past decade (*3*). For 2019, data show that, globally, 29% of non-pregnant women of reproductive age (15–49 years) suffer from anaemia. The burden is highest in South-east Asia (46%) and Africa (40%). Although data specific to adolescents aged 10–19 years are lacking globally, about 30% are estimated to be anaemic (*4*). Anaemia impairs resistance to infection and reduces physical capacity and work performance in all age groups; for adolescents, it can also have consequences for academic performance and energy to participate as an active member of the community. In addition, adolescent girls and women with anaemia who become pregnant are at higher risk of negative maternal and neonatal outcomes (*5*).

Low haemoglobin concentrations can be caused by: inherited red blood cell disorders, such as sickle-cell disease and thalassaemia; dietary inadequacy; malaria; schistosomiasis; hookworm infection; HIV infection; and some noncommunicable diseases. The proportion of all anaemia associated with iron deficiency is estimated at about 50% in non-pregnant and pregnant women and 42% in children (*6*). Iron-deficiency anaemia occurs as a result of inadequate intakes and poor bioavailability of dietary iron. This, in turn, causes decreased concentrations iron in the blood, leading to iron deficiency and lower haemoglobin concentrations (*7*).

Inadequate folate status can lead to adverse health consequences of public health significance, such as megaloblastic anaemia (folate-deficiency anaemia) and in adolescent girls and women an increased risk of pregnancies affected by neural tube defects (folate insufficiency) (*8*). Neural tube defects are associated with substantial mortality, morbidity, disability, and psychological and economic

costs. Many are preventable with folic acid supplementation. Recent estimates, however, suggest that neural tube defects are still prevalent worldwide with 260 100 births with neural tube defects worldwide (prevalence 18.6/10 000 live births) occurring in 2015 alone (*9*).

Summary of evidence: benefits

A 2019 Cochrane systematic review of 25 randomized or quasi-randomized trials (10 966 participants) evaluated the efficacy, effectiveness and safety of intermittent iron supplementation to reduce anaemia in adolescent and adult menstruating women (*10*). Overall, intermittent oral supplementation with iron in menstruating women increased haemoglobin concentration (mean difference (MD) 5.19 g/L, 95% confidence interval (CI) 3.07 to 7.32 g/L; 15 studies, 2886 participants; moderate-quality evidence) and ferritin concentration (MD 7.46 micrograms/L, 95% CI 5.02 to 9.90 micrograms/L; seven studies, 1067 participants; low-quality evidence) and reduced the risk of anaemia (risk ratio (RR) 0.65, 95% CI 0.49 to 0.87; 11 studies, 3135 participants; low-quality evidence) compared with no supplementation or placebo. For the comparison of weekly versus daily supplementation, women receiving iron supplements intermittently were as likely to have reduced anaemia at the end of the intervention as those receiving iron supplements daily (RR 1.09, 95% CI 0.93 to 1.29; eight studies, 1749 participants; moderate-quality evidence). Compared with daily supplementation, intermittent supplementation produced similar haemoglobin concentrations (MD 0.43 g/L, 95% CI −1.44 to 2.31 g/L; 10 studies, 2127 participants; low-quality evidence), lower ferritin concentrations (MD −6.07 micrograms/L, 95% CI −10.66 to −1.48 micrograms/L; four studies, 988 participants; low-quality evidence), and may reduce the risk of iron deficiency (RR 4.30, 95% CI 0.56 to 33.20; one study, 198 participants; very low-quality evidence).

A secondary analysis from a randomized trial in Malaysia evaluated the effects of folic acid in weekly iron and folic acid supplements compared with iron alone on haemoglobin concentration, anaemia reduction or iron status in 311 non-pregnant women treated with 60 mg iron with no, 0.4 mg or 2.8 mg folic acid for 16 weeks (*11*). After 16 weeks, no significant differences were found between treatment groups for mean haemoglobin concentration or iron status. In all women, the risks of anaemia (RR 0.65, 95% CI 0.45 to 0.96) and iron deficiency based on ferritin (RR 0.30, 95% CI 0.20 to 0.44) were lower at 16 weeks than at baseline. The inclusion of folic acid in weekly iron supplementation did not reduce anaemia or improve iron status over iron supplementation alone.

Data from a pre–post, longitudinal programme was used to evaluate the effectiveness of school-based weekly iron and folic acid supplementation over a 30–36 week school year in reducing anaemia and increasing haemoglobin concentrations in 1387 adolescent girls (10–19 years) in Ghana (*12*). A significant

reduction was seen in the prevalence of anaemia over one school year of the intervention from 25.1% to 19.6%, with a corresponding increase in mean haemoglobin concentration of 0.2 g/dL. Participants consumed a mean of 16.4 tablets during the study period (range 0–36). Each additional tablet consumed over the school year was associated with a 5% reduction in the adjusted odds of anaemia at follow-up, however the relationship was non-linear.

A community-based randomized trial evaluated the effect of weekly iron and folic acid supplementation for 3 months on serum ferritin, serum folate and haemoglobin concentration among 226 adolescent girls (10–19 years) in Ethiopia (*13*). Significant differences in haemoglobin, serum ferritin and serum folate concentrations were observed between the intervention and the control group after 3 months of supplementation. After adjusting for confounding factors, 3-month weekly iron and folic acid supplementation was associated with significant improvements of 4.10 ng/mL in serum folate, 39.1 micrograms/L in serum ferritin and 1.2 g/dL in haemoglobin concentrations relative to the control group.

Two studies compared a weekly folic acid dose (2.8 mg (*14*) and 4 mg (*15*)) with a daily dose of 0.4 mg. In both studies, the larger weekly dose was not as effective as the daily dose in raising blood folate levels above a level associated with a lower risk of neural tube defects. Another study comparing weekly folic acid doses of 2.8 mg and 0.4 mg (plus iron) found that women who received the higher folic acid dose were 7.3 times more likely to have red blood cell folate concentrations higher than the level associated with lower risk of neural tube defects (*16*).

Adherence and compliance

The 2019 Cochrane systematic review included four studies (507 participants) that examined adherence (defined as percentage of participants who consumed ≥ 70% of the prescribed dosage) to intermittent versus daily supplementation (*10*). Pooled meta-analysis of these studies found no difference in adherence between treatment groups (RR 1.04, 95% CI 0.99 to 1.09).

Compliance outcomes for 4417 menstruating women were reported from a double-blind randomized trial in Viet Nam in which 78% of women consumed more than 80% of the preconception supplements. Women of minority ethnicity (odds ratio (OR) 0.78, 95% CI 0.67 to 0.91) and farmers (OR 0.71, 95% CI 0.58 to 0.88) were less likely to consume more than 80% of the preconception supplements. Socioeconomic status was positively associated with more than 80% adherence (OR 2.71 highest versus lowest quintile, 95% CI 2.10 to 3.52) (*17*).

A prospective cohort study in Ghana evaluated the effectiveness of school-based weekly iron and folic acid supplementation in reducing anaemia and increasing haemoglobin concentrations in 1387 girls aged 10–19 years (*12*). In this study, 90% of the girls had ever consumed the tablet, and 56% had

consumed at least 15 weekly tablets. The average intake adherence was about half of the available tablets. Among ever consumers, 88% of the girls liked the tablet and 27% reported undesirable changes (primarily heavy menstrual flow).

A prospective cohort study in Viet Nam in 2017 followed up a cohort of 389 women of childbearing age from baseline until 6 years after the introduction of a weekly iron and folic acid (200 mg + 0.4 mg) and deworming (400 mg albendazole twice yearly) programme (*18*). Reduced but reasonable adherence with weekly iron and folic acid was reported after 54 and 72 months, respectively (76% and 72%), suggesting that the programme remained popular with the target population over time and adherence to once weekly supplements was maintained. Impediments to participating in the programme included interruption of supply and inadequate training of new health staff over the 6 years of implementation. Limitations of this study included a reduced participation rate in the later surveys. The study reported that this reduced participation was most likely due to the long follow-up period and the movement of some families out of the area. The relatively high loss to follow-up was acknowledged as a possible bias to estimates of adherence and effectiveness, as non-adherent women may have chosen not to take part, while healthier adherent women may have remained engaged.

Adherence rates of 89% and higher have been reported in programmes supported by Nutritional International in Ethiopia, Indonesia, Kenya, Pakistan, Senegal and United Republic of Tanzania.

Summary of evidence: harms

There are no recorded safety concerns linked to weekly iron and folic acid supplementation. Gastrointestinal side-effects from iron are well known and include black stools, nausea, constipation, abdominal cramping and vomiting.

The 2019 Cochrane review reported that women receiving iron supplements intermittently were less likely to have any adverse effects than those receiving iron supplements daily (RR 0.41, 95% CI 0.21 to 0.82; six studies, 1166 participants; moderate-quality evidence) (*10*).

Some concerns are emerging about potential interactions with antimalarial drugs and folic acid supplementation. A protocol for a Cochrane review to examine the effects of folic acid supplementation, at various doses, on the risk of malaria infection and severity in people living in areas with various degrees of malaria endemicity has been published (*19*). Currently available evidence focuses on sulfadoxine + pyrimethamine, which is frequently used to prevent and treat malaria in endemic malarial areas and works by inhibiting folate synthesis in the parasite (*20*). Evidence has shown that *Plasmodium* parasites can use exogenous folic acid salvaged from the host (*21*). At higher intakes, folic acid passes into the circulation unmetabolized and may reduce the efficacy of antifolate drugs, such as sulfadoxine + pyrimethamine.

The effect of folic acid on the therapeutic efficacy of sulfadoxine + pyrimethamine against *Plasmodium* infection has been examined in many studies in sub-Saharan Africa. In two studies of children aged 6 months to 9 years (*22,23*), folic acid supplementation at doses ranging from 1 mg to 10 mg daily increased the risk of parasitological failure with sulfadoxine + pyrimethamine. In a study of all age groups, folic acid reduced the time to treatment failure as assessed by parasitological examination (*24*). In a study of pregnant women in Kenya with Plasmodium infection, daily supplementation with 5 mg folic acid doubled the risk of treatment failure with sulfadoxine + pyrimethamine at 14 days, while a dose of 0.4 mg a day did not increase the risk of treatment failure (*25*). Another study of pregnant women in the Gambia found that folic acid supplementation in doses of 0.5 mg to 1.5 mg a day did not affect the efficacy of intermittent sulfadoxine + pyrimethamine in preventing malaria (*26*).

WHO guidelines

The 2011 WHO guidelines for intermittent iron and folic acid supplementation include a strong recommendation for use of this supplementation as a public health intervention in menstruating women living in areas where anaemia is highly prevalent, to improve their haemoglobin concentrations and iron status and reduce the risk of anaemia (*27*). The suggested dose is 60 mg elemental iron plus 2.8 mg folic acid, once a week for 3 months, followed by 3 months of no supplementation.

The 2016 WHO guidelines on antenatal care for a positive pregnancy experience include a context-specific recommendation for use of intermittent oral iron and folic acid supplementation (120 mg of elemental iron plus 2.8 mg folic acid) once a week for pregnant women to improve maternal and neonatal outcomes, if daily iron is not acceptable due to side-effects and in populations with an anaemia prevalence in pregnant women of less than 20% (*28*).

In 2018, WHO published guidance that summarized the global evidence-informed recommendations that address malnutrition in all its forms in adolescents with the aim of ensuring healthy lives and well-being in this group. In this guidance, intermittent iron and folic acid supplementation is included as one of eight evidence-based nutrition interventions and policies that could affect adolescent nutrition. This guidance draws on the recommendation made by the 2011 guidance described above for menstruating adolescent girls and women (*29*).

Costs/cost–effectiveness

Cost–effectiveness data for weekly iron and folic acid supplementation using the proposed formulation are not currently available.

The United Nations Children's Fund (UNICEF) supply catalogue currently lists the 60 mg + 2.8 mg formulation at an indicative price of US$ 1.56 for a bottle of 100 tablets. In comparison the UNICEF supply catalogue indicative price for the 60 mg + 0.4 mg formulation is US$ 0.84 for a bottle of 100 tablets (*30*).

Availability

Market availability of the 60 mg + 2.8 mg formulation of iron and folic acid has been limited but has recently improved. There are currently two approved suppliers of the formulation supplied by UNICEF, who have provided nearly 1.2 million bottles of the supplement since 2019.

Committee recommendations

The Expert Committee noted the public health relevance of iron and folic acid supplementation in the prevention of anaemia in women of reproductive age and for reducing the risk of pregnancies affected by neural tube defects. The Committee also noted the global target of a 50% reduction of anaemia in adolescent girls and women by 2025, and that intermittent iron and folic acid supplementation is a recommended intervention in various WHO guidelines.

The Committee noted that the evidence presented in the application supported weekly intermittent supplementation being associated with similar efficacy outcomes to daily iron and folic acid supplementation, with potentially fewer adverse effects. The Committee also considered that it was likely that weekly iron and folic acid supplementation would be associated with better adherence.

The Expert Committee therefore recommended the inclusion of a new strength formulation of ferrous salt + folic acid (60 mg elemental iron + 2.8 mg folic acid) on the core list of the EML as a weekly administered supplement for preventing anaemia in menstruating women and adolescent girls, and reducing the risk of pregnancies affected by neural tube defects.

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10.3 Other medicines for haemoglobinopathies

Deferasirox and deferoxamine – change square box listing – EML and EMLc

Deferoxamine	ATC code: V03AC01
Deferasirox	ATC code: V03AC03

Proposal

Change to the representative medicine in the square box listing from deferoxamine to deferasirox on the EML and EMLc.

Applicant

Novartis Pharma AG, Basel, Switzerland

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

10.3 Other medicines for haemoglobinopathies

Dose form(s) & strengths(s)

Deferasirox – Tablet: 90 mg, 180 mg, 360 mg

Deferasirox – Tablet (dispersible): 100 mg, 125 mg, 250 mg, 400 mg, 500 mg

Deferoxamine – Powder for injection: 500 mg (as mesylate) in vial

Core/complementary

Complementary

Individual/square box listing

Square box

Background

Deferoxamine has been included on the EML since 1979 as a treatment for acute iron poisoning and chronic iron overload. A review of iron chelating agents for acute and chronic iron poisoning, and treatment of sickle-cell disease was considered by the Expert Committee in 2011 (*1*). The Committee's findings and recommendations are summarized below.

The Committee noted that a systematic review of observational and prospective studies suggested beneficial effects of deferoxamine on morbidity

(notably cardiac disease and liver iron overload) and mortality, including subcutaneous use. In sickle-cell disease, evidence is more limited but supports the use of deferoxamine. Deferoxamine has adverse effects on growth and maturation, and auditory and ophthalmic function. The Committee considered that the main limitation of deferoxamine was however the need for prolonged parenteral administration, and a trial showed less compliance with parenteral deferoxamine than oral deferiprone.

The Committee noted that the evidence supporting the use of deferiprone consisted of small trials – mostly observational including both adults and children and summarized in a Cochrane Review in 2007 (10 trials including 398 participants). The dose used in the trials was generally 75 mg/kg a day, and reported adverse effects included neutropenia and agranulocytosis, which require weekly monitoring of blood cell counts. Gastrointestinal symptoms are common and knee arthralgia is reversible. Neurological signs at doses of more than 100 mg/kg have been reported in children. The use of the combination of deferiprone and deferoxamine was found to be more effective than single agents with promising results of normalization of ferritinaemia. The review concluded that there was no consistent effect on reduction of iron overload among various treatments. Deferoxamine was more effective on iron excretion in three of four trials. The trials did not report on mortality or end-organ damage. The Committee concluded that the evidence supporting the effectiveness of deferiprone was insufficient.

The evidence of effectiveness of deferasirox was more recent and of better quality than was the case for deferiprone. The Committee noted a large non-randomized uncontrolled prospective company-sponsored trial in 192 patients (64 aged younger than 16 years), which showed a statistically significant decrease in cardiac iron (assessed by magnetic resonance imaging) after 1 year of treatment. A Cochrane review of deferasirox in sickle-cell disease identified only one study and concluded that deferasirox appeared to be as effective as deferoxamine, but important outcomes were missing. No data were available to support the current use of deferasirox in myelodysplastic syndromes. The Committee noted that deferasirox has renal adverse effects, which require regular monitoring of renal function. Dose-dependent increases in serum creatinine, which may occur in up to 36% of patients, may not always be reversible. Tubulopathy has also been reported in children with thalassaemia.

The Committee considered the costs of deferoxamine, including laboratory monitoring costs, adverse effects and/or worsening of underlying disease as a result of non-compliance, hospitalization, parenteral injections, need for carers and missed school days. The cost of deferasirox treatment may be 2–3 times higher than that of deferoxamine, and the cost of deferiprone could be twice that of deferoxamine. The Committee noted that several reports suggest that

deferasirox therapy is more cost-effective than traditional deferoxamine therapy, but considered that a truly unbiased cost comparison between deferiprone and deferasirox had not been published. The Committee noted that reports of cost analysis highlighted variations in acquisition costs and resources used. The acquisition cost of deferasirox is an important barrier to access, but adherence to infused deferoxamine is also problematic and administration costs also need to be considered. Although noting the advantages of the oral route, the Committee did not recommend the inclusion of deferasirox in the EML and EMLc at that stage, but recommended adding an asterisk to deferoxamine, noting the alternative oral form (deferasirox 500 mg dispersible oral solid dosage form) was available.

Public health relevance

Iron overload is generally the result of disorders such as thalassaemia or sickle-cell disease, which are associated with repeated blood transfusions. It is also associated with hereditary haemochromatosis and other conditions such as porphyria that affect iron absorption or regulation.

Thalassaemia is an inherited blood disorder characterized by reduced haemoglobin and depleted red blood cells. Thalassaemia results in the inability to form functional haemoglobin, leading to life-threatening anaemia. Patients require life-long blood transfusions, resulting in iron overload (2). The global prevalence of thalassaemia in 2019 was 13.7/100 000 (all ages), with the highest prevalence in South-east Asia, East Asia and Oceania, and the lowest prevalence in Latin America and the Caribbean (3).

Sickle-cell disease is a hereditary condition that affects haemoglobin, generating an altered form of the protein known as haemoglobin S (HbS). Polymerization of HbS may occur, leading to sickle-like deformation of red blood cells, vascular obstruction, pain and organ damage. Blood transfusions are an important supportive therapy for treatment and prevention of sickle cell disease complications. Repeated transfusions can lead to iron overload (4). The global prevalence of sickle-cell disorders in 2019 was 73.57/100 000 (all ages), with the highest prevalence in sub-Saharan Africa (3), where an estimated 240 000 babies with HbS are born each year (5).

Hereditary haemochromatosis is an inherited disorder of iron metabolism which can lead to increased systemic iron concentrations as a consequence of excessive intestinal absorption of dietary iron. Prevalence estimates using genetic screening range from 0.00006% (6) to 2.3% (7).

Porphyrias are metabolic disorders characterized by a genetically determined enzymatic defect in the haem biosynthesis pathway. They are associated with serum ferritin accumulation and iron overload. The global prevalence of porphyria has been reported to be 53 per million people (8).

Summary of evidence: benefits

The application presented the findings of multiple meta-analyses of randomized studies comparing the efficacy and safety of deferoxamine and deferasirox.

A Cochrane systematic review of nine randomized controlled trials (1251 participants) comparing deferasirox and deferoxamine for management of iron overload in people with thalassaemia reported that similar efficacy can be achieved depending on the ratio of doses of deferasirox and deferoxamine being compared (*9*). Deferasirox was not superior to deferoxamine at the usually recommended dose ratio of 1 mg to 2 mg. Pooled effects across different dosing ratios reported heterogeneous findings that could potentially be explained by the use of different dosing ratios. Patient satisfaction with treatment favoured deferasirox. The authors concluded that deferasirox could be offered as the first-line option to individuals who show strong preference for deferasirox, and that it may be a reasonable treatment option for patients intolerant of or poorly adherent to deferoxamine, following detailed discussion of potential benefits and risks.

A Cochrane systematic review of two randomized controlled trials (415 participants) compared the efficacy and safety of deferasirox and deferoxamine for management of transfusional iron overload in patients with sickle-cell disease (*10*). Serum ferritin reduction was similar in both groups (mean difference (MD) 375.00 micrograms/L in favour of deferoxamine, 95% confidence interval (CI) −106.08 to 856.08). No difference was observed between treatments for liver ion concentration for the overall group of patients (MD −0.20 mg Fe/g dry weight, 95% CI −3.15 to 2.75 Fe/g dry weight). Patient satisfaction and convenience of treatment were significantly better with deferasirox.

A Cochrane systematic review of 16 randomized controlled trials (1525 participants) assessed interventions for improving adherence to iron chelation therapy in people with sickle-cell disease or thalassaemia (*11*). One included trial compared deferasirox and deferoxamine monotherapy, in which adherence rates were high for both treatment groups, but from which it was not possible to determine a difference in adherence between treatment groups (MD −1.40, 95% CI −3.66 to 0.86).

A multiple treatment comparison network meta-analysis of 32 clinical trials compared the efficacy and safety of different iron chelators (monotherapy and combination) in patients with thalassaemia or sickle-cell disease (*12*). Relative estimates suggested that combination therapy with deferasirox and deferoxamine was associated with better serum ferritin and lower liver iron concentrations compared with deferoxamine monotherapy; however, the strength of evidence was very low for most comparisons.

A meta-analysis of six studies comparing deferasirox with deferoxamine and placebo evaluated the effectiveness and safety of deferasirox in patients with thalassaemia (*13*). For the outcome of reduction of liver iron concentration,

deferasirox was more effective than deferoxamine when given at a dose of 30 mg/kg a day (MD –2.5, 95% CI –4.55 to –0.45). At all other doses (5, 10, 20 and 40 mg/kg a day), deferoxamine was more effective than deferasirox. Pooled analysis across all doses showed no significant difference between treatments. Similar findings were observed for the outcome of serum ferritin reduction.

The application also presented summaries of individual randomized controlled trials included in the above-mentioned systematic reviews and meta-analyses and other clinical studies (*4,14–25*). The applicants conclude that the body of evidence suggests that deferasirox is as effective as deferoxamine in clinical practice for treatment of chronic iron overload conditions and offers relevant advantages of oral compared with parenteral administration.

Summary of evidence: harms

Deferoxamine and deferasirox have been available on the market for many years, with annual patient exposures of about 7000–8000 patient treatment-years and 50 000–55 000 patient treatment-years, respectively. Their safety profiles are well known. A summary of adverse events reported in clinical studies and in postmarketing, as reported in approved United Kingdom prescribing information (*26,27*) was presented in the application. For deferoxamine, common and very common adverse reactions include headache, nausea, urticaria, arthralgia, myalgia, growth retardation, bone disorders, injection site pain, swelling, infiltration, erythema, pruritus, eschar and pyrexia. For deferasirox, common and very common adverse reactions include headache, gastrointestinal effects, increased transaminases, rash, pruritus, increased blood creatinine and proteinuria.

Deferasirox may cause acute kidney injury (including acute renal failure requiring dialysis and renal tubular toxicity including Fanconi syndrome), hepatic toxicity and gastrointestinal haemorrhage. Therapy with deferasirox therefore requires close patient monitoring, including laboratory tests of renal and hepatic function (*27,28*).

A Cochrane systematic review of nine randomized controlled trials (1251 participants) comparing deferasirox and deferoxamine for management of iron overload in people with thalassaemia reported no statistically significant difference in mortality, serious adverse events, or any adverse events between treatment groups (*9*). Increases in creatinine occurred significantly more often with deferasirox than deferoxamine. Satisfaction with, convenience of and willingness to continue treatment was significantly higher in patients receiving deferasirox who had previously received deferoxamine, and time lost from normal activities due to treatment was significantly less with deferasirox. Adherence, defined as the percentage of the planned dose taken by participants, was evaluated in one study with no significant difference observed between treatment groups (*23*). Data from randomized trials on rare toxicities and long-term safety are still limited.

A Cochrane systematic review of two randomized controlled trials (415 participants) comparing the efficacy and safety of deferasirox and deferoxamine for management of transfusional iron overload in patients with sickle-cell disease (*10*) reported that the occurrence of serious adverse events did not differ between treatment groups. Nausea, diarrhoea and rash occurred significantly more often in patients treated with deferasirox, any adverse events were reported more often in patients treated with deferoxamine.

A review of the safety of iron chelation therapies in young patients (< 25 years) with haemoglobinopathies (34 studies, 2040 participants) (*29*) found that iron chelation therapy was generally safe in young patients and in line with the safety data reported in the summaries of product characteristics. Discontinuation rates due to severe or serious adverse events were generally low for all regimens.

A meta-analysis of six studies evaluating the effectiveness and safety of deferasirox in patients with thalassaemia (*13*) found a significantly higher risk of increased serum creatinine (risk ratio (RR) 2.69, 95% CI 1.98 to 3.67) and alanine transaminase (RR 5.67, 95% CI 1.01 to 31.79) with deferasirox compared with deferoxamine. Gastrointestinal events, rash and serious adverse events were more common with deferasirox than deferoxamine, but differences were not statistically significant. No statistically significant difference was found between treatments for mortality.

WHO guidelines

WHO guidelines for treatment of transfusional iron overload in patient with sickle-cell disorders, β-thalassaemia or other anaemias are not currently available.

The use of iron chelating agents for the treatment of transfusional iron overload is recommended in many national and international guidelines (*30–41*).

Costs/cost–effectiveness

National prices for deferoxamine and deferasirox dispersible tablets in least developed, lower middle-income and upper middle-income countries were reported in the application as summarized in Table 18.

Table 18
Price of iron chelating agents in lower middle- and upper middle-income countries

Country	Price, US$/g	
	Deferoxamine	Deferasirox dispersible tablets
Albania	4.80	10.00
Azerbaijan	9.80	16.30

Table 18 *continued*

Country	Price, US$/g	
	Deferoxamine	Deferasirox dispersible tablets
Bangladesh	5.10	4.50
China	13.70	21.80
India	1.90	0.97
Iran, Islamic Republic of	5.90	7.10
Jordan	8.70	22.80
Maldives	15.40	3.60
Morocco	11.50	15.30
Pakistan	2.80	3.40
Philippines	1.30	1.80
Thailand	13.20	15.60

National prices for deferoxamine, deferasirox dispersible tablets and deferasirox film-coated tablets in high-income countries were reported in the application as summarized in Table 19.

Table 19
Price of iron chelating agents in high-income countries

Country	Price, US$/g		
	Deferoxamine	Deferasirox dispersible tablets	Deferasirox film-coated tablets
Bulgaria	6.70	–	31.50
Denmark	20.80	–	9.50
France	10.20	–	28.70
Germany	27.30	–	4.80
Greece	6.70	–	42.90
Israel	8.20	69.30	–
Italy	8.70	–	37.50
Portugal	8.20	–	32.90

Table 19 *continued*

Country	Price, US$/g		
	Deferoxamine	**Deferasirox dispersible tablets**	**Deferasirox film-coated tablets**
Qatar	13.80	33.10	90.20
Saudi Arabia	5.90	30.90	51.20
Sweden	8.60	–	1.80
Switzerland	16.60	–	54.40

– means the price information was is not available or reported.

A 2017 cost–utility analysis of iron chelators as monotherapy for chronic iron overload in patients with β-thalassaemia major from an Italian health care system perspective found deferiprone to be dominant and the most cost-effective treatment, and deferasirox to produce a higher quality-adjusted life year gained than deferoxamine but with a greater total cost (*42*).

A 2020 cost–utility analysis of film-coated deferasirox versus deferoxamine in patients with β-thalassaemia from a payer perspective in the Islamic Republic of Iran explored two scenarios based on age at starting treatment (2 years or 18 years), estimating lifetime costs and utilities (*43*). Deferasirox film-coated tablets produced an incremental cost–effectiveness ratio of US$ 1470.60 and US$ 2544.70, respectively for starting treatment at 2 years and 18 years, compared with branded deferoxamine. The incremental cost–effectiveness ratios for deferasirox compared with generic deferoxamine were US$ 2837.09 and US$ 6924.13, respectively, for starting treatment at 2 years and 18 years.

A cost–utility analysis from the Chinese health care perspective also evaluated the cost–effectiveness of four chelation regimens for β-thalassaemia major (*44*). Deferiprone was also found to be the most cost-effective chelation regimen, followed by deferoxamine, deferasirox and combination therapy. Deferoxamine administration costs were estimated to range between US$ 2000/year and US$ 3500/year. Monitoring costs were estimated to be US$ 20–200/year for deferoxamine and US$ 100–400/year for deferasirox (*42–44*).

Availability

The application reported that branded deferoxamine is marketed in 65 countries in the world. Generic brands are also available. Deferoxamine has been deregistered in 16 countries in the past 15 years.

Branded deferasirox (as dispersible or film-coated tablets) is marketed in 95 countries in the world. Generic brands are also available. Since the introduction

to the market of deferasirox film-coated tablets, deferasirox dispersible tablets have been discontinued in some countries.

Other considerations

A separate application to the 2023 Expert Committee meeting requested listing of oral deferiprone as a therapeutic alternative to deferoxamine for the treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias.

Committee recommendations

The Expert Committee noted that iron overload is a major concern for patients receiving regular blood transfusions; it is associated with multiorgan damage, particularly to the heart and liver, and leads to premature death if untreated.

The Expert Committee considered this application together with a separate application requesting the addition of another iron chelating agent, deferiprone, for the treatment of transfusional iron overload in adults and children with thalassaemia syndromes, sickle-cell disease and other chronic anaemias.

The Committee considered that the comparative efficacy and safety of deferiprone, deferoxamine and deferasirox are generally similar. The Committee considered that orally administered treatments may be preferred over intravenously administered deferoxamine.

The Committee noted that deferasirox is available in innovator and generic brands as both film-coated tablets and dispersible tablets. Dispersible tablet formulations are considered important for administration to young children and other patients unable to swallow a solid dosage form. However, the two dosage forms are not bioequivalent on a milligram to milligram basis and so care must be taken to ensure appropriate dosing using the respective dosage forms.

The Committee noted that the prices of iron chelating agents, and their availability, vary globally. Therefore, the Committee considered that having multiple iron chelating agents included on the Model Lists was important to enable countries to make appropriate national selection decisions taking into consideration relevant contextual factors.

The Committee therefore recommended that the square box be removed from the current listing for deferoxamine, and that deferoxamine remain listed independently on the complementary list of the EML and EMLc. Because of the advantages offered by orally administered iron chelating agents, the Committee recommended deferasirox dispersible and film-coated tablets be transferred to the core list of the EML and EMLc, with a square box indicating oral deferiprone as a therapeutic alternative.

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Deferiprone – addition – EML and EMLc

Deferiprone	ATC code: V03AC02

Proposal

Addition of deferiprone to the complementary list of the EML and EMLc as a therapeutic alternative to deferoxamine for treatment of transfusional iron overload in adult and paediatric patients with thalassaemia syndromes, sickle-cell disease or other anaemias.

Applicant

Chiesi Farmaceutici S.p.A, Parma, Italy

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

10.3 Other medicines for haemoglobinopathies

Dose form(s) & strengths(s)

Oral liquid: 100 mg/mL

Tablet (immediate-release): 500 mg, 1000 mg

Tablet (modified-release): 1000 mg

Core/complementary

Complementary

Individual/square box listing

Square box

Background

Deferiprone was previously considered by the Expert Committee in 2011 as part of a review of iron chelation therapy for acute iron poisoning in children (*1*). The outcome of this review was the listing of deferoxamine injection on the EML and EMLc as an antidote for acute iron poisoning and for treatment of sickle-cell disease. Oral deferasirox was noted as a therapeutic alternative for sickle-cell disease. Deferiprone was not recommended for listing. The Committee's findings and recommendations are summarized below.

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The Committee noted that a systematic review of observational and prospective studies suggested beneficial effects of deferoxamine on morbidity (notably cardiac disease and liver iron overload) and mortality, including subcutaneous use. In sickle-cell disease, evidence is more limited but supports the use of deferoxamine. Deferoxamine has adverse effects on growth and maturation, and auditory and ophthalmic function. The Committee considered that the main limitation of deferoxamine was however the need for prolonged parenteral administration, and a trial showed less compliance with parenteral deferoxamine than oral deferiprone.

The Committee noted that the evidence supporting the use of deferiprone consisted of small trials – mostly observational including both adults and children summarized in a Cochrane Review from 2007 (10 trials including 398 participants). The dose used in trials was generally 75 mg/kg a day, and reported adverse effects included neutropenia and agranulocytosis, which require weekly monitoring of blood cell counts. Gastrointestinal symptoms are common and knee arthralgia is reversible. Neurological signs at doses of more than 100 mg/kg have been reported in children. The use of the combination of deferiprone and deferoxamine was found to be more effective than single agents with promising results of normalization of ferritinaemia. The review concluded that there was no consistent effect on reduction of iron overload among various treatments. Deferoxamine was more effective on iron excretion in three of four trials. Trials did not report on mortality or end-organ damage. The Committee concluded that the evidence supporting the effectiveness of deferiprone was insufficient.

The evidence of effectiveness of deferasirox was more recent and of better quality than was the case for deferiprone. The Committee noted a large non-randomized uncontrolled prospective company-sponsored trial in 192 patients (64 aged younger than 16 years), which showed a statistically significant decrease in cardiac iron (assessed by magnetic resonance imaging) after 1 year of treatment. A Cochrane review of deferasirox in sickle-cell disease identified only one study and concluded that deferasirox appeared to be as effective as deferoxamine, but important outcomes were missing. No data were available to support the current use of deferasirox in myelodysplastic syndromes. The Committee noted that deferasirox has adverse renal effects, which require regular monitoring of renal function. Dose-dependent increases in serum creatinine, which may occur in up to 36% of patients, may not always be reversible. Tubulopathy has also been reported in children with thalassaemia.

The Committee considered the costs of deferoxamine, including laboratory monitoring cost, adverse effects and/or worsening of underlying disease as a result of non-compliance, hospitalization, parenteral injections, need for carers and missed school days. The cost of deferasirox treatment may be two to three times higher than that of deferoxamine, and the cost of deferiprone could

be twice that of deferoxamine. The Committee noted that several reports suggest that deferasirox therapy is more cost-effective than traditional deferoxamine therapy but considered that a truly unbiased cost comparison between deferiprone and deferasirox had not been published. The Committee noted that reports of cost analysis highlighted variations in acquisition costs and resources used. The acquisition cost of deferasirox is an important barrier to access, but adherence to infused deferoxamine is also problematic and administration costs also need to be considered. Although noting the advantages of the oral route, the Committee did not recommend the inclusion of deferasirox in the EML and EMLc at that stage, but recommended adding an asterisk to deferoxamine, noting the alternative oral form (deferasirox 500 mg dispersible oral solid dosage form) was available.

Public health relevance

Sickle-cell disease is a multisystem disorder that affects almost every organ in the body. It is characterized by the presence of sickle haemoglobin which causes sickle-shaped erythrocytes. It is a life-threatening disease that leads to haemolytic anaemia and blockages in small blood vessels, which may potentially lead to ischaemia, infarction and organ damage (*2*). Sickle-cell disease is one of the most common haemoglobinopathies worldwide and is recognized by WHO as a global public health problem (*3*). Worldwide in 2019, 605 00 people were born with sickle-cell disorders, an estimated 5.7 million people were living with sickle-cell disorders and 42 000 people died as a result of sickle-cell disorders (all ages) (*4*). The prevalence of sickle-cell disorders varies by region and is highest in Africa, Mediterranean countries and the Middle East (*5,6*). More than half of all individuals living with sickle cell disorders live in sub-Saharan Africa or India (*5*).

The condition β-thalassaemia is an inherited haemoglobinopathy in which the reduced or absent production of functional haemoglobin results in severe and life-threatening anaemia. The annual incidence of symptomatic individuals with β-thalassaemia is estimated to be 1 in 100 000. The incidence of β-thalassaemia varies by region. About 60 000 people are born each year with symptomatic β-thalassaemia. The prevalence is highest in the Mediterranean region, the Middle East, central Asia, India, southern China, and east and south-east Asia (*7*).

Blood transfusions are one of the cornerstones in the management of sickle-cell disease and β-thalassaemia. A main cause of morbidity in patients with these conditions is iron overload due to chronic blood transfusions (*8–10*). Untreated or inadequately treated iron overload can lead to complications such as liver fibrosis and cirrhosis, hepatocellular carcinoma, cardiomyopathy and endocrine disorders (*11–13*).

Summary of evidence: benefits

Sickle-cell disease

The application presented the findings of a systematic literature review and network meta-analysis which indirectly compared deferiprone, deferasirox and deferoxamine in patients with sickle-cell disease. Efficacy endpoints were change from baseline to 12 months in liver iron concentration and serum ferritin. Two randomized, open-label trials (423 participants) were included (*14,15*).

Liver iron concentration

In the intention-to-treat population, the mean difference (MD) from baseline to 12 months relative to deferiprone was –0.40 (95% credible Interval (CrI) –1.70 to 0.89) for deferoxamine and –0.68 (95% CrI –3.63 to 2.25) for deferasirox. The MD relative to deferiprone using the sickle-cell disease subpopulation was –0.58 (95% CrI –1.83 to 0.66) for deferoxamine and –0.84 (95% CrI –3.74 to 2.19) for deferasirox. The MD relative to deferiprone using the subpopulation with serum creatinine lower than the upper limit of normal was –0.43 (95% CrI –1.70 to 0.85) for deferoxamine and –0.72 (95% CrI –3.86 to 2.25) for deferasirox. No statistically significant differences between deferiprone and deferoxamine or deferasirox were found, nor between deferoxamine and deferasirox.

Serum ferritin

In the intention-to-treat population, the MD from baseline to 12 months relative to deferiprone was –364.39 (95% CrI –961.37 to 237.22) for deferoxamine and 11.15 (95% CrI –688.24 to 712.52) for deferasirox. Deferoxamine was numerically preferable to deferasirox (MD –376.15, 95% CrI –739.09 to –5.29). For the sickle-cell disease subpopulation, the MD relative to deferiprone was –556.18 (95% CrI –1217.68 to 117.79) for deferoxamine and –182.56 (95% CrI –942.53 to 588.51) for deferasirox. Deferoxamine was numerically preferable to deferasirox (MD –374.70, 95% CrI –738.39 to –7.08). For the subpopulation with serum creatinine lower than the upper limit of normal, the MD relative to deferiprone was –387.68 (95% CrI –994.05 to 211.54) for deferoxamine and –12.77 (95% CrI –724.22 to 692.78) for deferasirox. Deferoxamine was numerically preferable to deferasirox (MD –373.59, 95% CrI –740.39 to –6.34).

β-thalassaemia

The application presented the findings of a systematic literature review and network meta-analysis that indirectly compared deferiprone, deferasirox and deferoxamine in patients with β-thalassaemia. Efficacy endpoints were change from baseline to 12 months in liver iron concentration, serum ferritin, cardiac MRI T2* and left ventricular ejection fraction (LVEF). Six randomized trials (1129 participants) were included (*16–21*).

Liver iron concentration

Four randomized controlled trials reported on liver iron concentration (*16,17,20,21*). Pooled analysis of two randomized controlled trials comparing deferiprone and deferoxamine monotherapy (*16,17*) showed no significant difference between treatments on liver iron concentration (weighted MD –0.16 mg/g dry weight (95% confidence interval (CI) –1.39 to 1.06 mg/g). An indirect comparison of deferiprone and deferasirox via deferoxamine showed no statistically significant difference between treatment arms. One randomized controlled trial comparing deferiprone–deferoxamine sequential therapy with deferoxamine monotherapy reported no statistically significant difference between treatment arms, although the effect was numerically larger in the deferoxamine monotherapy arm. An indirect comparison of deferiprone–deferoxamine sequential therapy with deferiprone monotherapy showed no statistically significant difference.

Serum ferritin

Five randomized controlled trials reported on serum ferritin (*16,17,19–21*). Pooled analysis of two randomized controlled trials comparing deferiprone and deferoxamine monotherapy (*16,17*) showed no significant difference between treatments on serum ferritin levels (weighted MD 92.56, 95% CI –154.49 to 339.61). An indirect comparison of deferiprone and deferasirox via deferoxamine showed deferiprone to be significantly more effective, while an indirect comparison via deferiprone-deferoxamine sequential therapy did not show a significant difference. Meta-analyses of the randomized controlled trial comparing deferasirox and deferoxamine (*21*) showed high heterogeneity between subgroups with different baseline liver iron concentration levels, in which smaller differences in effect size were observed for patients with higher baseline liver iron concentration. To test the effect of this heterogeneity on the indirect comparison of deferiprone and deferasirox, a sensitivity analysis including only patients with baseline liver iron concentration ≥ 7 mg/g dry weight was conducted, which suggested deferiprone and deferasirox were equally efficacious in their effect on serum ferritin. One randomized controlled trial comparing sequential deferiprone–deferoxamine and deferoxamine monotherapy showed no significant difference in effect on serum ferritin. Another randomized controlled trial comparing sequential deferiprone–deferoxamine and deferiprone monotherapy showed a greater improvement in serum ferritin with sequential therapy compared with deferiprone monotherapy (weighted MD –285.00, 95% CI –495.46 to –74.54).

Cardiac T2*

Two randomized controlled trials reported log-transformed cardiac MRI T2* (*16,18*). One trial comparing deferiprone and deferoxamine showed a significant improvement in cardiac iron in patients treated with deferiprone compared with

deferoxamine (ratio of geometric means 1.12, 95% CI 1.07 to 1.17) (*16*). One trial comparing deferiprone–deferoxamine combination therapy versus deferoxamine monotherapy showed a significant improvement in cardiac iron for the combination therapy arm (ratio of geometric means 1.1, 95% CI 1.2 to 1.19) (*18*). Indirect comparison of deferiprone versus deferiprone–deferoxamine combination therapy (via deferoxamine monotherapy) showed no significant difference in effect between treatments (ratio of geometric means 0.98, 95% CI 0.89 to 1.08).

Left ventricular ejection fraction

Two randomized controlled trials reported improvements in left ventricular ejection fraction in patients treated with deferiprone compared with deferoxamine (*16,17*). A random-effects meta-analysis showed deferiprone was associated with a 2.1% greater absolute improvement in left ventricular ejection fraction compared with deferoxamine (weighted MD 0.02, 95% CI 0.00 to 0.04). One randomized controlled trials comparing deferiprone–deferoxamine combination therapy with deferoxamine alone (*18*), and indirectly comparing combination therapy with deferiprone monotherapy (via deferoxamine monotherapy), did not show statistically significant differences between treatments.

Combination therapy

Evidence supports the use of combination therapy with iron chelating agents to increase the effectiveness of treatment in patients who do not adequately respond to monotherapy, or when prevention or treatment of life-threatening consequences of iron overload justifies rapid intensive correction (*18–20,22–24*). Combination therapy is also recommended for certain patients in the guidelines of the Thalassaemia International Federation (*13*) and the British Society for Haematology (*25*).

Summary of evidence: harms

Sickle-cell disease

The most common adverse reactions reported during clinical trials occurring in ≥ 5% of patients treated with deferiprone include pyrexia (28%), abdominal pain (26%), bone pain (25%), headache (20%), vomiting (19%) and extremity pain (18%). Clinically relevant adverse reactions occurring in < 5% of patients treated with deferiprone include neutropenia and agranulocytosis (*26*).

In patients treated with deferiprone in the FIRST trial, those with sickle-cell disease and other anaemias who received deferiprone were more likely to experience a treatment-related increase in alanine aminotransferase compared with patients who received deferoxamine (9.2% versus 0%) (*14*). In an Italian randomized controlled trial comparing deferiprone with deferoxamine in sickle-cell disease, 10% of patients receiving deferiprone experienced liver damage or increased alanine aminotransferase more than twice the normal value, compared

with no patients treated with deferoxamine (*27*). Greater increases in serum creatinine have been reported with deferasirox compared with deferoxamine (6.3 micromol/L versus 3.06 micromol/L, respectively) (*15*). Neutropenia and agranulocytosis were more commonly reported in studies evaluating deferiprone, with the percentage of patients affected ranging from 5.9% to 9.0% for neutropenia and 0% to 1.5% for agranulocytosis.

β-thalassaemia

The most common adverse reactions reported during clinical trials occurring in ≥ 5% of patients treated with deferiprone include nausea (12.6%), abdominal pain (10.0%), vomiting (9.8%), arthralgia (9.8%), increased alanine aminotransferase (7.5%) and neutropenia (6.2%) (*26,28*). A lack of consistent data-reporting prevented robust statistical analysis of safety data in randomized controlled trials on β-thalassaemia.

Combination therapy

Clinical experience with combination use of deferiprone and deferoxamine suggests no significant toxicity issues with the combination (*29*). Adverse events associated with combination therapy with deferiprone and deferasirox were reported to be consistent with those reported for component monotherapy. The most common adverse events included gastrointestinal symptoms, elevation in alanine aminotransferase and/or aspartate aminotransferase, arthralgia/joint symptoms, increased serum creatinine, proteinuria and red-coloured urine. The number of patients experiencing neutropenia or thrombocytopenia was low (*30*).

Paediatric use

A study with 100 children aged 1–10 years with transfusion-dependent anaemia treated with deferiprone oral solution did not identify any new safety concerns compared with other studies of deferiprone tablets in older children and adults (*31*). In a randomized controlled trial comparing deferiprone and deferasirox in paediatric patients aged 1 month to 18 years with transfusion-dependent haemoglobinopathies, deferiprone had an acceptable safety profile. No significant differences were seen between treatment arms in serious and drug-related adverse events. Adverse events were similar to those seen in the adult population. No safety concerns in very young children were identified (*22*).

WHO guidelines

WHO guidelines for the treatment of transfusional iron overload in patient with sickle-cell disorders, β-thalassaemia or other anaemias are not currently available.

The use of iron chelating agents for the treatment of transfusional iron overload is recommended in multiple national and international guidelines (*13,25,32–41*).

Costs/cost–effectiveness

A systematic review of 19 cost–utility studies evaluated the cost–effectiveness of four chelation regimens for β-thalassaemia major therapy – deferoxamine, deferiprone or deferasirox monotherapy, and deferoxamine + deferiprone combination therapy (*42*). Deferiprone was found to be cost-effective compared with deferasirox in three studies, compared with deferoxamine in three studies, and compared with combination therapy in one study. The authors concluded that for iron chelator monotherapy, deferiprone was the most cost-effective option, followed by deferoxamine and deferasirox. However, the authors noted substantial differences in costs between countries and regions and that the local economic context played a substantial role in the results of the pharmacoeconomic evaluation. National prices for iron chelators are summarized in Table 20.

Table 20

Prices for iron chelating agents by country

Country	Price, US$/g		
	Deferoxamine	**Deferiprone**	**Deferasirox**
Australia	8.52–9.34	3.04	33.60
China	20.00	–	60.70
Italy	31.68	4.19	–
Poland	12.69	3.38	1.89
Thailand	10.77	0.20–2.09	58.56
United Kingdom	11.12	4.19	43.97
United States of America	35.77	–	84.49

– means not reported.

A cost–utility analysis from the Chinese health care perspective also evaluated the cost–effectiveness of four chelation regimens for β-thalassaemia major (43). This study also found deferiprone to be the most cost-effective chelation regimen, followed by deferoxamine, deferasirox and combination therapy.

Availability

Immediate-release deferiprone has marketing authorization in more than 30 countries. Generic brands are available in some settings. Currently, the modified-release deferiprone formulation is only approved and marketed in the United States, but is reported to be undergoing regulatory consideration in other countries.

Other considerations

A separate application to the 2023 Expert Committee meeting requested a change to current listing for intravenous deferoxamine for treatment of haemoglobinopathies, to make oral deferasirox the representative iron chelating agent under the square box listing.

Committee recommendations

The Expert Committee noted that iron overload is a major concern for patients receiving regular blood transfusions. It is associated with multiorgan damage, particularly to the heart and liver, and leads to premature death if untreated. Iron chelating agents deferoxamine (intravenous) and therapeutic alternative deferasirox (oral) have been included on the Model Lists for transfusional iron overload for more than 10 years.

The Expert Committee considered this application together with the application requesting a change to the representative listed iron chelating agent from intravenous deferoxamine to oral deferasirox for the treatment of transfusional iron overload in adults and children with thalassaemia syndromes, sickle-cell disease and other chronic anaemias.

The Committee considered that the available evidence supported the clinical efficacy of deferiprone in reducing serum ferritin and organ iron deposits. Evidence also indicated that it is generally well tolerated, with an acceptable safety profile. Furthermore, the Committee considered that the comparative efficacy and safety of deferiprone, deferoxamine and deferasirox were generally similar.

The Committee noted that the prices of iron chelating agents, and their availability, vary globally. The Committee recognized the value in having multiple iron chelating agents included on the Model Lists to enable countries to make appropriate decisions on national selection, taking into consideration relevant contextual factors.

The Expert Committee recommended that oral deferasirox be transferred to the core list of the EML and EMLc for use in the treatment of transfusional iron overload in patients with thalassaemia syndromes, sickle-cell disease and other chronic anaemias, with a square box listing specifying oral deferiprone as a therapeutic alternative. The Committee also recommended that intravenous deferoxamine remain listed on the complementary list of the EML and EMLc for these indications, and the square box associated with the current listing for deferoxamine be removed.

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Section 11: Blood products of human origin and plasma substitutes
11.1 Blood and blood components
Cryoprecipitate, pathogen-reduced – addition – EML and EMLc

Cryoprecipitate, pathogen reduced	ATC code: B05AA02

Proposal

Addition of pathogen-reduced cryoprecipitate (cryoprecipitate-PR) to the core list of the EML and EMLc to replace coagulation factors in cases of massive haemorrhage, von Willebrand disease and deficiency of coagulation factor XIII, and as a therapeutic alternative to coagulation factor VIII for treatment of haemophilia A in settings where coagulation factor VIII is not available or affordable.

Applicant

International Society of Blood Transfusion

WHO technical department

Blood and Other Products of Human Origin Team, Department of Health Products Policy and Standards

EML/EMLc

EML and EMLc

Section

11.1 Blood and blood components

Dose form(s) & strengths(s)

Frozen liquid in bag or lyophilized powder in vial containing: > 50 IU factor VIII + > 100 IU von Willebrand factor + > 140 mg clottable fibrinogen per unit

Core/complementary

Core

Individual/square box listing

Square box listing for cryoprecipitate, pathogen reduced, with cryoprecipitate (non-pathogen-reduced) as a therapeutic alternative.

Background

Cryoprecipitate-PR has not previously been considered for inclusion on the Model Lists.

At its meeting in 1989, the Expert Committee recommended addition of a square box symbol to the listing for coagulation factor VIII, to accommodate cryoprecipitate as a therapeutic alternative (*1*).

Public health relevance

Fresh frozen plasma is listed on the WHO Model Lists and has been used historically to replace clotting factors in severely bleeding patients. However, it does not contain the deficient clotting factors in concentrated form and when used in severe bleeding, volume overload (transfusion-related acute circulatory overload) due to large volume infusions limits the correction of plasmatic coagulation in the bleeding patient. In particular, in massive bleeding, fibrinogen is low in comparison with other clotting factors necessitating targeted replacement. In contrast, cryoprecipitate-PR and cryoprecipitate contain the following procoagulant plasma proteins in concentrated form: factor VIII (anti-haemophilic factor (AHF)); von Willebrand factor; fibrinogen; and factor XIII. Thus, they can be used for treatment of patients with defined inherited bleeding disorders or acquired bleeding disorders.

Incidence and prevalence of inherited and acquired bleeding disorders

Haemophilia A has a reported incidence of 1 in 4000 male births (*2*). The worldwide prevalence is around 200 000 diagnosed patients (*3*). The actual prevalence may be higher as many people with haemophilia A in low- and middle-income countries are undiagnosed. Almost all patients are males and the incidence of haemophilia is the same regardless of race or ethnicity (*4,5*).

Symptomatic von Willebrand disease has a reported incidence of 1 in 10 000 (*2*). The prevalence of symptomatic patients with von Willebrand disease is around 90 000 (*3*). The overall prevalence (including all types and severity forms) is relatively high, with up to 1% of the population being affected (*6,7*). The incidence is the same in females and males, although women suffer more often from clinical bleeding due to menstruation and child delivery.

Afibrinogenaemia, dysfibrinogenaemia and factor XIII deficiency each have reported incidence of 1 in 1 million and the prevalence is very low (*8*).

The incidence of acquired hypofibrinogenaemia and acquired factor XIII deficiency due to peripartum haemorrhage correlates with the level of care and surveillance during pregnancy and with gynaeco-obstetric services at child delivery. The magnitude of the disease can be derived from data on maternal mortality, which is largely due to intra- and postpartum massive haemorrhage. According to WHO, about 287 000 women died during and following pregnancy

and childbirth in 2020. The maternal mortality ratio in low-income countries in 2020 was 430 per 100 000 live births. WHO data indicate that the vast majority of deaths occurred in low- and middle- income countries, ranging from 30 to 1223 per 100 000 live births in nine countries considered as so-called fragile states (*9*). Postpartum haemorrhage is the main cause of maternal mortality and morbidity across the world, responsible for more than 25% of such deaths annually. WHO statistics suggest that 60% of maternal deaths in developing countries were due to postpartum haemorrhage, accounting for more than 100 000 maternal deaths a year worldwide.

The frequency of massive bleeding and resulting clotting disorders due to (poly)trauma (often related to traffic crashes or work accidents) is also correlated with, for example, the human development index, gross domestic product and performance of national/local health care systems. Developing economies record higher rates of road traffic injuries, with 93% of fatalities from low- and middle-income countries (*10*).

Use of specific coagulation factor concentrates is preferred to the use of cryoprecipitate-PR and cryoprecipitate in these conditions. However, supplies of coagulation factor concentrates (plasma-derived or recombinant) are insufficient in low-income countries and are limited relative to demand in lower middle-income countries mainly because of their high costs. Where coagulation factor concentrates are available in low-income settings, they are generally products donated by industry and distributed mainly by charitable organizations or through the World Federation of Hemophilia Humanitarian Aid Program.

Summary of evidence: benefits

Similar to other blood components that have been in widespread use before the era of rigorous controlled trials, effectiveness of cryoprecipitate was never formally demonstrated. Nevertheless, clinical experience over more than 50 years has established the superiority of cryoprecipitate to plasma for replacement of certain clotting factors (factors I, VIII and XIII, and von Willebrand factor) based on its ability to deliver these plasma proteins with a low-volume of product.

Comparative effectiveness data of cryoprecipitate-PR versus cryoprecipitate are limited. The application described different types of cryoprecipitate-PR available and used in different countries.

Cryoprecipitate-PR made with VIPS solvent detergent virus inactivation kits (VIPS S/D), is prepared from pools of about 30–35 units of conventional low-volume (i.e. highly depleted of cryoprecipitate-poor plasma called "dry") cryoprecipitate that are treated by solvent detergent and bacterial filtrations to inactivate and remove pathogens. Consistency of the content of active factor VIII, von Willebrand factor, clottable fibrinogen and factor XIII has been demonstrated (*11*). Human trials in Egypt included pharmacokinetics of

factor VIII, a safety and efficacy study in therapeutic plasma exchange, and a small observational study in children with severe haemophilia A who received prophylactic therapy with VIPS S/D cryoprecipitate for 2–5 years. Additional safety and efficacy data were reported based on clinical use in more than 2000 patients. The study results and additional clinical reports demonstrated and confirmed that the pharmacokinetics, safety and efficacy of cryoprecipitate factor VIII derived from solvent detergent virus inactivation kits is similar to plasma-derived and recombinant factor VIII concentrates prepared by large-scale plasma fractionation, and possibly also has a reduced risk of factor VIII inhibitor development (*12*).

Heat-treated freeze-dried cryoprecipitate made from small pools of plasma has been used for factor VIII replacement in Thailand since 1997 (*13*). Factor VIII concentrate is now manufactured by plasma fractionation locally in Thailand; however, heat-treated freeze-dried cryoprecipitate is still produced to further cover the needs of patients with von Willebrand disease, and fibrinogen or factor XIII deficiency (*14*).

Cryoprecipitate (methylene-blue treated and removed and leukocyte depleted) is described as a source of concentrated factor VIII:C, von Willebrand factor, fibrinogen, factor XIII and fibronectin for use in neonates in the guidelines of the Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee for the blood transfusion service (*15*).

In 2021, the United States Food and Drug Administration approved pathogen-reduced cryoprecipitated fibrinogen complex made with the INTERCEPT Blood System for Cryoprecipitation® for: treatment and control of bleeding including massive haemorrhage associated with fibrinogen deficiency; control of bleeding when recombinant and/or specific virally inactivated preparations of factor XIII or von Willebrand factor are not available; second-line therapy for von Willebrand disease; and control of uraemic bleeding after other treatment methods have failed. It is not recommended for use for replacement of factor VIII (*16*). This cryoprecipitate is produced from plasma processed in the INTERCEPT system to inactivate pathogens using exposure to a specific psoralen compound (amotosalen) and irradiation with ultraviolet A light followed by adsorption of residual amotosalen.

Cryoprecipitate was used for decades before the development of industrially manufactured concentrates of coagulation factor VIII. Use of cryoprecipitate, preferably pathogen-reduced, is recommended in recognized national and international guidelines when factor VIII clotting factor concentrates are not available. Comparable effectiveness of cryoprecipitate and cryoprecipitate-PR compared with coagulation factor VIII to replace factor VIII in acute treatment of bleeding in haemophilia A results from the fact that infusions of cryoprecipitate and cryoprecipitate-PR can provide equivalent

levels of factor VIII compared with clotting factor concentrates, albeit at larger administered volumes. Prophylactic therapy to prevent bleeding is considered the standard of treatment in haemophilia A and home infusion is encouraged to decrease the logistic burden on patients and their families. While useful in acute treatment of bleeding, cryoprecipitate and cryoprecipitate-PR cannot readily be used for prophylactic therapy nor used easily at home.

Summary of evidence: harms

Cryoprecipitate has been in clinical use for more than 60 years with very few reports of adverse events. Inherent risks are those of plasma, which include transmission of viruses and bacteria, and allergic transfusion reactions. Compared with plasma, the risks of haemolytic transfusion reactions and volume overload with cryoprecipitate are lower because of the smaller volumes administered. Thrombosis is known to be associated with large volume transfusion therapies with plasma and cryoprecipitate. However, a causal relationship, presumably due to elevated levels of fibrinogen, is not clear (*17*).

The risks of cryoprecipitate-PR include those of cryoprecipitate with added potential risks related to the method of pathogen reduction used in preparation of the specific product. Publicly available data are limited on specific cryoprecipitate-PR products, however safety reporting on two products in current use has indicated no significant added concerns.

Pathogen-reduced cryoprecipitated fibrinogen complex made with the INTERCEPT Blood System for Cryoprecipitation® is prepared from INTERCEPT processed plasma. The package insert notes a 15-year history of safe use of INTERCEPT-processed plasma in the European Union for treatment of congenital coagulopathy including fibrinogen deficiency, acquired coagulopathy including liver transplant, and for therapeutic plasma exchange, where there were no safety signals indicative of excess treatment-related morbidity (*16*).

Safety experience is also reported for VIPS S/D cryoprecipitate. Locally prepared VIPS S/D cryoprecipitate in Egypt has been used since 2013 for treatment of more than 2000 patients with haemophilia A who received 32 million units of coagulation factor VIII. Extensive preclinical studies predicted a low risk of hazards. Clinical studies by the manufacturer and observational clinical studies at one large centre in Egypt revealed no acute or chronic toxicities. Longitudinal studies included 12 children with haemophilia A who received prophylaxis with a mean annual dose of factor VIII of 1029 IU/kg (range 545–1684 IU/kg) for 2–5 years (internal unpublished data from Shabrawishi Hospital Blood Transfusion Centre in Egypt). Additionally, 32 patients received large volume plasma exchanges with VIPS S/D plasma. Four of the 32 patients showed mild adverse events similar to those seen when transfusing normal plasma (*18*). No signs of acute toxicity due to the solvent and detergent used to reduce pathogens were

seen in this product (*18*). Postmarketing clinical data after 5 years of placement on the market of the first VIPS S/D device did not show any demonstrable adverse events whether immediate or delayed. Together, the studies showed that VIPS S/D plasma and cryoprecipitate have similar degrees of safety and efficacy compared with factor VIII clotting factor concentrates.

Additional evidence

The following evidence for the effectiveness of cryoprecipitate was identified during the expert review process of the application.

A randomized study in Brazil evaluated the haemostatic effects of fibrinogen concentrate compared with cryoprecipitate in 63 children following cardiac surgery with cardiopulmonary bypass (*19*). No significant difference was seen between treatment groups in the primary outcome of 48-hour postoperative blood loss (median 320 mL, interquartile range (IQR) 157 to 750 mL in the fibrinogen concentrate group (*n* = 30) versus 410 mL, IQR 215 to 510 mL in the cryoprecipitate group (*n* = 33); *P* = 0.672). The post-treatment incidence of allogenic blood transfusion was also similar between treatment groups.

WHO guidelines

WHO guidelines on the use of cryoprecipitate-PR are not currently available. However, in 2021, WHO announced an initiative to develop guidelines on implementation of patient blood management (*20*).

The WHO Expert Committee on Biological Standardization has developed requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (*21*), guidelines for viral inactivation and removal procedures intended to assure the viral safety of human blood products (*22*), and guidelines on the management of blood and blood components as essential medicines (*23*).

Costs/cost–effectiveness

Cryoprecipitate and cryoprecipitate-PR may be less costly to provide than clotting factor concentrates. While this may enable their cost-effective use in resource-constrained settings, cryoprecipitate and cryoprecipitate-PR should not be preferred to clotting factor concentrates. Therefore, facilitation of their preparation and use should not divert national efforts to assure availability of clotting factor concentrates.

The relative cost of non-pathogen-reduced cryoprecipitate versus clotting factor concentrates has been examined in comparative efficacy studies. For example, in studies comparing cryoprecipitate with commercial concentrates of fibrinogen, fibrinogen concentrates cost two-to-four times that of cryoprecipitate per gram of fibrinogen (*24,25*).

Data on the comparative cost of cryoprecipitate-PR versus plasma-derived and recombinant clotting factor concentrates are limited, but appear to demonstrate savings in some settings (*26*). With locally prepared VIPS S/D cryoprecipitate in Egypt, the cost per unit of factor VIII from cryoprecipitate-PR was US$ 0.07 compared with US$ 0.14 for commercial factor VIII concentrates. The average cost per unit of FVIII:C for all types of commercial clotting factor concentrates was higher at US$ 0.21 (*26*).

The application reported that the current cost per IU of FVIII:C and of von Willebrand factor:RCo for locally prepared VIPS S/D cryoprecipitate in Egypt was between US$ 0.09 and US$ 0.16 based on the yield per processed pool of 30–35 cryoprecipitates. The cost per gram of fibrinogen for locally prepared VIPS S/D cryoprecipitate in Egypt is US$ 24–29. In Thailand, the current cost per IU of FVIII:C for heat-treated freeze-dried cryoprecipitate was reported to be US$ 0.11. The cost per gram of fibrinogen for heat-treated freeze-dried cryoprecipitate in Thailand is less than US$ 51.

In comparison, the cost per IU of FVIII:C of an imported commercial clotting factor concentrate made in France is typically more than twice the unit price of locally prepared cryoprecipitate-PR products made in Egypt and Thailand. Similarly, the cost per gram of fibrinogen is US$ 470, significantly more than the cost for locally prepared cryoprecipitate-PR products made in Egypt and Thailand.

In high-income countries, the cost per IU of FVIII:C may be greater for cryoprecipitate-PR than for commercial clotting factor concentrates. For example, in the United Kingdom in 2015, the cost of cryoprecipitate – pooled, methylene blue treated and removed, leukocyte depleted – was reported in the application to be £4.30 per unit of FVIII:C. In comparison, in 2017, the average cost per unit of FVIII:C for commercial clotting factor concentrates was £0.74. This disparity arises primarily from the difference in preparation methods, namely production of cryoprecipitate-PR from single units of plasma in high-income countries versus production from pools of cryoprecipitate in low- and middle-income countries. Differences in the unit costs of labour and materials may also contribute to this disparity.

Availability

The application reported that at present, cryoprecipitate has regulatory authorization in Egypt, Thailand and the United States. In Egypt and Thailand, cryoprecipitate-PR is available for replacement of factor VIII and von Willebrand factor (and, based on content labelling, presumptively for fibrinogen). Widespread use of cryoprecipitate-PR as an alternative to industrially fractionated clotting factor concentrates has only been reported in Egypt. Production at one large blood establishment in Cairo has met one third of the annual need for factor

VIII replacement in the country through an organized system of distribution. In the United States, cryoprecipitate-PR is authorized only for replacement of fibrinogen complex. The extent to which its use may replace non-pathogen-reduced cryoprecipitate has not been established. In the United Kingdom, cryoprecipitate-PR is recognized for replacement of factor VIII, von Willebrand factor, fibrinogen and fibronectin, but its use is limited to persons born after 1 January 1996, as part of a programme to prevent transmission of variant Creutzfeldt–Jakob disease from blood products.

Other considerations

In 2009, the WHO Blood Regulators Network issued the following position statement on the use of cryoprecipitate-PR in settings where commercial clotting factor concentrates are unavailable or unaffordable (*27*).

> *Plasma-derived and recombinant CFC* [coagulation factor concentrates] *are recognized by relevant professional organizations as the treatment of choice for hemophilia A and von Willebrand disease based on their established quality, safety, efficacy and ease of use. However, resource limitations in many low- and medium-income countries currently make these products unavailable for the vast majority of patients, resulting in significant morbidity and mortality from otherwise preventable bleeding. In these settings, consideration should be given to local production of pathogen-reduced cryoprecipitate made under Good Preparation Practices in blood establishments from pooled whole blood-derived plasma or pooled cryoprecipitates using technologies that have been approved by advanced regulatory authorities. Plasma units obtained as a byproduct of whole blood collection can provide a stable and ongoing local source for preparation of pathogen-reduced cryoprecipitate in an organized and regulated national blood system. Pathogen-reduced cryoprecipitate can also provide a safe source of fibrinogen when used for treatment of fibrinogen disorders in various medical conditions including acquired deficiencies due to massive hemorrhage in trauma or obstetrics.*
>
> *Where feasible, non-pathogen-reduced cryoprecipitate should be replaced by pathogen-reduced cryoprecipitate in the treatment of patients with hemophilia A, von Willebrand Disease and fibrinogen disorders. Pathogen-reduction may be performed on plasma used for the preparation of cryoprecipitate, or on the product itself using a validated method. The residual risk of virus transmission is strongly dependent on the regional virus epidemiology and the screening technology applied. Hence, implementation of a pathogen*

inactivation technology for cryoprecipitate should not be a substitute for Good Preparation Practices in donor selection, blood collection, laboratory testing for HIV, HBV and HCV and other relevant agents including emerging viruses, product processing, traceability and hemovigilance reporting, as described in WHO recommendations and Guidelines.

In line with the recommendation of the World Federation of Hemophilia locally generated pathogen-reduced cryoprecipitate should be regarded as a step-wise improvement in the treatment of patients with bleeding disorders that should not supplant and may coexist with programs to expand patient access to CFC through local or regional plasma fractionation, toll fractionation of domestic plasma or importation of the products. Treatment with cryoprecipitate that is not pathogen-reduced should be discouraged, particularly in the setting of repeated use due to the risk of contamination with blood-borne viruses that is amplified by plasma pooling. Based on these considerations, the WHO Blood Regulators Network advocates use of pathogen-reduced cryoprecipitate in resource limited settings until CFC are available and affordable, subject to a careful assessment of risk and benefits and an organized nationally regulated blood system operating under Good Preparation Practices.

Committee recommendations

The Expert Committee recognized that insufficient access to clotting factor replacement products contributes to early death in patients with bleeding disorders. Accessibility to these products is especially problematic in low- and middle-income countries where many patients have no access to any form of treatment.

The Committee considered that evidence and extensive clinical experience suggest that cryoprecipitate is superior to plasma for replacement of certain clotting factors in a variety of indications in adults and children. However, the Expert Committee noted that concentrated clotting factors remain the preferred treatment for many bleeding disorders and should be prioritized for selection and use wherever possible. The Committee noted and agreed with the WHO Blood Regulatory Network position statement and emphasized that cryoprecipitate-PR ought only to be used in settings where commercial clotting factors are unaffordable or unavailable. The Committee was not in the position to recommend specific methods of pathogen reduction but considered that cryoprecipitate-PR developed using validated, approved pathogen-reduction methods should be ensured.

The Committee also noted that comparative evidence for cryoprecipitate-PR versus non-pathogen-reduced cryoprecipitate was limited but acknowledged that pathogen reduction can eliminate major risks of transmission of bloodborne infectious agents and increase the safety of administration. While there is a risk of alloimmunization and allergic transfusion reaction, these adverse events are lower than rates reported for other blood components, including fresh frozen plasma.

The Expert Committee therefore recommended the inclusion of cryoprecipitate-PR on the core list of the EML and EMLc for use in the replacement of coagulation factors in cases of massive haemorrhage, von Willebrand disease and shortage of coagulation factor XIII. It may also be used as an alternative to coagulation factor VIII concentrate for patients with haemophilia A in settings where this product is unavailable or unaffordable. The Committee also recommended that non-pathogen-reduced cryoprecipitate be included in the Model Lists as a therapeutic alternative given that transition to cryoprecipitate-PR at the country level may take time. The Committee acknowledged that solvent and detergent virus inactivation technologies and medical devices used in the plasma fractionation industry are gaining momentum, and are being adopted by an increasing number of blood establishments and national blood service centres. The Committee considered that every effort should be made to facilitate the transition to cryoprecipitate-PR, and processing systems should be adopted based on virus inactivation technologies. For this reason, the Committee considered that removal of non-pathogen-reduced cryoprecipitate from the Model Lists as a therapeutic alternative to cryoprecipitate-PR should be considered at the earliest opportunity (i.e. 2025) unless an application is received to support its retention.

The Committee emphasized the requirement that all blood, blood components and plasma derivatives used as essential medicines should comply with WHO requirements developed by the WHO Expert Committee on Biological Standardization. The Committee also emphasized that blood donor and donation screening for infections before use of blood products should always be implemented.

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11.2 Plasma-derived medicines
11.2.2 Blood coagulation factors
Coagulation factors for haemophilia – review of square box alternatives – EML and EMLc

Coagulation factor VIII	**ATC code: B02BD02**
Coagulation factor IX	**ATC code: B02BD04**

Proposal

Inclusion of therapeutic alternatives to plasma-derived coagulation factors VIII and IX used in the treatment of haemophilia on the complementary list of the EML and EMLc.

Applicant

World Federation of Hemophilia

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

11.2.2 Blood coagulation factors

Dose form(s) & strengths(s)

Coagulation factor VIII: powder for injection in vial

Coagulation factor IX: powder for injection in vial

Core/complementary

Complementary

Individual/square box listing

Square box

Background

Plasma-derived coagulation factors VIII and IX are each listed on the EML and EMLc with a square box, which is intended to indicate similar clinical performance of different medicines within the pharmacological class and that suitable therapeutic alternative may be considered for selection at the country level for national essential medicines lists. The square box was originally added to

the listings in 1989 to accommodate cryoprecipitate as a therapeutic alternative to factor VIII, and plasma and cryoprecipitate-poor plasma as therapeutic alternatives to factor IX (*1*). In 2007, when plasma-derived coagulation factors VIII and IX were included on the first EMLc, the Expert Committee recognized that recombinant products should be used in preference to dried and plasma-derived products and that recombinant products would be captured by the square box listings (*2*).

At its meeting in 2021, the Expert Committee considered a review of square box listings on the EML and EMLc and recommended that all square box listings be qualified to explicitly indicate the recommended therapeutic alternatives. The Committee requested that the therapeutic alternatives for plasma-derived coagulation factors VIII and IX be reviewed and updated in 2023 (*3*). Thus, the Secretariat invited the World Federation of Hemophilia to submit an application reviewing the therapeutic alternatives for these medicines.

Public health relevance

The public health relevance of coagulation factors for use in the treatment of haemophilia is well established.

Summary of evidence: benefits

The application proposed a series of changes to listings as summarized below.

Coagulation factor VIII

The World Federation of Hemophilia recommended not specifying the 500 IU strength with the listing for coagulation factor VIII as this could be unnecessarily limiting. This is because factor VIII concentrates are manufactured in a variety of vial sizes, labelled with strengths ranging from 250 to 3000 IU per vial. The administered dose is determined by the respective treatment protocol and patient weight.

The Federation recommended the inclusion of recombinant factor VIII as a therapeutic alternative based on: human-derived and recombinant factor VII products being classified with the same Anatomical Therapeutic Chemical (ATC) code (B02BD02); the recognition by the Expert Committee in 2007 that recombinant products should be used in preference to plasma-derived products and would be captured under the existing square box listing (*2*); and recommendations in Federation's guidelines for the management of haemophilia (*4*). A comprehensive review of the available evidence was not provided in the application.

The World Federation of Hemophilia recommended the inclusion of bypassing agents (recombinant activated factor VIIa or activated prothrombin complex concentrate) as therapeutic alternatives for treatment and prevention of bleeding complications in patients with haemophilia A and B who develop

Factor VIII or factor IX alloantibodies that typically neutralize the function of infused clotting factor concentrates. The Federation's guidelines recommend that a bypassing agent be used for people with haemophilia A with an inhibitor requiring treatment for acute bleeding complications or surgery, and for people with haemophilia B with an inhibitor and with a history of an anaphylactic reaction to factor IV-containing clotting factor concentrates (recombinant activated factor VIIa only) (*4*). A comprehensive review of the available evidence was not provided in the application.

The World Federation of Hemophilia recommended the inclusion of emicizumab, a bispecific monoclonal antibody factor VIII mimetic as a therapeutic alternative to plasma-derived factor VIII. Emicizumab is a non-factor replacement therapy that is administered subcutaneously, in some cases as infrequently as once or twice a month. The application stated that non-factor replacement agents such as emicizumab were not associated with the peak and trough curves of protection that are now seen with factor prophylaxis regimens. The Federation's guidelines include recommendations for use of emicizumab in patients with haemophilia A with an inhibitor for regular prophylaxis to prevent bleeding events. Emicizumab may also be used for regular prophylaxis in patients with haemophilia without an inhibitor (*4*). Emicizumab cannot be used to treat acute bleeding episodes. A comprehensive review of the available evidence was not provided in the application.

The World Federation of Hemophilia recommended the inclusion of desmopressin acetate as a therapeutic alternative to factor VIII for patients with mild or moderate haemophilia and carriers of haemophilia A, in accordance with recommendations in the Federation's guidelines (*4*).

Coagulation factor IX

The World Federation of Hemophilia recommended not specifying the 500 IU and 1000 IU strengths with the listing for coagulation factor IX as this could be unnecessarily limiting. This is because factor IX concentrates are manufactured in a variety of vial sizes, labelled with strengths ranging from 250 IU to 4000 IU per vial. The administered dose is determined by the respective treatment protocol and patient weight.

The World Federation of Hemophilia recommended the inclusion of recombinant factor IX as a therapeutic alternative based on: human-derived and recombinant factor IX products being classified with the same ATC code (B02BD04); the recognition by the Expert Committee in 2007 that recombinant products should be used in preference to plasma-derived products and would be captured under the existing square box listing (*2*); and recommendations in the Federation's guidelines for the management of haemophilia (*4*). A comprehensive review of the available evidence was not provided in the application.

The World Federation of Hemophilia recommended the inclusion of coagulation factor IX complex (prothrombin complex concentrate) as a therapeutic alternative. However, for patients with haemophilia B, the the Federation's guidelines recommend use of products containing only factor IX in preference to prothrombin complex concentrates which also contain other clotting factors (e.g. factors II, VII and X), which may become activated during manufacture and predispose the patient to thromboembolism. Pure factor IX products have a reduced risk of thrombosis or disseminated intravascular coagulation compared with large doses of older-generation prothrombin complex concentrates. Newer prothrombin complex concentrates are considered safer than earlier products due to the inclusion of coagulation inhibitors (*4*).

The World Federation of Hemophilia also recommended the inclusion of bypassing agents as therapeutic alternatives (see previous paragraph *Coagulation factor VIII*).

Dextran 70

The World Federation of Hemophilia recommended the removal of the plasma substitute dextran 70 from the Model Lists since this product is not used for the treatment of haemophilia.

Summary of evidence: harms

A comprehensive review of the available evidence for safety was not provided in the application.

WHO guidelines

WHO guidelines for the treatment of haemophilia are not currently available.

The WHO Expert Committee on Biological Standardization has developed requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (*5*), guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood products (*6*), and guidelines on management of blood and blood components as essential medicines (*7*).

Costs/cost–effectiveness

No information was provided in the application.

Availability

No information was provided in the application.

Committee recommendations

The Expert Committee recalled the recommendation of the 2021 Committee that the square box listings for blood-derived coagulation factors VIII and IX be

reviewed in 2023, such that the listings should explicitly indicate the recommended therapeutic alternatives. The application from the World Federation of Hemophilia proposed therapeutic alternatives to coagulation factor VIII (recombinant factor VIII, bypassing agents, bispecific monoclonal antibody factor VIII mimetic and desmopressin) and coagulation factor IX (recombinant factor IX, coagulation factor IX complex and bypassing agents), but did not provide a comprehensive review of the evidence supporting these suggestions.

In consideration of the application, the Committee made the following comments and recommendations.

Recombinant coagulation factors.

The Committee noted that when plasma-derived coagulation factors were considered for inclusion on the first EMLc in 2007, the Committee at that time considered that recombinant products would be covered by the existing square box listings. However, a comprehensive review of the evidence for the comparative efficacy, safety and cost/cost–effectiveness of recombinant products had not been conducted nor evaluated at that time. The 2023 Committee therefore recommended that a full application, compliant with EML application requirements, be requested so that the available evidence could be evaluated. Until such time, recombinant coagulation factors should not be included as therapeutic alternatives to plasma-derived coagulation factors on the Model Lists.

Bypassing agents

The Committee considered that bypassing agents were not, as such, therapeutic alternatives to coagulation factors, but rather were currently used in a subset of patients who develop factor VIII or factor IX alloantibodies (inhibitors). With regard to the bispecific monoclonal antibody, emicizumab, the Committee also considered that this was not as such, a therapeutic alternative to factor VIII, but rather could be used as a separate treatment strategy for patients with haemophilia A. Therefore, the Committee recommended that these therapies not be included as alternatives under the current square box listings. The Committee acknowledged the potential future role of these therapies in changing the treatment paradigm of patients with haemophilia but also noted that currently they may not be considered as cost-effective, nor are they widely available. The Committee considered that high-quality applications, compliant with EML application requirements for these therapies could be considered for independent inclusion in the Model Lists in the future.

Desmopressin

The Committee acknowledged that desmopressin was a therapeutic alternative to plasma-derived factor VIII. Desmopressin is already included on the EML and EMLc for use in the treatment of patients with haemophilia A and von Willebrand

disease, in Section 10 (Medicines affecting the blood), instead of as a square box alternative to factor VIII in Section 11 (Blood products of human origin and plasma substitutes) since it is not a blood product of human origin.

Coagulation factor IX complex

The Committee noted that this complex had been previously listed on the Model Lists until 2013, when it was replaced by coagulation factor IX when Section 11 of the lists for blood products of human origin and plasma substitutes was revised and restructured. The Committee considered that coagulation factor IX complex could be considered a suitable therapeutic alternative to coagulation factor IX in situations where purified factor IX was not available. Therefore, the Committee recommended that the square box listing for coagulation factor IX specify coagulation factor IX complex as a therapeutic alternative under such circumstances.

Dextran

In response to the suggestion in the application to remove the plasma substitute dextran from the Model Lists because it is not used in the treatment of haemophilia, the Committee advised that dextran was still an essential plasma substitute for other patients in need of blood volume replacement and therefore should remain listed.

Strengths of factor VIII and factor IX

The application proposed the removal of the specification of strengths of factor VIII and factor IX from the listings, because factor VIII and IX concentrates are manufactured and supplied in strengths ranging from 250 IU to 4000 IU per vial. The Committee agreed that specifying a single strength vial could be unnecessarily limiting. The Committee recommended that for factor VIII, additional strengths of 250 IU and 1000 IU be included as these are the most commonly used and available. The Committee considered that the existing listed strengths of factor IX were appropriate and therefore did not recommend inclusion of the other strengths proposed.

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Section 12: Cardiovascular medicines
12.5 Antithrombotic medicines
12.5.1 Anti-platelet medicines
Ticagrelor – addition – EML

Ticagrelor	**ATC code: B01AC24**

Proposal

Addition of ticagrelor to the core list of the EML for the prevention of atherothrombotic events in adults with acute coronary syndrome or a history of myocardial infarction and at high risk of developing an atherothrombotic event.

Applicant

AstraZeneca PLC, Cambridge, United Kingdom

WHO technical department

The technical team for Screening, Diagnosis and Treatment in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department did not support the inclusion of ticagrelor on the EML for the following reasons: an unfavourable cost-to-benefit ratio; very limited uptake of less costly aspirin for secondary prevention of cardiovascular disease; and preference to support uptake efforts for statins and aspirin, in line with WHO guidance in the package of essential noncommunicable diseases interventions, and HEARTS technical packages.

EML/EMLc

EML

Section

12.5.1 Anti-platelet medicines

Dose form(s) & strengths(s)

Tablet: 60 mg, 90 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Ticagrelor has not previously been evaluated for inclusion on the Model List.

In 2015, the Expert Committee recommended the addition of clopidogrel to the EML as an antithrombotic agent for treatment of patients with acute coronary syndrome or following percutaneous coronary interventions. The Committee accepted that based on the evidence presented, dual anti-platelet therapy with clopidogrel in combination with aspirin was effective in reducing the risk of major cardiovascular events and was superior to aspirin monotherapy for patients with acute coronary syndrome or undergoing percutaneous coronary interventions. In these patient populations, the Committee considered that the benefits of dual therapy outweighed the potential harms (*1*).

Public health relevance

Worldwide, in 2019, ischaemic heart disease and stroke were the first and second highest causes of death, respectively, in people older than 50 years (*2*).

The global burden of cardiovascular disease and stroke-related mortality and disability-adjusted life years (DALY) are driven by the burden in low- and middle-income countries. A report from the European Society of Cardiology, which analysed data from 56 member countries, showed that the disease burden DALY per 100 000 people due to cardiovascular disease was more than three times as high in middle-income versus high-income countries. Cardiovascular disease mortality was also higher in middle-income countries where it accounted for a greater proportion of potential years of life lost compared with high-income countries (*3*).

All-cause mortality in low- and middle-income countries has fallen over the past three decades, but there has been no reduction in mortality from cardiovascular disease and stroke (*2,4,5*).

Summary of evidence: benefits

The application presented summaries of recent systematic reviews, network meta-analyses, and primary research articles on the clinical effects of ticagrelor in comparison with other agents.

Ticagrelor versus active comparators

The PLATO study was a randomized, multicentre, double-blind study that compared ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) versus clopidogrel (300–600 mg loading dose, 75 mg daily thereafter) on the prevention of cardiovascular events in patients admitted to hospital with an acute coronary syndrome (18 624 participants) (*6*). After 12 months of treatment, ticagrelor was associated with significantly lower rates of death from vascular causes, myocardial infarction or stroke compared with clopidogrel (9.8% versus 11.7%,

P < 0.001). Patients treated with ticagrelor had significantly lower rates of myocardial infarction (5.8% versus 6.9%, *P* = 0.005) and death from vascular causes (4.0% versus 5.1%, *P* = 0.001), but not stroke alone compared with patients treated with clopidogrel. The rate of death from any cause was also lower with ticagrelor than clopidogrel (4.5% versus 5.9%, *P* < 0.001). No significant increase was seen in the risk of major or fatal bleeding, although there was an increase in non-coronary-artery bypass graft-related major bleeding with ticagrelor versus clopidogrel (4.5% versus 3.8%, *P* = 0.03). A substudy of PLATO (10 285 participants) analysed the effects of CYP2C19 and ABCB1 genotypes, which are known to influence the effects of clopidogrel, on outcomes with ticagrelor versus clopidogrel. Cardiovascular death occurred less often with ticagrelor than clopidogrel, irrespective of CYP2C19 or ABCB1 genotype (*7*). The reduced risk of cardiovascular death with ticagrelor, regardless of genotype, suggests that the use of ticagrelor may be started for patients without the need for recommended genetic testing and may be a potential option for patients who are resistant or unresponsive to clopidogrel.

The PLATELET substudy of the PLATO trial compared antiplatelet effects of ticagrelor versus clopidogrel in patients with acute coronary syndrome (69 participants, 28 days maintenance treatment with ticagrelor (90 mg twice daily) or clopidogrel (75 mg daily) (*8*). Ticagrelor produced significantly lower platelet reaction units with both the loading dose at 4 hours and the maintenance doses (both trough and peak), demonstrating a greater platelet inhibitor effect with ticagrelor than clopidogrel in patients with acute coronary syndrome both in the first hours of treatment and during maintenance.

A meta-analysis of 10 randomized studies (56 385 participants) evaluated the safety and efficacy of ticagrelor versus clopidogrel in patients with acute coronary syndrome (*9*). Analysis of pooled data from eight studies indicated no significant differences in the risk of bleeding (odds ratio (OR) OR 1.07, 95% confidence interval (CI) 0.91 to 1.26), or rate of myocardial infarction (OR 0.87, 95% CI 0.72 to 1.05) between treatments. Analysis of pooled data from seven studies also indicated no significant differences in the risk of stroke between treatments (OR 0.93, 95% CI 0.64 to 1.34).

A network meta-analysis of 12 randomized trials (52 816 participants) compared the efficacy and safety of prasugrel, ticagrelor and clopidogrel in acute coronary syndrome (*10*). Ticagrelor was associated with significantly lower cardiovascular mortality (hazard ratio (HR) 0.82, 95% CI 0.72 to 0.92) and all-cause mortality (HR 0.83, 95% CI 0.75 to 0.92) compared than clopidogrel. No significant differences were observed between ticagrelor and clopidogrel for non-cardiovascular mortality or reduction in myocardial infarction events. Seven studies provided data for the outcome of definite or probable stent thrombosis events. Both ticagrelor (HR 0.72, 95% CI 0.58 to 0.90) and prasugrel

(HR 0.50, 95% CI 0.38 to 0.64) were associated with a significantly lower risk of stent thrombosis compared with clopidogrel. Prasugrel was associated with a significantly lower risk of stent thrombosis than ticagrelor (HR 0.68, 95% CI 0.50 to 0.93).

A retrospective observational study using data from a Chinese nationwide database assessed clinical characteristics of patients with ST-segment elevation myocardial infarction with in-hospital cardiac arrest, as well as predictors and treatments associated with the risk of in-hospital cardiac arrest (*11*). Patients presenting with ST-segment elevation myocardial infarction within 24 hours after symptom onset were stratified according to in-hospital cardiac arrest or no in-hospital cardiac arrest during index hospitalization. Of the 40 670 patients with ST-segment elevation myocardial infarction, 2.2% experienced in-hospital cardiac arrest, which in turn was responsible for more than half of inpatient deaths. However, primary percutaneous coronary intervention (adjusted HR 0.82, 95% CI 0.71 to 0.95), β-blockers (adjusted HR 0.63, 95% CI 0.47 to 0.86) and ticagrelor (adjusted HR 0.57, 95% CI 0.42 to 0.76) treatments were associated with a reduced risk of in-hospital cardiac arrest (*11*).

A systematic review of seven trials (511 participants) compared the efficacy of ticagrelor versus clopidogrel in improving endothelial function in patients with coronary artery disease (*12*). Compared with clopidogrel, ticagrelor resulted in a significantly higher elevation of progenitor cells CD34+KDR+ and CD34+133+, with a significantly lower rate of endothelial cell apoptosis. In addition, ticagrelor was superior to clopidogrel with regard to nitric oxide, radical oxygen species and soluble P-selectin levels. Overall, ticagrelor appeared to lead to greater improved endothelial cell function compared with clopidogrel.

A network meta-analysis of nine randomized trials (91 115 participants) evaluated comparative efficacy and safety of antiplatelet and anticoagulant therapy in patients with chronic coronary syndromes after percutaneous coronary intervention (*13*). Compared with aspirin alone, the addition of prasugrel or ticagrelor to aspirin was associated with a lower risk of myocardial infarction (prasugrel: OR 0.48, 95% CI 0.38 to 0.62; ticagrelor: OR 0.81–0.84, 95% CI 0.69 to 0.98), but was associated with an increased risk of major bleeding (prasugrel: OR 1.79, 95% CI 1.34 to 2.39; ticagrelor: OR 2.08–2.38, 95% CI 1.56 to 3.28). Significant differences between antithrombotic treatments for the primary outcome of major adverse cardiovascular event were not observed.

A systematic review and meta-analysis of 24 randomized trials (48 759 participants) assessed antithrombotic therapy for symptomatic peripheral arterial disease (*14*). For the primary endpoint of reducing major adverse cardiovascular events, clopidogrel (relative risk (RR) 0.78, 95% CI 0.66 to 0.93), ticagrelor (RR 0.79, 95% CI 0.65 to 0.97), aspirin plus ticagrelor (RR 0.79, 95% CI 0.64 to

0.97) and aspirin plus low-dose rivaroxaban (RR 0.84, 95% CI 0.76 to 0.93) were more effective than aspirin alone, and equally effective as each another.

A systematic review and meta-analysis of 22 studies (35 004 participants) evaluated the efficacy and safety of ticagrelor compared with clopidogrel in patients with general acute coronary syndrome and a group of patients with diabetes mellitus (*15*). The primary endpoint was a composite endpoint of any myocardial infarction, cardiovascular death or stroke. Five studies (33 258 participants) provided data for the composite endpoint and found that compared with clopidogrel, ticagrelor was associated with a lower incidence of the composite endpoint among patients with general acute coronary syndrome (OR 0.83, 95% CI 0.77 to 0.90). Eight studies (33 282 participants) provided data for the secondary endpoint of incidence of myocardial infarction. The incidence of myocardial infarction was significantly lower in the ticagrelor group than in the clopidogrel and prasugrel groups (OR 0.81, 95% CI 0.74 to 0.89). No significant differences were seen between the ticagrelor group and the clopidogrel and prasugrel groups for incidence of cardiovascular death or stroke.

A single-centre retrospective cohort study evaluated the effectiveness and safety of ticagrelor versus clopidogrel as dual antiplatelet therapy with aspirin in 908 Chinese patients aged ≥ 75 years with coronary artery disease after percutaneous coronary intervention for up to 12 months (*16*). Ticagrelor was associated with a lower incidence of major adverse cardiovascular events compared with clopidogrel (OR 0.49, 95% CI 0.36 to 0.68). There was no difference in the risk of bleeding between the two groups.

Ticagrelor versus placebo

The PEGASUS-TIMI-54 study was a randomized, double-blind, multicentre study to assess the prevention of atherothrombotic events with ticagrelor given at two doses (either 90 mg twice daily or 60 mg twice daily) versus placebo in patients with a history of myocardial infarction within 1–3 years and additional risk factors for atherothrombosis (21 162 participants) (*17*). All participants also received low dose aspirin (75–150 mg). The primary efficacy endpoint was the composite of cardiovascular death, myocardial infarction or stroke. Both ticagrelor doses were associated with significant reductions in the composite endpoint compared with placebo (90 mg: HR 0.85, 95% CI 0.75 to 0.96; 60 mg: HR 0.84, 95% CI 0.74 to 0.95). No evidence of benefit was seen (no reduction in the primary composite endpoint, but an increase in major bleeding) when ticagrelor 60 mg twice daily was introduced in clinically stable patients more than 2 years after the myocardial infarction, or more than 1 year after stopping previous treatment with adenosine diphosphate receptor inhibitor.

Summary of evidence: harms

The application presented the special warnings and precautions for use for ticagrelor as described in the summary of product characteristics issued by the European Medicines Agency (*18*). Selected safety findings from clinical trials are described below.

Risk of bleeding

In the PLATO trial of ticagrelor versus clopidogrel, no significant differences were seen in the rates of major bleeding between treatment arms as defined in the trial (HR 1.04, 95% CI 0.95 to 1.13), major bleeding defined according to the Thrombolysis in Myocardial Infarction criteria (HR 1.03, 95% CI 0.93 to 1.15), fatal or life-threatening bleeding (HR 1.03, 95% CI 0.90 to 1.16), or major bleeding related to coronary artery bypass graft surgery (HR 0.95, 95% CI 0.85 to 1.06) or bleeding requiring transfusion of red cells (OR 1.00, 95% CI 091 to 1.11). Ticagrelor was associated with significantly higher rates of major bleeding not related to coronary artery bypass graft surgery according to the study criteria (HR 1.19, 95% CI 1.02 to 1.38) and the Thrombolysis in Myocardial Infarction criteria (HR 1.25, 95% CI 1.03 to 1.53). Ticagrelor was also associated with significantly more episodes of intracranial bleeding (HR 1.87, 95% CI 0.98 to 3.58), including fatal intracranial bleeding. There were fewer episodes of non-intracranial fatal bleeding in the ticagrelor group (*6*).

In the PEGASUS-TIMI-54 placebo-controlled study of ticagrelor in patients with a history of myocardial infarction, ticagrelor 60 mg (the only dose approved for use in this patient population) was associated with significantly higher rates of bleeding, including major (HR 2.32, 95% CI 1.68 to 3.21) and minor (HR 3.31, 95% CI 1.94 to 5.63) bleeding as defined by Thrombolysis in Myocardial Infarction criteria, bleeding requiring transfusion (HR 3.08, 95% CI 2.12 to 4.48) and bleeding leading to treatment discontinuation (HR 4.40, 95% CI 3.48 to 5.57) compared with placebo. A non-significant increase in fatal bleeding or non-fatal intracranial haemorrhage was observed with ticagrelor 60 mg treatment (HR 1.20, 95% CI 0.73 to 1.97) compared with placebo (*17*).

Dyspnoea

In the PLATO study, any dyspnoea was reported significantly more frequently in the ticagrelor arm than the clopidogrel arm (HR 1.84, 95% CI 1.68 to 2.02). Dyspnoea leading to treatment discontinuation was also more frequent in patients treated with ticagrelor (HR 6.12, 95% CI 3.41 to 11.01) (*6*).

In the PEGASUS trial, dyspnoea was reported significantly more frequently in patients taking ticagrelor 60 mg compared with aspirin alone (HR 2.81, 95% CI 2.50 to 3.17) and more frequently led to treatment discontinuation (HR 6.06, 95% CI 4.50 to 8.15) (*17*).

Uric acid elevations

In the PLATO trial, serum uric acid increased to more than the upper limit of normal in 22% of patients receiving ticagrelor compared with 13% of patients receiving clopidogrel. The corresponding numbers in PEGASUS were 9.1%, 8.8% and 5.5% for ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively. Mean serum uric acid increased about 15% with ticagrelor compared with about 7.5% with clopidogrel. After treatment was stopped, uric acid decreased to about 7% in patients on ticagrelor but no decrease was observed for clopidogrel. In PEGASUS, a reversible increase in mean serum uric acid levels of 6.3% and 5.6% was found for ticagrelor 90 mg and 60 mg, respectively, compared with a 1.5% decrease in the placebo group. In PLATO, the frequency of gouty arthritis was 0.2% for ticagrelor versus 0.1% for clopidogrel. The corresponding numbers for gout/gouty arthritis in PEGASUS were 1.6%, 1.5% and 1.1% for ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively (*18*).

WHO guidelines

The WHO HEARTS technical package for cardiovascular disease management in primary health care includes recommendations on interventions for the management of hypertension, diabetes and elevated lipid levels in primary care (*19*). Recommendations specifically for the secondary prevention of atherothrombotic events in adults with acute coronary syndromes or a history of myocardial infarction and at high risk of developing an atherothrombotic event are not currently included.

Costs/cost–effectiveness

The application identified and briefly summarized findings from cost–effectiveness analyses comparing ticagrelor and clopidogrel in Brazil (*20*), Colombia (*21*), Egypt (*22,23*), Germany (*20*), Singapore (*24*), Sweden (*20*), Thailand (*25*), United Kingdom (*20*) and Viet Nam (*26*) which determined ticagrelor to be cost-effective versus clopidogrel based on national perspectives and willingness-to-pay thresholds.

The application also presented a comparison of the price per day of treatment in United States dollars for ticagrelor and clopidogrel from selected low- and middle-income countries where prices were available for both medicines (Table 21). Prices are published list prices and do not take into account confidential discounts or rebates that may be in place.

Table 21

Average published price per day of treatment with ticagrelor and clopidogrel, by country

Country	Price per day, US$	
	Ticagrelor 90 mg	Clopidogrel 75 mg
Bangladesh	0.05	0.10
Egypt	0.56	0.16
India	0.72	0.10
Indonesia	2.79	0.97
Morocco	2.05	0.45
Nicaragua	3.18	1.26
Tunisia	1.83	0.44
Ukraine	2.00	0.06
Viet Nam	1.33	0.32

Source: Navlin; 2023 (https://data.navlin.com/alspc/#!/).

Availability

Ticagrelor has regulatory approval worldwide and remains under patent protection until 2024. Generics are available in some settings.

Committee recommendations

The Expert Committee considered that reducing mortality from cardiovascular diseases was a global health priority and acknowledged that prevention and treatment of cardiovascular disease remained an area of unmet need, especially in low- and middle-income countries.

The Committee noted that evidence from randomized trials, systematic reviews and network meta-analyses comparing ticagrelor with placebo and with active comparators presented in the application showed somewhat heterogeneous results, giving rise to uncertainty in the efficacy outcomes.

In the PEGASUS study in patients with a history of myocardial infarction, the Committee noted that ticagrelor in combination with aspirin was superior to aspirin alone in preventing atherothrombotic events; however, no benefit was observed when ticagrelor was introduced in clinically stable patients. In the PLATO study in hospitalized patients with acute coronary syndromes, the Committee noted that the use of ticagrelor did not improve outcomes more than clopidogrel in all patient subpopulations – those with body weight lower than the

sex-specific median values and participants from North America. In addition, the Committee noted that participants from Hungary and Poland made up about 20% of the trial population and provided nearly half of the data in favour of ticagrelor. When data from these participants were excluded, ticagrelor was no longer superior to clopidogrel. Finally, when myocardial infarctions were assessed only by site investigators, and not by the clinical adjudication committee, ticagrelor was no longer superior to clopidogrel. The Committee noted that in both the PEGASUS and PLATO trials, ticagrelor was associated with an increased risk of some important bleeding outcomes, such as fatal intracranial bleeding.

The Committee also noted data (not presented in the application) from studies comparing ticagrelor and clopidogrel in Asian patients with acute coronary syndromes, which indicated that ticagrelor was not superior to clopidogrel and carried a greater risk of major bleeding (*27,28*).

The Committee noted that ticagrelor has generally been found to be cost-effective versus clopidogrel in high-income settings. However, while generics of ticagrelor are available in some countries, it remains more expensive than clopidogrel in most markets.

Therefore, the Expert Committee did not recommend the inclusion of ticagrelor on the EML for the prevention of atherothrombotic events in adults with acute coronary syndromes or a history of myocardial infarction and at high risk of developing an atherothrombotic event.

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12.7 Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease

Fixed-dose combinations of cardiovascular medicines – addition – EML

Acetylsalicylic acid + atorvastatin + ramipril	**ATC code: C10BX06**
Acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide	**ATC code: not available**
Atorvastatin + perindopril + amlodipine	**ATC code: C10BX11**

Proposal

Addition of fixed-dose combination formulations including acetylsalicylic acid, antihypertensive medicines and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) on the core list of the EML for primary and secondary prevention of atherosclerotic cardiovascular diseases in adults.

Two combinations (acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide, and atorvastatin + perindopril + amlodipine) are proposed for primary prevention of incident atherosclerotic cardiovascular disease in individuals with a predicted risk of over 10% within a span of 10 years.

The combination of acetylsalicylic acid + atorvastatin + ramipril is proposed for secondary prevention in patients who already have existing atherosclerotic cardiovascular disease.

Applicant

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WHO technical department

The WHO Noncommunicable Diseases Department is in favour of including fixed-dose combinations for both primary and secondary prevention of cardiovascular diseases. Their support is based on: clear evidence of benefit; improved management of secondary prevention, especially in terms of adherence and persistence with the treatment; wide market availability globally; and generally being considered cost-effective and affordable.

EML/EMLc

EML

Section

Section 12.7 Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease (new subsection)

Dose form(s) & strengths(s)

Acetylsalicylic acid + atorvastatin + ramipril – Tablet: 100 mg + 20 mg + 2.5 mg, 100 mg + 20 mg + 5 mg, 100 mg + 20 mg + 10 mg, 100 mg + 40 mg + 2.5 mg, 100 mg + 40 mg + 5 mg, 100 mg + 40 mg + 10 mg

Acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide – Tablet: 100 mg + 20 mg + 5 mg + 50 mg + 12.5 mg

Atorvastatin + perindopril + amlodipine – Tablet: 20 mg + 5 mg + 5 mg, 20 mg + 10 mg + 10 mg, 40 mg + 5 mg + 5 mg, 40 mg + 10 mg + 10 mg

Core/complementary

Core

Individual/square box listing

Square box, with therapeutic alternatives for individual component medicines consistent with those currently included in the EML.

Background

Applications for the inclusion of various fixed-dose combination formulations of medicines for secondary prevention of atherosclerotic cardiovascular disease in adults had previously been considered by the Expert Committee in 2013, 2015 and 2017. On each occasion, listing was not recommended. Refer to the corresponding technical reports from each meeting for more information (*1–3*). The current application builds on the evidence presented in the previous applications.

The medicines included in the fixed-dose combinations formulations proposed in the current application are all already included individually on the EML.

Public health relevance

Cardiovascular diseases, primarily ischaemic heart disease and stroke, are the leading cause of death worldwide. Data from the Global Burden of Disease study showed that in 2019, cardiovascular diseases were responsible for an estimated 18.6 million deaths globally (an increase from 12.1 million in 1990) and constituted almost one third of all global deaths. In addition, prevalent cases of total cardiovascular diseases increased from 271 million in 1990 to 523 million in 2019. Global trends also increased for disability-adjusted life years (DALYs)

and years of life lost (YLL), and years lived with disability (YLD) doubled over the same time period (*4*).

Clinical guidelines recommend pharmacotherapy using cholesterol and blood pressure-lowering medicines for secondary prevention in individuals with prevalent disease, and for primary prevention in individuals at high risk of cardiovascular disease. Antiplatelet therapy with aspirin is also recommended for secondary prevention. Pharmacotherapy was also recommended in WHO's global action plan for the prevention and control of noncommunicable diseases 2013–2020 (*5*) for patients with and at high risk of cardiovascular disease. These medicines, individually and as pharmacological classes have long been included in the Model List of Essential Medicines because of their efficacy, safety and cost–effectiveness for both prevalent cardiovascular disease patients and those at high risk of incident disease. The WHO HEARTS technical package emphasizes a risk-based approach for country-level implementation (*6*).

Despite the availability of effective medicines, the uptake of individual medicines for cardiovascular disease prevention remains low (*7*). Data from 40 demographic health surveys in low- and middle-income countries (2013–2019) show that less than 10% of eligible adults use recommended pharmacotherapy (statins, blood pressure-lowering medicines and aspirin) for primary or secondary prevention of cardiovascular disease (*8,9*). Low rates of use are also reported in high-income countries. For example, in the United States, data indicate that one out of every four adults with prevalent cardiovascular disease takes the combination of antiplatelet, statin and blood pressure-lowering therapy for secondary prevention of atherosclerotic cardiovascular disease (*10,11*). The longitudinal rates of medication use as secondary prevention for cardiovascular disease were studied in the Prospective Urban Rural Epidemiology (PURE) study in 17 countries. The study spanned 12 years period and found little improvement in the use of medicines for secondary prevention of cardiovascular disease over time. This lack of change was observed in countries of all income levels (*7*).

Summary of evidence: benefits

A systematic review by the applicants builds on a 2017 Cochrane systematic review of fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases (13 randomized controlled trials, 9059 participants) (*12*). The applicant's review included data from an additional 13 clinical trials (18 277 participants). Among these new trials, three (PolyIran (*13*), TIPS-3 (*14*) and SECURE (*15*)) published in the past 3 years have contributed to strengthening the evidence for fixed-dose combination therapy. In total, the evidence presented for fixed-dose combination therapy includes 26 trials (27 336 participants). Details of the included studies are presented in the application. Control groups in the trials included placebo, usual care and individual medicine monotherapy.

Primary prevention

Based on study level meta-analyses, fixed-dose combination therapy was associated with a 29% reduction in the risk of fatal and non-fatal major adverse cardiovascular events (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.63 to 0.79; five randomized controlled trials, high-quality evidence) and an 11% reduction in the risk of all-cause mortality (5.6% versus 6.3%; RR 0.89, 95% CI 0.78 to 1.00; four randomized controlled trials; high-quality evidence) compared with control.

Based on study-level meta-analyses, fixed-dose combination therapy was associated with significant reductions in risk factors, including a decrease in systolic blood pressure (weighted mean difference (MD) –8.08 mmHg, 95% CI –10.83 to –5.34 mmHg; 17 randomized controlled trials; high-quality evidence) and low-density lipoprotein cholesterol (weighted MD –1.06 mmol/L, 95% CI –1.36 to -0.76 mmol/L; 16 randomized controlled trials; high-quality evidence).

These findings are supported by data from an individual participant data meta-analysis of three outcome-driven primary prevention trials comparing a fixed-dose combination treatment strategy versus placebo or usual care (PolyIran (*13*), TIPS-3 (*14*) and HOPE-3 (*16*)) conducted by the Polypill Trialists' Collaboration. The results showed a 38% overall reduction in the risk of cardiovascular death, myocardial infarction, stroke, or arterial revascularization with fixed-dose combination therapy (3.0% versus 4.9%, hazard ratio (HR) 0.62, 95% CI 0.53 to 0.73). The results were consistent for fixed-dose combinations that included aspirin (2.6% versus 4.8%; HR 0.53, 95% CI 0.41 to 0.67) and did not include aspirin (3.3% versus 4.9%; HR 0.68, 95% CI 0.57 to 0.81). The meta-analysis also found fixed-dose combination therapy to be associated with reductions in systolic blood pressure (mean difference –4.7 mmHg, 95% CI –4.2 to –5.2 mmHg) and low-density lipoprotein cholesterol (mean difference –0.59 mmol/L, 95% CI –0.55 to –0.62 mmol/L). Additionally, there was no evidence of heterogeneity across tertiles of baseline predicted risk levels or other characteristics (*17*).

Secondary prevention

The SECURE trial was a randomized phase III trial (2499 participants) that assessed fixed-dose combination therapy with aspirin + ramipril + atorvastatin versus usual care in patients with myocardial infarction within the previous 6 months (*15*). Fixed-dose combination therapy was associated with a 24% relative risk reduction for the primary composite outcome of cardiovascular death, non-fatal type 1 myocardial infarction, non-fatal ischaemic stroke or urgent revascularization (9.5% versus 12.7%; HR 0.76, 95% CI 0.60 to 0.96) compared with usual care. For the secondary outcome of a composite of cardiovascular death, non-fatal type 1 myocardial infarction, or non-fatal ischaemic stroke,

there was a 30% relative risk reduction associated with fixed-dose combination therapy (8.2% versus 11.7%; HR 0.70, 95% CI 0.54 to 0.90). The reductions in cardiovascular disease events were likely due to improvements in adherence, as the fixed-dose combination therapy group showed higher adherence rates (74.1% versus 63.2% at 24 months; RR 1.17, 95% CI 1.10 to 1.25).

The PolyIran trial included 737 participants with cardiovascular disease at baseline. Fixed-dose combination therapy was associated with a reduced rate of major adverse cardiovascular events in this subgroup, similar in direction and magnitude to the overall trial results, with no evidence of an interaction based on baseline disease status (adjusted HR 0.80, 95% CI 0.57 to 1.12, $P_{interaction} = 0.19$) (*13*).

The application stated that other trials with at least 15% of participants with prevalent cardiovascular disease showed substantial heterogeneity with results likely being driven by the small number of events from trials that were not designed to evaluate the effect of fixed-dose combination therapy on clinical outcomes. These results were not determined to be reliable and therefore estimates for secondary prevention were derived exclusively from secondary prevention populations reported in the SECURE and PolyIran trials.

Mixed primary and secondary prevention

A meta-analysis of trials in mixed primary and secondary prevention showed that fixed-dose combination therapy resulted in a reduction in risk factors compared with usual care, including systolic blood pressure (weighted MD –1.23 mmHg, 95% CI –2.10 to –0.36 mmHg, seven randomized controlled trials, high-quality evidence) and low-density lipoprotein cholesterol (weighted MD 0.02 mmol/L, 95% CI –0.06 to 0.03 mmol/L, seven randomized controlled trials, moderate-quality evidence). The applicants concluded that overall, the expected benefits of fixed-dose combination therapy in a general population would be greater due to the reported low baseline treatment rates.

Health-related quality of life

Health-related quality of life showed no significant differences between treatment groups in EQ-5D scores (MD 0.22, 95% CI –1.02 to 1.46, three randomized controlled trials, 2109 participants).

Adherence

Patients randomized to fixed-dose combination therapy had higher adherence rates than controls (RR 1.16, 95% CI 1.03 to 1.29, 11 randomized controlled trials). However, there was considerable heterogeneity in this outcome, making it difficult to assess the true effect on adherence, especially in an unselected population where adherence rates might differ from clinical trial participants who usually have higher adherence rates than the general population.

Evidence in different populations and settings

Data from the SECURE trial showed no evidence of heterogeneity of effect based on country (although SECURE included data only from high-income European countries) (*15*).

The HOPE-4 cluster randomized trial (30 clusters, 1371 participants) also showed the feasibility, effectiveness and safety of delivering the combination of angiotensin receptor blocker + statin in patients without prior cardiovascular disease through non-physician health workers in Colombia and Malaysia (*18*). These health workers were supported by computer-based simplified management algorithms. The intervention resulted in a 43% relative risk reduction in predicted risk (–6.4%, 95% CI –8.0% to –4.8%) in the control group and –11.2%, 95% CI –12.9% to –9.5%) in the intervention group, which were driven by greater reductions in systolic blood pressure (–11.5 mmHg, 95% CI –14.9 to –8.0 mmHg) and low-density lipoprotein cholesterol (–0.41 mmol/L, 95% CI –0.6 to –0.2 mmol/L).

Implementation of the combination of aspirin + ramipril + atorvastatin has also been shown to be feasible and acceptable in patients with prevalent cardiovascular disease in a humanitarian setting in Lebanon (*19*).

A 2022 meta-analysis of 16 randomized trials (26 567 participants) evaluated the efficacy of fixed-dose combination therapy versus placebo or usual care as primary or secondary prevention of cardiovascular disease (*20*). This review included, a subgroup analysis based on country income level which showed that in low- and middle-income countries, fixed-dose combination therapy was associated with lower rates of major adverse cardiovascular events (RR 0.67, 95% CI 0.56 to 0.79) compared with high-income countries (RR 1.04, 95% CI 0.69 to 1.58). This difference is likely influenced by the background treatment rate of the comparator group.

Summary of evidence: harms

In primary prevention trials, fixed-dose combination therapy was shown to increase the risk of any adverse event by 21% compared with controls (11.6% versus 9.6%; RR 1.21, 95% CI 1.12 to 1.31; 15 randomized controlled trials; high-quality evidence). The applicants proposed that this may be a result of increased exposure to these medicines as a result of improved adherence. Most adverse events associated with fixed-dose combination therapy were mild and reversible, and were consistent with the known adverse events of the individual medicines (e.g. dizziness and muscle pain).

The findings from the individual participant data meta-analysis, which focused on patients with a primary prevention indication, support these results (*17*).

In secondary prevention trials, fixed-dose combination therapy increased the risk of adverse events by 7% (27.5% versus 25.9%; RR 1.07, 95% CI 0.99 to

1.15; eight randomized controlled trials; moderate-quality evidence). The quality of evidence was downgraded because of heterogeneity and the true effect may be influenced by the treatment rate in the comparator group.

Data from the SECURE trial of secondary prevention showed no significant difference in adverse events between the fixed-dose combination therapy group and the usual care group (*15*).

Discontinuation rates were similar between groups in the nine trials that reported this outcome (RR 1.05%, 95% CI 0.99 to 1.11).

The proposed fixed-dose combinations are contraindicated in pregnant or breastfeeding women, following the contraindications of the individual components.

WHO guidelines

The 2007 WHO pocket guidelines for assessment and management of cardiovascular risk recommends that all individuals with established coronary heart disease, cerebrovascular disease or peripheral vascular disease should receive treatment with blood pressure-lowering therapy, a statin and aspirin. Lifestyle advice should also be offered (e.g. smoking cessation, dietary changes, physical activity, weight control and alcohol intake) (*21*).

The 2016 HEARTS technical package for cardiovascular disease management in primary care provides information on evidence-based treatment protocols and risk-based management of cardiovascular disease. These include recommendations for the use of antihypertensive therapy, statins and anti-platelet therapy (*6*).

The 2021 WHO guidelines for the pharmacological treatment of hypertension in adults includes a strong recommendation for the use of thiazide and thiazide-like diuretics, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, or long-acting dihydropyridine calcium channel blockers as initial treatment for adults with hypertension requiring pharmacological treatment (strong recommendation; high-certainty evidence). The guidelines also include a conditional recommendation for combination therapy, preferably with a single-pill combination (to improve adherence and persistence) as initial treatment in adults with hypertension requiring pharmacological treatment and recommends that the medicines used in combination be chosen from the above-mentioned medicine classes (*22*).

Other current clinical practice guidelines

Statins and antihypertensive medicines are recommended for all individuals with a history of atherosclerotic cardiovascular disease in guidelines from various regions, including Australia (*23*), Brazil (*24*) Europe (*25*), Japan (*26*), the United States (*27*), and others, with additional support from the World Heart Federation (*28*). These medicines are also advised for individuals at high predicted risk of

incident atherosclerotic cardiovascular disease, particularly those with type 2 diabetes mellitus 40 years and older (*29*).

Antiplatelet therapy is also recommended for individuals with prevalent atherosclerotic cardiovascular disease, but there is no consensus yet on its use in primary prevention.

Costs/cost–effectiveness

The application included the results of a survey to collect primary data on market authorization, retail prices and affordability of fixed-dose combinations in 12 countries (Argentina, Bangladesh, Cameroon, Colombia, India, Iraq, Mauritius, Mexico, Nepal, Nigeria, Spain and Sweden). Fixed-dose combinations were stocked by private pharmacies in Argentina, India, Mauritius and Spain. None of the public pharmacies visited stocked any combination. Affordability was determined based on the WHO/Health Action International standards, which consider a medicine to be affordable if the cost of 1 month's supply is lower than the lowest daily wage of a government worker in that area. The findings are presented in Table 22.

Table 22
Price and affordability of fixed-dose combinations by country

Country	Fixed-dose combination	Price/ tablet, US$	Cost for 1 month supply, US$	Minimum daily wage, US$	Number of days' wages
Proposed formulations					
India	ASP + ATO + RAM	0.04	1.26	5.41	0.23
India	ASP + SIM + RAM + ATE + HCTZ	0.34	10.14	5.41	1.87
Spain	ASP + ATO + RAM	0.74	22.20	32.66	0.68
Other formulations					
Argentina	ROS + CAN + HCTZ	0.31	9.30	7.64	1.21
India	MET + ATO + RAM	0.13	4.04	5.41	0.75
India	ASP + ATO + RAM + MET	0.12	3.60	5.41	0.67
India	LOS + AT0 + ASP + ATE	0.17	5.22	5.41	0.96
Mauritius	ATP + PER + AML	0.88	26.46	9.52	2.78

AML: amlodipine; ASP: aspirin; ATE: atenolol; ATO: atorvastatin; CAN: candesartan; HCTZ: hydrochlorothiazide; LOS: losartan; MET: metoprolol; PER: perindopril; RAM: ramipril; ROS: rosuvastatin; SIM: simvastatin.

A 2020 systematic review analysed 24 studies that evaluated the cost–effectiveness of fixed-dose combinations for primary and secondary prevention of cardiovascular disease (*30*). Most of the included studies were conducted in European countries, with three conducted in Asia. Four multicountry studies were conducted. Three quarters of the studies analysed cost–effectiveness from a health care perspective, and the remainder from payer or societal perspectives. Across all studies, incremental cost–effectiveness ratios ranged from US$ 24 to US$ 31 000. Fourteen studies investigated fixed-dose combination therapy as primary prevention. The systematic review found that fixed-dose combination therapy was considered cost-effective in five studies, including two in which it was determined to be dominant (i.e. more effective and cost-saving). In two studies, fixed-dose combination therapy was dominated (i.e. less effective and higher cost) or not cost-effective. Twelve studies investigated fixed-dose combination therapy as secondary prevention. The review found that fixed-dose combination therapy was cost-effective in six studies, and dominant in a further four studies compared with usual care with multiple monotherapies. One study concluded that fixed-dose combination therapy was not cost-effective. A study in which fixed-dose combination therapy was compared with no treatment found the intervention to be cost-effective. The key determinants of cost–effectiveness for fixed-dose combination therapy were the price of the combination, followed by the effect of age and the risk for cardiovascular disease.

A 2021 economic analysis based on the International Polycap Study 3 (TIPS-3) examined the cost implications of fixed-dose combinations as a primary prevention strategy (*31*). Over the 4.6 years of the trial, the use of fixed-dose combinations led to a higher mean total cost per patient in lower middle- and upper middle-income countries, but it was cost-neutral (dominant) in high-income countries. The difference in costs per patient between fixed-dose combinations and placebo over the trial period was US$ 291 in lower middle-income countries, US$ 1068 in upper middle-income countries and US$ 48 in high-income countries. These variations were influenced by higher acquisition costs in low- and middle-income countries. Cost-savings from fewer procedures and hospitalizations associated with fixed-dose combination therapy were insufficient to offset acquisition costs in lower income settings. Overall, the authors considered that fixed-dose combination therapy was affordable in all income groups when estimated using monthly household capacity to pay or a threshold of 4% of the gross national income per capita.

A cost–effectiveness analysis for the proposed fixed-dose combination of aspirin + atorvastatin, + ramipril versus usual care with individual monotherapies from a Portuguese payer perspective reported an incremental cost–effectiveness ratio of €5130 per life year gained for the overall population. The incremental cost–utility ratio was €5332 per quality-adjusted life year (QALY) gained for the overall

population. At a willingness-to-pay threshold of €30000 per QALY gained, the study the chance of fixed-dose combination therapy being cost-effective was 76.1% and the chance of it being cost-saving compared with usual care was 27.8% (*32*).

Availability

The application reported that the proposed fixed-dose combinations have variable authorization for marketing and are available in more than 70 countries worldwide.

Committee recommendations

The Expert Committee acknowledged the substantial public health burden of cardiovascular disease, primarily ischaemic heart disease and stroke, which continues to rise in many settings and is the leading cause of death globally. The Committee noted that the current use of medicines to prevent and control atherosclerotic cardiovascular disease, including antiplatelet therapy and cholesterol- and blood pressure-lowering medicines, has remained low over the past 2 decades, despite high-quality evidence of their benefits as separate medicine classes. The Committee considered that small, incremental effects on cardiovascular outcomes and mortality are relevant from a public health perspective as when applied to the global population these benefits can be substantial.

The Committee recalled the previous applications for inclusion of fixed-dose combinations and commended the efforts of scientists and policy-makers around the world in accumulating evidence to better understand the merits of these formulations in primary and secondary prevention of cardiovascular disease. The Committee considered that the totality of the evidence presented both previously and built upon in the current application was substantial, including multiple large randomized trials, and demonstrated that fixed-dose combination therapy reduced the risk of fatal and non-fatal major cardiovascular adverse events. The Committee also noted that the available data indicate that fixed-dose combination therapy was associated with improvements in adherence and quality of life.

The Committee noted the concerns expressed by previous Expert Committees about cost and cost–effectiveness and considered that these concerns had been satisfactorily addressed, noting that fixed-dose combination therapy has been found to be cost-effective in multiple studies, and also noting the increasing availability of generic formulations in several countries and improved affordability. The Committee considered that the cost of fixed-dose combinations should be equal to or ideally lower than the sum of the corresponding component monotherapies. The Committee considered that the fixed-dose combinations could be proposed for WHO prequalification to ensure that products met

acceptable standards of quality, safety and efficacy. This process could facilitate access in low- and middle-income countries where national regulatory capacity may be lacking.

The Committee considered potential risks associated with using fixed-dose combination therapy as initial treatment instead of multiple component monotherapy and noted the need to be able to adjust doses and in some cases to tailor treatment to individual patients depending on comorbidities, contraindications and other individual patient factors. The Committee therefore emphasized that the ongoing availability of single agent cardiovascular medicines was critical to allow treatment modification where necessary, and that combination products should not displace single components at the country level. The Committee commended the efforts of WHO in developing the HEARTS technical package for cardiovascular disease management and the guidelines for pharmacological treatment of hypertension. The Committee recommended that WHO evaluate the potential benefits of developing guidance specific for the clinical use and national implementation of fixed-dose combinations for cardiovascular disease prevention to supplement existing guidance and support health professionals prescribing these formulations.

Based on these considerations, the Expert Committee recommended the inclusion of the three fixed-dose combinations of cardiovascular medicines (acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide; acetylsalicylic acid + atorvastatin + ramipril; and atorvastatin + perindopril + amlodipine) on the core list of the EML for use in the primary and secondary prevention of atherosclerotic cardiovascular diseases. Components of the combinations should be listed with a square box, indicating other medicines within the respective pharmacological classes represent therapeutic alternatives, consistent with the current square box listings for hydrochlorothiazide, antihypertensive medicines and statins.

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Section 13: Dermatological medicines

Sunscreen – addition – EML and EMLc

Sunscreen	ATC code: D02BA

Proposal

Addition of broad-spectrum sunscreen to the core list of the EML and EMLc for the prevention of skin cancer in people with albinism.

Applicant

United Nations Independent Expert on the Enjoyment of Rights by Persons with Albinism

The Global Albinism Alliance

WHO technical department

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical team advised that based on the available evidence, it supported the inclusion of topical sunscreen in multiple dosage forms on the EML and EMLc to reduce the risk of skin cancer in the target population.

EML/EMLc

EML and EMLc

Section

13 Dermatological medicines

Dose form(s) & strengths(s)

Topical dosage forms (cream, lotion, stick, gel, oil, butter, paste, ointment and spray)

Sun protection factor (SPF) 50+

Core/complementary

Core

Individual/square box listing

Individual

Background

Currently, there are no sun protection agents on the EML or EMLc.

P-aminobenzoic acid (PABA) and benzophenones with SPF 15 were first added to the EML in 1989. In 1991, zinc oxide was added as an agent to prevent skin cancer induced by ultraviolet (UV) light in people whose occupations expose them to sun. However, in 1995 p-aminobenzoic acid was removed. In 1997, the benzophenones and zinc oxide were replaced by a broad-spectrum topical sun protection.

In 2005, all sun protection agents were removed from the EML. At the time, the Committee noted the high public health relevance but justified removal on the basis that sunscreens were not normally provided by public facilities (*1*).

Public health relevance

Albinism is a rare, non-contagious, genetic congenital condition characterized by decreased or absent pigmentation (i.e. lack of melanin pigment) in the hair, skin and/or eyes. Albinism occurs worldwide regardless of ethnicity or sex. The incidence of albinism in western societies has been documented to range from 1:14 000 to 1:17 000. In African countries, it is said to range between 1:1500 and 1:15 000 (*2*). A high incidence of albinism ranging from 1:28 to 1:6500 has also been reported in indigenous communities in the Americas (*3*).

Due to the reduced or absent melanin in the skin, patients with albinism are highly susceptible to the harmful effects of UV radiation and are at increased risk of acute and chronic actinic damage to their skin, in particular solar elastosis, actinic keratosis and skin cancers (*4–6*). Exposure of people with albinism to the sun without sun protection is a cause of premature death from skin cancer, in addition to causing high morbidity and reduced quality of life due to premature skin photo-ageing, multiple skin lesions and scarring following surgical excision of malignant skin lesions. For example, people with albinism in Africa (where there is higher UV radiation) are reportedly 1000 times more likely to develop squamous cell carcinoma than the general population (*7*). Other studies show that persons with albinism predominantly develop skin cancers by the time they are 20 and do not commonly live beyond the age of 30 years (*8,9*). The use of sunscreen is important for all persons with albinism regardless of geographic location, including regions with relatively low incidence of UV radiation (*10*).

The application also provided information on the public health relevance in the context of human rights, government/legislation and nongovernmental organizations.

Human rights

Access to sunscreen by persons with albinism is a right in terms of Article 12 of the International Covenant on Economic, Social and Cultural Rights (*11*), which

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enshrines the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, as well as Article 25 of the Convention of the Rights of Persons with Disabilities (*12*), particularly Article 25(b) which requires states to, "provide those health services needed by persons with disabilities specifically because of their disabilities". The UN Committee on the Rights of Persons with Disabilities and the UN Independent Expert on albinism have recognized the visual impairment and lack of melanin in persons with albinism as disabilities (*13,14*). Providing access to sunscreen for persons with albinism also aligns with the UN Sustainable Development Goal to ensure healthy lives and promote well-being for all at all ages (SDG 3).

Government and legislation

Government programmes and existing laws support the public health imperative relative to sunscreen as an essential medicine for persons with albinism. Several countries (e.g. Brazil and Uganda) have provided subsidies for people with albinism to obtain sunscreen The Executive Council of the African Union adopted a Plan of Action on Ending Attacks and Discrimination against People with Albinism in July 2019. Section 4.3(a) of the implementation matrix for the plan of action calls on state members of the African Union to, "ensure access to health support, services and health goods such as visual aids and sunscreen for all persons with albinism particularly in rural areas and with emphasis on skin cancer prevention and treatment as well as specialist services for low vision and dermatological care" (*15*).

Nongovernmental organizations

Some nongovernmental organizations have recognized the public health imperative for persons with albinism by creating programmes to meet their need for sun protection. Three nongovernmental organizations serving people with albinism in various countries in Africa, and whose programmes include local production of sunscreen, are Beyond Suncare, Standing Voice, and the Pierre Fabre Foundation.

Summary of evidence: benefits

The topical application of broad-spectrum sunscreens is recommended as a safe adjunct measure in protecting human skin from UV radiation when other protection measures (e.g. clothing or sun avoidance) cannot be used or are insufficient. In the context of persons with albinism, sunscreen use is considered part of healthy sun protection practices (*16*).

Research has shown the benefits of using sunscreen in reducing the incidence of skin cancer (*17*).

A randomized trial of 1621 adults in Australia evaluated daily sunscreen application (SPF 15+) versus no daily sunscreen for the prevention of squamous

cell and basal cell carcinomas (*18*). After 4.5 years of follow-up, no significant differences were reported in the incidence of first new skin cancers between the daily sunscreen and no daily sunscreen groups: basal cell carcinoma 2588 versus 2509 per 100 000; rate ratio (RR) 1.03, 95% confidence interval (CI) 0.73 to −1.46 and squamous cell carcinoma 876 versus 996 per 100 000; RR 0.88, 95% CI 0.50 to 1.56). In terms of the number of tumours, no effect was observed on the incidence of basal cell carcinoma by sunscreen use. However, the incidence of squamous cell carcinoma was significantly lower in the daily sunscreen group than the no daily sunscreen group (1115 versus 1832 per 100 000; RR 0.61, 95% CI 0.46 to 0.81). After a further 8 years of follow-up, a non-significant decrease in basal-cell carcinoma tumour rates was found in the daily sunscreen group compared with the no sunscreen group. For squamous-cell carcinoma tumour rates, a significant decrease was observed in the daily sunscreen group compared with the no sunscreen group (RR 0.62, 95% CI 0.38 to 0.99) (*19*).

A 2022 study using data from the United States National Health and Nutritional Examination Survey (2015–2016) evaluated the association of sunscreen use, sun avoidance and wearing of protective clothing with skin cancer prevalence (*20*). Sunscreen use was the only one of the three interventions that showed a statistically significant reduction in skin cancer prevalence (odds ratio (OR) 3.75, 95% CI 1.78 to 8.89).

A retrospective study compared the effects of sun exposure on the occurrence of skin cancers in 22 participants with albinism and 30 without albinism (*21*). The average ages of participants with and without albinism with skin cancers were 34.6 years and 65.1 years, respectively. Of the participants with skin cancers, about 43% those with albinism and 80% of those without albinism reported prolonged sun exposure. Of note, among participants with albinism who had used sunscreen since childhood, 2/19 (10.5%) developed skin cancer, while of participants with albinism who did not use sunscreen, 20/27 (74.1%) developed skin cancer.

A 2021 expert panel review investigated the effect of solar wavelength according to skin phototype and dermatoses, and proposed the need for tailoring recommendations for sunscreen type accordingly, as well as taking into consideration geographical latitude and altitude (*22*). For example, protection against UVB radiation is especially important for light skin as there is a high risk of sunburn, DNA damage and skin cancers. Darker skin may be naturally better protected against UVB but is more prone to hyperpigmentation induced by visible light and UVA radiation. For the prevention of skin cancers, the expert panel recommended daily use of sunscreen with high SPF (50+) and good UVA protection factor, and a SPF to UVA protection factor ratio between 1 and 3.

Summary of evidence: harms

Concerns about the toxicity of UV filters and reduced vitamin D synthesis related to the use of sunscreen have been raised. The management of sunscreens must therefore balance their essential protective effect against the potential toxicity of the UV filters for humans and the environment.

Photoallergic reactions are the most common adverse effect of topical sunscreens. This effect is particularly associated with the benzophenone class of organic UV filters. Contact dermatitis and photoallergy have also been reported with ethylhexyl methoxycinnamate and octocrylene (*23*). Allergenic effects are rare with mineral UV filters (e.g. titanium dioxide), but concerns have been raised about systemic absorption of micronized particles (*23*). A review of titanium dioxide in nanoparticle form found no evidence of carcinogenicity, mutagenicity or toxicity following dermal exposure. However, there are restrictions in Europe on the use of nanoparticle titanium dioxide formulations that can lead to lung exposure through inhalation (e.g. spray and powder products) (*24*).

A quasi-experimental study conducted during winter in Brazil evaluated vitamin D synthesis with suberythemal sun exposure in 95 adults (*25*). Participants were randomized to one of three groups: use of SPF 30 sunscreen on the face, neck and chest (*n* = 64), no sunscreen (*n* = 10) or no sun exposure (*n* = 21). No difference was found between the sunscreen and no sunscreen groups for change in vitamin D level from baseline to 24 hours after sun exposure (5.4 ng/mg, 95% CI 4.4 to 6.5 ng/mg versus 4.1 ng/mg, 95% CI 2.5 to 6.0 ng/mg, $P < 0.01$).

A literature review of sunscreen photoprotection and vitamin D status identified nine controlled studies on the effect of daily/recreational sunscreen use on vitamin D synthesis (*26*). Of the nine studies identified, seven showed no change in serum vitamin D with sunscreen use. Two studies found a reduction in vitamin D levels with sunscreen use. However, these studies did not consider important factors that may have influenced the outcome, such as personal UV exposure, sunscreen application thickness and exposed body surface area. The authors of the review concluded that broad-spectrum sunscreen use was unlikely to compromise vitamin D status in healthy populations.

Sunscreens may cause environmental harm (*17*). In this regard, some regulatory agencies have updated the indications, doses, labelling and testing of over-the-counter sunscreen agents (*27*).

WHO guidelines

WHO guidelines for the use of sunscreen are not currently available. WHO recommends the use of broad-spectrum sunscreen on skin areas that cannot be covered by clothes, as one of a series of recommended measures to protect against excessive UV exposure (*28*).

Costs/cost–effectiveness

Skin cancer is a significant cost and population burden for many countries and expenditure will grow as incidence increases. Public investment in skin cancer prevention and early detection programmes suggest health and economic benefits (*29*).

While many persons with albinism are aware of the need to protect themselves from the harmful effects of UV radiation, studies have shown that they are prevented from doing so due to the cost of sunscreen, as well as cost of travel and travel distance to enable them to obtain sunscreen (*30*).

Studies have concluded that systematic sunscreen use at a population level will prevent substantial numbers of new skin lesions and reduce the costs of treatment and loss of life (*31–33*). This is especially relevant for persons with albinism because of their higher risk of developing skin lesions.

An Australian study evaluated daily versus discretionary sunscreen use, considering use of health-care resources, costs and health outcomes of basal-cell carcinoma and squamous cell carcinoma prevention (*33*). From a societal perspective, over 5 years, the net costs for daily versus discretionary sunscreen use were US$ 329 149 and US$ 222 700, respectively. The cost for the daily sunscreen group was offset in part by reduced costs for medical treatment as a result of skin cancers and actinic keratoses avoided. From the Australian government perspective (as funder of medical care for treatment of skin cancers), daily sunscreen use was cost-saving compared with discretionary sunscreen use.

Availability

Sunscreens are available as personal care products or over-the-counter medicines in most middle- and high-income countries. Definitions and labelling standards are set by regulatory agencies.

Committee recommendations

The Expert Committee acknowledged that people with albinism and xeroderma pigmentosum were a subgroup of the general population that has a significantly higher risk of skin cancer due to the harmful effects of UV radiation on their unprotected skin and for whom use of broad-spectrum sunscreen is an important preventive intervention. The Committee similarly acknowledged the public health relevance and effectiveness of sunscreen in preventing skin cancer in both the general population and persons with albinism. The Committee agreed that globally promoting the use of sunscreens, as well as other sun-protection and sun-avoidance strategies and behaviours, was a crucial preventive measure to reduce the incidence and prevalence of skin cancers, including melanoma. The Committee noted that the burden of disease of such cancers is increasing and

that their treatment is associated with significant costs for both individuals and health systems, especially in low- and middle-income settings. The Committee recognized the importance of effective preventive interventions in addressing this growing public health burden.

The Committee recalled that broad-spectrum sun protection products had previously been included on the EML for the general population but were recommended for removal in 2005. In making this recommendation, the 2005 Expert Committee acknowledged the high public health relevance of topical sun protection agents for the prevention of skin cancer but noted that "sunscreens are normally not provided by public facilities and that provision through such sources was not needed."

However, the Committee noted that many different sunscreen products exist on the global market, containing a wide variety of organic agents (which absorb UV radiation) and/or inorganic agents (which reflect or scatter UV radiation). Sunscreen products also vary widely in their sun protection factor rating. Furthermore, the Committee noted that national standards and regulations of sunscreen products also vary considerably between countries – in some settings, they are regulated as therapeutics, while in others they are regulated as non-therapeutic so-called cosmetic products.

The Committee considered that before being able to recommend sunscreen products for inclusion on the Model Lists, it would be necessary to define relevant standards and specifications for therapeutic (as distinct from cosmetic) sunscreen products protecting against both UVA and UVB rays (broad spectrum). This would include details of specific active ingredients and their concentration and the range of sun protection factor rating. This information needs to be supported by evidence and implications for labelling standards to provide clear and reliable guidance for countries for selection and procurement of the most appropriate sunscreen products.

The Expert Committee therefore did not recommend the inclusion of sunscreen on the EML and EMLc for the prevention of skin cancer in people with albinism or xeroderma pigmentosum at this time. The Committee recommended that WHO undertake the necessary work to inform a resubmission for the consideration of sunscreen products by the 2025 Expert Committee.

One member of the Expert Committee held a different opinion in relation to this recommendation and was in favour of the inclusion of sunscreen on the Model Lists for the prevention of skin cancer in people with albinism and xeroderma pigmentosum. It was this person's opinion that the use of sunscreen in this extremely vulnerable subgroup of people represents an essential preventive public health intervention for skin cancer in low- and middle-income countries, and that EML listing would help to ensure availability of quality-assured sunscreen products.

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13.4 Medicines affecting skin differentiation and proliferation

Methotrexate – new indication – EML and EMLc

Methotrexate	ATC code: L04AX03

Proposal

Inclusion of methotrexate tablets on the complementary list of the EML and EMLc for the new indication of treatment of severe psoriasis.

Applicant

International League of Dermatological Societies

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

13.4 Medicines affecting skin differentiation and proliferation.

Dose form(s) & strengths(s)

Tablet: 2.5 mg, 10 mg (as sodium)

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Methotrexate has not previously been evaluated for inclusion on the Model Lists for the treatment of psoriasis.

Methotrexate, in oral and parenteral formulations, is included in the EML and EMLc for use in the treatment of various cancers. Oral methotrexate is included for use in the treatment of rheumatoid arthritis and juvenile idiopathic arthritis.

A separate application to the 2023 Expert Committee meeting requested inclusion of subcutaneous methotrexate on the EML and EMLc for the treatment of chronic inflammatory autoimmune conditions, including psoriasis, in patients not responding to maximum tolerable doses of oral methotrexate.

The Model Lists currently include only topical treatments for psoriasis: corticosteroids, calcipotriol, coal tar and salicylic acid solutions.

Public health relevance

According to the 2019 Global Burden of Disease study, psoriasis was reported to affect almost 41 million people globally and was responsible for 0.14% of global disability-adjusted life years (*1*). People with psoriasis have a reduced quality of life similar to or worse than those with other chronic diseases (*2,3*). A family history of psoriasis is common and genetic influences are thought to play a major role in the expression of disease. Psoriasis can present at any age but the mean age at onset for the first presentation of psoriasis ranges from 15 to 20 years, with a second peak occurring at 55 to 60 years (*2,4*).

Summary of evidence: benefits

A 2003 randomized trial compared methotrexate and ciclosporin in 88 adults with moderate-to-severe chronic plaque psoriasis (*5*). Participants were randomized to receive methotrexate 15 mg/week (initial dose, *n* = 44) or ciclosporin 3 mg/kg a day (*n* = 44). The primary outcome was the difference between treatment groups in psoriasis area and severity index (PASI) scores from baseline to 16 weeks. No significant difference was found between treatment groups. The mean PASI score decreased from 13.4 to 5.0 in the methotrexate group and from 14.0 to 3.8 in the ciclosporin group (absolute mean difference 1.3, 95% confidence interval (CI) −0.2 to 2.8). The physician's global assessment of the extent of psoriasis, the time to and the rates of remission, and the quality of life were similar in the two groups.

A 2008 randomized controlled trial also compared methotrexate and ciclosporin for the treatment of moderate-to-severe plaque psoriasis (*6*). Of 84 patients randomized, 68 received treatment and were included in the analysis. Participants were randomized to receive methotrexate 7.5 mg/week (initial dose, *n* = 37) or ciclosporin 3 mg/kg a day (*n* = 31). The primary outcome was the mean change in PASI score from baseline to 12 weeks. The secondary outcome was quality of life, measured by the Dermatology Life Quality Index and the 36-item Short Form Health Survey (SF-36). The mean PASI score decreased from 14.1 to 5.6 in the methotrexate group and from 15.5 to 3.6 in the ciclosporin group. The difference between treatment groups was statistically significant (*P* = 0.03). The methotrexate group showed significantly greater improvement in physical functioning on the SF-36, while no significant difference between treatment groups was observed for the Dermatology Life Quality Index.

A meta-analysis of 11 studies, involving 728 participants receiving methotrexate, evaluated treatment efficacy of methotrexate compared with placebo for psoriasis (*7*). The outcome assessed was the percentage of patients achieving a 75% in PASI score (PASI 75) from baseline to 12 or 16 weeks. The

pooled estimate for PASI 75 in patients treated with methotrexate was 45.2% (95% CI 34.1% to 60.0%) compared with a calculated PASI 75 of 4.4% (95% CI 3.5% to 5.6%) for placebo (relative risk 10.2, 95% CI 7.1 to 14.7). However, there was high heterogeneity between studies and a number of study limitations were noted (e.g. small patient numbers, different study designs and non-uniform outcome reporting).

A retrospective longitudinal study in India analysed data for 197 patients with psoriasis treated with methotrexate from 1981 to 2000 (*8*). The study protocol involved treatment with weekly oral methotrexate at full therapeutic dose during episodes of peak disease activity and tapering dose in response to improvement. Use of topical treatment and natural ultraviolet light exposure were encouraged. In total 243 cycles of methotrexate were given. PASI 75 was achieved in 88% of patients in 8.5 weeks (standard deviation (SD) 5.1 weeks) and PASI 90 was achieved in 84.3% of patients in 11.8 (SD 7.4) weeks. The mean cumulative dose was 709.3 mg (SD 369.2 mg) and the mean duration of follow-up was 16.5 months (SD 9.1 months).

More recently, randomized trials of biological medicines for severe psoriasis have included cohorts of patients treated with methotrexate and provide data on the effectiveness of methotrexate.

The CHAMPION study compared adalimumab with methotrexate in patients with moderate-to-severe chronic plaque psoriasis (*9*). Patients were randomized to receive subcutaneous adalimumab (80 mg at week 0, then 40 mg every 2 weeks, $n = 108$), oral methotrexate (7.5 mg weekly, increased as needed and tolerated to 25 mg weekly, $n = 110$) or placebo ($n = 53$). The primary efficacy endpoint was the proportion of patients achieving at least PASI 75 after 16 weeks. A PASI 75 response was achieved in 35.5% of patients in the methotrexate group, compared with 79.6% and 18.9% of patients in the adalimumab and placebo groups, respectively.

A randomized, double-blind, multicentre, phase III trial compared briakinumab with methotrexate in patients with moderate-to-severe psoriasis (*10*). Patients were randomized to receive subcutaneous briakinumab 200 mg at weeks 0 and 4 then 100 mg every 4 weeks thereafter ($n = 154$) or oral methotrexate 5 to 25 mg weekly ($n = 163$) for 52 weeks. Primary endpoints were the percentages of patients achieving PASI 75 at weeks 24 and 52, and a score of 0 (no apparent disease) or 1 (minimal disease) on the physician's global assessment at weeks 24 and 52. At week 24, 39.9% and 81.8% of patients in the methotrexate and briakinumab groups, respectively, group achieved PASI 75, and 34.4% and 80.5% of patients in the methotrexate and briakinumab groups, respectively, had a physician's global assessment of 0 or 1. At week 52, the corresponding percentages were 23.9% and 66.2% for PASI 75 and 20.2% and 63.0% for physician's global assessment.

The RESTORE1 study was an open-label randomized trial comparing infliximab with methotrexate in patients with moderate-to-severe plaque psoriasis (*11*). Patients were randomized to receive intravenous infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22 (*n* = 653) or oral methotrexate 15 mg weekly for 6 weeks, then increased to 20 mg weekly in patients with poor response (*n* = 215). The primary efficacy endpoint was PASI 75 response at week 16. At week 16, 42% and 78% of patients in the methotrexate and infliximab groups, respectively, had achieved PASI 75.

Randomized trials of methotrexate for psoriasis in children are lacking. No randomized controlled trials have evaluated the use of methotrexate in children with psoriasis.

A single-centre, longitudinal, long-term, observational subset analysis of data from a Dutch registry recorded the results of oral therapy with methotrexate in 25 children aged 6 to 17 years with plaque-type psoriasis (*12*). Primary endpoints were percentages of patients with PASI 75 at weeks 12 and 24. The primary endpoint was achieved in 4.3% and 33.3% of patients at weeks 12 and 24, respectively. At weeks 36 and 48, the percentages of patients achieving PASI 75 were 40% and 28.6%, respectively. Observed median PASI decreased significantly from 10.0 to 4.3 (mean difference (MD) 7.7, 95% CI 5.2 to 10.3) from baseline to 24 weeks. Body surface area involvement also decreased significantly from 11.0 to 2.6 (MD 9.8, 95% CI 5.8 to 13.9) from baseline to 24 weeks. A significant decrease was also seen in children's dermatology life quality index scores from 9.0 to 3.8 (MD 5.4, 95% CI 3.4 to 7.4).

A retrospective study in India analysed records of patients aged 2 to 14 years treated with methotrexate at a psoriasis clinic from 1993 to 2006 (*13*). Among 24 patients analysed, 22 achieved PASI 75. The mean time to control of disease (i.e. 50% reduction in PASI) was 5.1 weeks. The maximum dose of methotrexate ranged from 7.5 mg to 20 mg a week and the mean duration of treatment was 5 months (range 2 to 16 months).

Summary of evidence: harms

The safety profile of methotrexate is well established from its use in many other indications. Known adverse events include gastrointestinal disorders, hepatotoxicity, pneumonitis, haematological disorders, infections and nephrotoxicity (*14*).

Severe harms are rare but when encountered are most often secondary to myelosuppression.

Methotrexate is excreted by the kidneys and reduced renal function is associated with an increased risk of toxicity (*15*). Renal function should be monitored and dose reduction considered in patients with renal impairment.

Additional evidence

A 2022 Cochrane systematic review and network meta-analysis (167 randomized controlled trials, 58 912 participants) of systemic treatment for chronic plaque psoriasis was identified during the application review process (*16*).

The network meta-analysis found that methotrexate was superior to placebo for the outcome of PASI 90 (risk ratio (RR) 6.97, 95% CI 1.42 to 34.34; 388 patients, five studies, moderate certainty of evidence). Results were similar for other efficacy outcomes, such as PASI75, but they should be interpreted with caution given the limited number of studies (participants) in the network.

Direct evidence reported that the risk of serious adverse events was significantly lower for methotrexate compared with placebo (RR 0.16, 95% CI 0.03 to 0.88) and significantly higher for infliximab compared with methotrexate (RR 2.41, 95% CI 1.04 to 5.59). When both direct and indirect evidence was assessed, the risk of serious adverse events was significantly lower for participants on methotrexate compared with all interventions, except bimekizumab, certolizumab, netakimab, deucravacitinib and apremilast.

Evidence on the safety of methotrexate for use in children was reported in an international, multicentre, retrospective study evaluating safety of systemic treatments for psoriasis in children, identified during the application review process (*17*). Methotrexate was the most commonly used systemic treatment for moderate-to-severe psoriasis in children in both North America and Europe (about 70% of participants). The most frequently reported adverse effects of methotrexate were gastrointestinal (nausea and dyspepsia) and increased transaminase, while injection site reactions and infections were more frequent with biological medicines.

WHO guidelines

WHO guidelines for the treatment of psoriasis are not currently available.

Costs/cost–effectiveness

A 2015 study sought to estimate the cost–efficacy of systemic psoriasis treatments approved in the United States (*18*). Numbers needed to treat were obtained following a literature review of studies of systemic psoriasis treatments reporting PASI 75 as the primary outcome. Calculation of financial costs included medicine acquisition cost, medical visit costs and laboratory costs. Cost per month of treatment per number needed to treat to achieve PASI 75 was reported for each medicine. Methotrexate had the lowest adjusted monthly costs per number needed to treat to achieve PASI 75 at US$ 794 to US$ 1503.

Availability

Methotrexate has wide regulatory approval for treatment of severe psoriasis. Methotrexate tablets are available globally, including in generic brands. They are already included on national essential medicines lists in many countries.

Committee recommendations

The Expert Committee acknowledged the global burden of psoriasis and the public health need for effective treatments for this condition. To date, only topical therapies for psoriasis have been included on the Model Lists. The Committee acknowledged that topical therapy alone may be inadequate to effectively treat moderate-to-severe forms of the disease.

The Committee noted that methotrexate has been used in the treatment of psoriasis and other chronic inflammatory conditions for many years and the available evidence supported its effectiveness in achievement of PASI 75. The Committee also considered that methotrexate has a generally favourable and well known safety profile, although it has some risks that required monitoring and potential dose adjustment.

The Committee noted that methotrexate is recommended in several national and international guidelines for psoriasis as the first choice for systemic treatment. The Committee also noted that methotrexate is already included on national essential medicines lists and appeared to be available and affordable in most settings.

The Expert Committee therefore recommended the addition of methotrexate tablets to the complementary list of the EML and EMLc for second-line treatment of patients with psoriasis, given the favourable balance of desirable to undesirable effects.

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Ustekinumab – addition – EML

Ustekinumab	ATC code: L04AC05

Proposal

Addition of ustekinumab on the core list of the EML for the treatment of severe psoriasis.

Applicant

International League of Dermatological Societies

WHO technical department

Not applicable

EML/EMLc

EML

Section

13.4 Medicines affecting skin differentiation and proliferation

Dose form(s) & strengths(s)

Injection (subcutaneous): 45 mg/0.5 mL, 90 mg/mL in vial or prefilled syringe

Core/complementary

Core

Individual/square box listing

Individual

Background

Ustekinumab has not previously been evaluated for inclusion on the Model Lists for this indication.

Public health relevance

According to the 2019 Global Burden of Disease study, psoriasis was reported to affect almost 41 million people globally and was responsible for 0.14% of global disability-adjusted life years (*1*). People with psoriasis have a reduced quality of life similar to or worse than those with other chronic diseases (*2,3*). A family history of psoriasis is common and genetic influences are thought to play a major role in the expression of disease. Psoriasis can present at any age but the mean age at onset for the first presentation of psoriasis ranges from 15 to 20 years, with a second peak occurring at 55 to 60 years (*2,4*).

Summary of evidence: benefits

A 2017 Cochrane systematic review and network meta-analysis of 109 randomized trials (39 882 participants) compared the efficacy and safety of non-biological systemic agents, small molecules, and biological agents in adults with moderate-to-severe psoriasis (*5*). Nineteen treatments were compared and ranked according to their effectiveness, measured by Psoriasis Area and Severity Index (PASI) 90 score, and acceptability. Ranking analysis showed ustekinumab to be ranked sixth for PASI 90 and eighth for serious adverse events, when compared with placebo. The authors noted that the most effective treatments also had more serious adverse events than other treatments. On balance, it was considered that ustekinumab, infliximab and certolizumab had the better compromise between efficacy and acceptability of the treatments evaluated. The evidence considered was limited to induction therapy, with outcomes measured between 12 and 16 weeks after randomization; longer-term outcomes were not evaluated.

An updated version of this review included 167 randomized trials (58 912 participants) (*6*). The updated review included seven randomized controlled trials comparing ustekinumab with placebo, and 11 randomized controlled trials comparing ustekinumab with active comparators (etanercept, secukinumab, ixekizumab, risankizumab and brodalumab). At the medicine class level, all classes of medicines performed better than placebo for the outcome of the proportion of patients achieving a PASI 90 response. Active treatment comparisons showed that biological agents, including ustekinumab, performed better than non-biological agents for the proportion of patients achieving a PASI 90 response. Overall, there was high-certainty evidence that the most effective drugs compared with placebo for achieving a PASI 90 response were infliximab, bimekizumab, ixekizumab and risankizumab. Of 20 medicines evaluated, ustekinumab was ranked ninth for PASI 90 response and thirteenth for serious adverse events.

PHOENIX 1 was a randomized, double-blind, placebo-controlled phase III trial evaluating the efficacy and safety of ustekinumab in 766 adult participants with moderate to severe psoriasis (*7*). Participants were randomly assigned to receive ustekinumab 45 mg or 90 mg at weeks 0 and 4 then every 12 weeks thereafter, or placebo at weeks 0 and 4, followed by crossover to ustekinumab from week 12. The primary endpoint was the proportion of participants achieving PASI 75 at week 12. The proportions of participants achieving PASI 75 were 67.1%, 66.4% and 3.1% in the 45 mg, 90 mg and placebo groups, respectively. Long-term response (PASI 75 at weeks 28 and 40) was achieved by 150 and 172 participants in the 45 mg 90 mg groups, respectively. Of these, 162 participants were randomly assigned to maintenance ustekinumab and 160 to withdrawal. Participants receiving maintenance ustekinumab maintained a PASI 75 response to at least 1 year better than those who were withdrawn from treatment.

PHOENIX 2 was a randomized, placebo-controlled, double-blind, multicentre, phase III trial evaluating the efficacy and safety of ustekinumab in 1230 adult patients with moderate to severe psoriasis (8). Patients were randomly assigned to receive ustekinumab 45 mg or 90 mg at weeks 0 and 4 then every 12 weeks thereafter, or placebo. Participants achieving a partial response of between 50% and 75% improvement from baseline were re-randomized at week 28 to ustekinumab every 12 weeks or to continue dosing every 8 weeks. The primary endpoint was the proportion of patients achieving at least PASI 75 at week 12. The proportions of patients achieving the primary endpoint were 66.7%, 75.7% and 3.7% in patients receiving ustekinumab 45 mg, 90 mg and placebo, respectively. More partial responders at week 28 who received ustekinumab 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. No difference was seen in response to changes in dosing interval observed in partial responders who received ustekinumab 45 mg.

Similar results to those described above have been reported in other studies of ustekinumab in China (9), Japan (10) and Republic of Korea (11).

The application also presented summaries of the findings of other network meta-analyses (12), comparative randomized trials (13–15) and observational studies (16–18) that included ustekinumab.

Analyses of registry data have shown ustekinumab to have a higher drug survival (a marker for treatment sustainability in chronic diseases) as a first-line therapy for psoriasis compared with the tumour necrosis factor-alfa inhibitors infliximab, etanercept and adalimumab (19–21). Ustekinumab is also associated with less non-adherence to treatment (22).

Summary of evidence: harms

Adverse events reported with the use of ustekinumab by at least 1% of treated patients include nasopharyngitis, upper respiratory tract infection, headache, fatigue, diarrhoea, back pain, pruritus, injection-site erythema and depression (23).

Adverse reactions that occurred at rates less than 1% in the controlled period of the PHOENIX 1 and PHOENIX 2 studies through to week 12 included cellulitis, herpes zoster infection, diverticulitis and injection-site reactions (7,8). Serious infections occurred in 0.3% of participants treated with ustekinumab and in 0.4% of participants given placebo (23).

Analyses of registry data assessed the risk of serious infection associated with ustekinumab and other biological agents compared with non-biological systemic therapies (24–26). In general, the findings suggested no increased risk of serious infection associated with ustekinumab.

Malignancies have been reported with the use of ustekinumab in clinical trials with 1.7% of participants reported to have malignancies excluding non-melanoma skin cancers and 1.5% reported to have non-melanoma skin cancers.

Malignancies other than non-melanoma skin cancer in patients treated with ustekinumab during the controlled and uncontrolled parts of the studies were similar in type and number to what would be expected in the general United States population according to the SEER database (*23*).

WHO guidelines

WHO guidelines for the treatment of psoriasis are not currently available.

Costs/cost–effectiveness

A 2013 cost–effectiveness analysis of ustekinumab versus etanercept from a United States societal perspective found that using a 3-year time horizon, ustekinumab 45 mg dominated etanercept 50 mg. However, the incremental cost–effectiveness ratio comparing ustekinumab 90 mg with etanercept 50 mg was US$ 384 401 per quality-adjusted life year (QALY) gained, which was considered not to be cost-effective using typical willingness-to-pay thresholds (*27*). A 2011 cost–utility analysis from the Canadian perspective and using a 10-year time horizon also found ustekinumab 45 mg to be more cost-effective than etanercept for patients with moderate-to-severe plaque psoriasis (*28*). Other analyses of cost–effectiveness studies have reported similar results (*29,30*).

The effect on drug acquisition costs after the introduction of biosimilar molecules of both ustekinumab and biological comparators will affect the cost–effectiveness.

Availability

Ustekinumab is reported to be widely available in the countries where it is marketed. The patent for the innovator brand of ustekinumab will expire in September 2023 and a number of biosimilar products are in trial and development.

Committee recommendations

The Expert Committee acknowledged the global burden of psoriasis and the public health need for effective treatments for this condition. To date, only topical therapies for psoriasis have been included on the Model Lists.

The Committee noted that multiple randomized trials have shown ustekinumab to be more effective than placebo in the proportion of patients achieving a PASI 75 and PASI 90 response.

The Committee noted that biological disease-modifying therapies such as ustekinumab have an important role in the management of moderate-to-severe forms of psoriasis.

The Committee noted that the network meta-analyses presented in the application demonstrated varying degrees of efficacy and toxicity among pharmacological classes and individual biological medicines in the treatment of

moderate-to-severe psoriasis. The Committee considered that the optimal choice of one agent over another was not straightforward, especially when taking into account their high costs and limited availability, which are major barriers to access in low- and middle-income countries.

The Expert Committee therefore did not recommend the inclusion of ustekinumab on the EML for the treatment of severe psoriasis in adults. The Committee recommended a comprehensive review of all biological disease-modifying medicines in the treatment of moderate-to-severe forms of psoriasis be undertaken to better inform the selection of the most effective and cost-effective agents for future consideration for inclusion on the Model Lists. This review should also consider safety and feasibility of use across global settings.

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Section 18: Medicines for endocrine disorders

Alfacalcidol and calcitriol – addition – EML and EMLc

Alfacalcidol	**ATC code: A11CC03**
Calcitriol	**ATC code: A11CC04**

Proposal

Addition of alfacalcidol and calcitriol to the complementary list of the EML and EMLc for the management of relevant disorders of bone and calcium metabolism in adults and children.

Applicant

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WHO technical department

Not applicable

EML/EMLc

EML and EMLc

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Dose form(s) & strengths(s)

Alfacalcidol – capsule: 0.25 micrograms, 1 microgram; oral liquid: 2 micrograms/mL

Calcitriol – capsule: 0.25 micrograms, 0.5 micrograms

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Alfacalcidol and calcitriol have not previously been considered for inclusion in the Model Lists for management of disorders of bone and calcium metabolism, or any other indication.

The Model Lists currently include vitamin D as cholecalciferol and ergocalciferol for the management of vitamin D deficiency.

Public health relevance

Vitamin D analogues are used in situations where endogenous vitamin D cannot be produced, or exogenous 25 hydroxyvitamin D (25(OH)D) cannot be absorbed or converted to active vitamin D in the kidney and liver. These situations include chronic kidney disease, hypophosphataemic rickets (including X-linked) and hypoparathyroidism (*1*).

Data from the Global Burden of Disease study indicate that the global prevalence of chronic kidney disease was estimated to be almost 700 million in 2019 (*2*). The prevalence varies between countries, with a large burden in low- and middle-income countries.

X-linked hypophosphataemia has a reported incidence of 3.9 per 100 000 live births and a prevalence of 4.8 per 100 000 population (all ages) (*3*).

Hypoparathyroidism has a number of potential causes and overall population prevalence data are difficult to obtain. A study in Denmark suggested a population prevalence (all ages) for surgical and non-surgical hypoparathyroidism of 22 per 100 000 and 2.3 per 100 000, respectively (*4–6*). Incidence rates for some of the conditions that cause hypoparathyroidism in childhood are available. The annual birth incidence of 22q11 deletion syndrome has been reported as 14 per 100 000 in a study in Sweden (*7*), and 22 per 100 000 in a study in Australia (*8*).

Summary of evidence: benefits

The application stated that treatment for the proposed indications with vitamin D analogues is long-standing and well established. Their use is recommended in guidelines for management of chronic kidney disease (*9*), hypophosphataemic rickets (*10,11*) and hypoparathyroidism (*12*). Most recent clinical trials compare other medications with vitamin D analogues as the gold standard. As such, no recent placebo-controlled clinical trials of these medicines are available.

A randomized, open-label trial compared alfacalcidol and calcitriol for the management of patients with hypoparathyroidism. Patients with hypoparathyroidism with optimal calcaemic control on alfacalcidol were randomized to continue alfacalcidol (*n* = 20) or switch to calcitriol (*n* = 25) at half the ongoing alfacalcidol dose for 6 months. No significant differences were observed between the alfacalcidol and calcitriol arms from baseline to 6 months

for the main outcomes of: mean serum phosphate level (5.0 mg/L versus 4.9 mg/dL, $P = 0.75$); proportion of patients with hyperphosphataemia (75% versus 80%, $P = 0.73$); 24-hour urine calcium-to-creatinine ratio (0.23 versus 0.28, $P = 0.26$); proportion of patients with hypercalciuria (65% versus 68%, $P = 0.99$); mean 24-hour urinary calcium excretion (198 mg versus 260 mg, $P = 0.08$); or mean 24-hour urinary sodium excretion (85 mmol versus 95 mmol, $P = 0.41$) (*13*).

Summary of evidence: harms

The application reported that, to date, alfacalcidol and calcitriol have large total patient exposure. The risks associated with treatment relate directly to the appropriateness of the dosage. No side-effects linked to intolerance to the medicines themselves are known. The most common risks associated with treatment include renal nephrocalcinosis and hypercalcaemia (in case of excessive dosage) or hypocalcaemia (in case of insufficient dosage), the risk of which varies by indication. Monitoring of serum and urine chemistry is recommended.

WHO guidelines

WHO guidelines for the management of disorders of bone and calcium metabolism are not currently available.

Costs/cost–effectiveness

No cost–effectiveness data were presented in the application. Table 23 shows the prices reported in the application for alfacalcidol and calcitriol.

Table 23
Prices of alfacalcidol and calcitriol by country

Country	Price per capsule or per mcg oral liquid, US$				
	Alfacalcidol			Calcitriol	
	0.25 mcg	1 mcg	Oral liquid	0.25 mcg	0.5 mcg
Argentina	–	–	–	0.30	–
India	0.08–0.13	–	–	0.35	–
Mexico	–	1.24	–	0.28	–
New Zealand	0.16	0.55	0.95	0.49	0.86
United Kingdom	0.19	0.19	1.28	0.31	0.90
South Africa	0.49	1.46	–	0.71[a]	

– means no information reported.
[a] Strength unknown.

Availability

Alfacalcidol and calcitriol are reported to be available globally, with generic versions available in many countries.

Other considerations

A 2021 systematic review and meta-analysis of 22 randomized trials that investigated different forms of vitamin D supplementation in patients with chronic kidney disease was identified during the application review process (*14*). Calcitriol and vitamin D analogues (alfacalcidol and paricalcitol) were associated with a reduction in parathyroid hormone concentration compared with vitamin D_2 or D_3 (mean difference –14.69 pg/mL, 95% confidence interval –36.29 to 6.90 pg/mL; four randomized controlled trials, 274 participants) and increase in fibroblast growth factor 23 (three randomized controlled trials, meta-analysis not performed), both indirect measures of important clinical outcomes, for example, fractures, cardiovascular disease risk and mortality. Inconsistent results for serum calcium and serum phosphate concentrations were noted. However, the evidence was considered uncertain because of the risk of bias, indirectness, inconsistencies and imprecision.

Committee recommendations

The Expert Committee noted that the application referred to three guidelines that conditionally recommended vitamin D analogues for the treatment of people with chronic kidney disease, hypophosphataemic rickets and hypoparathyroidism, but did not elaborate on any of the evidence underpinning the guideline recommendations.

The Committee noted a recent systematic review identified during the application review process that suggested that calcitriol and alfacalcidol might result in benefits for people with chronic kidney disease in terms of some surrogate outcomes for clinical benefit such as fewer fractures.

Overall, the Committee noted that the evidence base was uncertain due to the risk of bias, indirectness when assessing patient-important outcomes, inconsistencies and imprecision. The Committee considered that the limited likelihood of influencing important clinical outcomes was potentially outweighed by the risks associated with the use of alfacalcidol and calcitriol, such as hypercalciuria, decreased renal function and cardiovascular risk.

The Expert Committee therefore did not recommend the inclusion of alfacalcidol and calcitriol on the complementary list of the EML and EMLc for the proposed indications of hypoparathyroidism, hypophosphataemic rickets, hypocalcaemic vitamin D dependent/resistant rickets, neonatal hypocalcaemia, chronic kidney disease or other disorders of vitamin D metabolism or transport.

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Phosphorus – addition – EMLc

Phosphorus	ATC code: V03AG05

Proposal

Addition of phosphorus (phosphate salts) to the complementary list of the EMLc for management of hypophosphataemic rickets in children.

Applicant

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WHO technical department

Not applicable

EML/EMLc

EML

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Dose form(s) & strengths(s)

Granules: 500 mg (elemental phosphorus) in sachet

Tablet: 250 mg, 500 mg (elemental phosphorus)

Tablet (effervescent): 500 mg (elemental phosphorus)

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Phosphorus has not previously been considered for inclusion in the Model Lists for management of hypophosphataemic rickets in children or any other indication.

Public health relevance

X-linked hypophosphataemia is the most common cause of inherited phosphate wasting, with an incidence of 3.9 per 100 000 live births and a prevalence ranging from 1.7 per 100 000 children to 4.8 per 100 000 population (all ages) (*1*). It is a progressive lifelong disease of phosphorus metabolism where renal phosphorus wasting causes abnormal bone mineralization and rickets that do not respond to vitamin D and calcium supplements. As the disease progresses, long-term complications including poor growth (long bone deformity), osteoarthritis, increased risk of fractures, dental abscesses, bone and muscle pain, and stiffness and fatigue can significantly decrease overall quality of life.

Renal phosphorus wasting starts in early infancy. Skeletal manifestations become obvious later as the child begins to weight bear, when long bone deformities develop such as genu valgum or varum. Growth deceleration and rickets begin to occur during the first 2 years of life, when growth velocity is physiologically maximum.

Summary of evidence: benefits

Treatment of hypophosphataemic rickets with phosphate salts and vitamin D has been reported to improve bone mineralization, radiographical resolution of rickets and linear growth in a number of small observational studies (*2–5*).

A study of 11 children (10 girls, one boy, 2–12 years old) with vitamin D-resistant rickets treated with phosphate alone, or in combination with ergocalciferol or calcitriol, found that long-term use of phosphate induced mineralization of the growth plate but not of the endosteal bone surface. Long-term use of phosphate in combination with calcitriol greatly improved the mineralization of the trabecular bone (*2*).

A study of nine children (three girls, six boys, 6 months to 16 years old) with familial X-linked hypophosphataemic rickets treated with phosphate and alfacalcidol found that combination oral therapy was effective at improving growth rate, bone histology and the radiological picture of rickets. All children had positive outcomes for healing or rickets, change in growth rate, decreased alkaline phosphatase activity and symptomatic improvements, assessed over 4–6 years (*3*).

In a study of 24 children (15 girls, nine boys, 1–16 years old) with X-linked hypophosphataemic rickets treated with oral phosphate and calcitriol or ergocalciferol, 19 patients treated for at least 2 years before the onset of puberty had greater mean height SD score than untreated historical controls: mean difference 0.97 (95% confidence interval (CI) 0.22 to 1.75). For 13 patients who had received phosphate and calcitriol for at least 2 years, the mean change in height standard deviation (SD) score was 0.33 (95% CI 0.0 to 0.33) (*4*).

A study of 22 adult Japanese patients (17 women, five men) with X-linked hypophosphataemic rickets evaluated the effect of combination therapy for more

than 5 years with phosphate and vitamin D (as vitamin D_2 or alfacalcidol) on final height (as standard deviation score). Final height of all participants was −1.69 (SD 1.11) which was significantly higher than the height at the start of treatment (−2.38 (SD 0.88)). There was no significant difference in final height in patients receiving different forms of vitamin D. The results of this study were reported to be similar to previous studies in Caucasian patients (*5*).

Early diagnosis and initiation of treatment has been associated with improved outcomes in multiple studies (*6–9*).

Summary of evidence: harms

Therapy with phosphate is associated with adverse effects that require careful monitoring and adjustment of the dosing regimen by specialist paediatricians.

The most common adverse effects of oral phosphate therapy are gastrointestinal effects including abdominal discomfort and diarrhoea that can result in poor compliance with treatment (*10*). Secondary and tertiary hyperparathyroidism may also occur (*11*). Treatment-induced secondary hyperparathyroidism can be reversed by increasing calcitriol doses and reducing phosphate doses. Long-term, high-dose phosphate therapy may be an independent risk factor for tertiary hyperparathyroidism.

Nephrocalcinosis (deposition of calcium in the renal parenchyma and tubules) can occur as a complication of phosphate and active vitamin D treatment, and is associated with higher doses of phosphate and/or overdose of calcitriol/alfacalcidol. Prevention is through careful dosage adjustment. Recommended safe doses have been reported as 20–40 mg/kg a day of phosphate and 20–30 ng/kg a day of calcitriol (*12*). Thiazide diuretics can be used in the management of nephrocalcinosis when it occurs (*13,14*).

WHO guidelines

WHO guidelines for the management of hypophosphataemic rickets are not currently available.

Costs/cost–effectiveness

The application reported prices per 500 mg elemental phosphorus for various formulations as US$ 0.30 in India, US$ 0.68 in Mexico and US$ 0.23 in the United Kingdom.

No cost–effectiveness data were presented in the application.

Availability

Phosphate salt formulations most suitable for use in children include effervescent tablets and granules. An oral solution known as Joulie solution can be prepared by compounding pharmacists. Different formulations may be available in different markets.

Committee recommendations

The Expert Committee noted that hypophosphataemic rickets is a rare genetic condition and the most common cause of inherited phosphate wasting that without treatment can lead to severe long-term complications.

The Committee noted evidence from small cohort studies which suggested that early introduction of treatment with phosphorus and vitamin D in children with hypophosphataemic rickets had beneficial effects on growth, bone mineralization and reducing bone deformities.

However, the Committee considered that hypophosphataemic rickets is a rare condition which constitutes only a small subgroup of all hypophosphataemic conditions that may benefit from phosphorus supplementation. The Committee noted that several other genetic conditions are associated with phosphorus loss and require replacement therapy as part of their management (e.g. autosomal dominant hypophosphataemic rickets, hereditary hypophosphataemic rickets with hypercalciuria and Fanconi syndrome). Other conditions that can require phosphate supplementation include primary or secondary hypoparathyroidism, renal failure, nephrotic syndrome after kidney transplant, tumour-induced osteomalacia and hyperphosphaturia after partial hepatectomy.

The Expert Committee did not recommend the inclusion of phosphorus on the complementary list of the EMLc for the treatment of hypophosphataemic rickets in children at this time. The Committee considered that a comprehensive review of the evidence for phosphorus treatment across all conditions for which it is indicated should be requested for future consideration.

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Zoledronic acid – new indication – EML and EMLc

Zoledronic acid	**ATC code: M05BA08**

Proposal

Addition of zoledronic acid on the complementary list of the EML and EMLc for a new indication for the management of moderate-to-severe osteogenesis imperfecta in neonates, infants, children and adolescents.

Applicant

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WHO technical department

Not applicable

EML/EMLc

EML and EMLc

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Dose form(s) & strengths(s)

Concentrate solution for infusion: 4 mg/5 mL in 5 mL vial

Solution for infusion: 4 mg/100 mL in 100 mL bottle

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Zoledronic acid has not previously been considered for inclusion in the Model Lists for the management of osteogenesis imperfecta.

Zoledronic acid has been included on the complementary list of the EML for the treatment of malignancy-related bone disease since 2017.

Public health relevance

Osteogenesis imperfecta is reported to occur in 1 in 10 000 to 20 000 births (*1*). Most cases result from a mutation in the genes that encode for alpha 1 (COL1A1 gene) or alpha 2 (COL1A2 gene) chains of type 1 collagen. This leads to a defect in the synthesis, structure or processing of type 1 collagen. Overall, there are more than 18 types of osteogenesis imperfecta (*2*). Osteogenesis imperfecta phenotypes I to IV have autosomal dominant transmission and account for about 95% of all cases – type I 45%, type II 10%, type III 25% and type IV 20% (*3*).

The worldwide population frequency of type I osteogenesis imperfecta has been reported to range from 2.35 to 4.7 per 100 000. The incidence of type II osteogenesis imperfecta has been reported to range from 1 in 40 000 to 1.4 in 100 000 live births. In resource-constrained countries, less severe forms are less likely to be seen. The genetic background is also likely to play a role (*3*).

A Swedish study found an overall prevalence of osteogenesis imperfecta type I of 7.4 in 100 000 (*4*). A Dutch study (674 patients with osteogenesis imperfecta across the country) showed that the life expectancy of these patients was adversely affected by the disease. The median annual incidence risk of osteogenesis imperfecta between 1992 and 2019 was 6.5 per 100 000 live births. Patients with osteogenesis imperfecta had a 2.9 times higher rate of hospitalization compared with the general Dutch population, especially in the patient group aged between 0 and 19 years, where the risk was 8.4 times higher (*5*).

Summary of evidence: benefits

Bisphosphonates are indicated for the management of osteogenesis imperfecta with moderate-to-severe pain and with bone fractures that are present in infancy, childhood and adolescence. In mild cases, no benefits of bisphosphonates have been demonstrated (*6*). The bisphosphonate first investigated for use in severe osteogenesis imperfecta was pamidronate (*7*). Since then, zoledronic acid has become available and is preferred in clinical practice based on convenience and lower hospital expense: zoledronic acid only needs to be administered once or twice a year while pamidronate needs to be administered 3–4 times a year. Administration of zoledronic acid is by a 30-minute infusion, while each administration of pamidronate consists of three consecutive daily infusions of several hours. As regards outcomes and side-effects, clinicians consider both products to be equivalent. A 1-year study comparing the efficacy and safety of zoledronic acid and pamidronate showed that zoledronic acid was as safe and effective as pamidronate in promoting clinical and densiometric improvements (*8*).

The benefits of zoledronic acid treatment for moderate and severe forms of osteogenesis imperfect include reduced bone pain, increased bone mineral density and a decrease in the number of fractures.

Bone pain

A cross-sectional study with 28 participants with osteogenesis imperfecta I, III and IV found that pain was present in almost all children with moderate-to-severe disease (*9*). This interfered with the children's everyday lives, affected participation in various activities and was associated with reduced self-perceived health status. The authors hypothesized that pain and the ensuing decrease in physical activity might further decrease bone density and increase the risk of fractures.

An observational study of the use of the bisphosphonate pamidronate in 30 children with severe osteogenesis imperfecta reported an improvement in bone pain which was associated with an improvement in mobility (*7*).

A prospective observational study evaluated pain and quality of life in 33 children and adolescents with osteogenesis imperfecta over a single intravenous bisphosphate treatment cycle (*10*). Participants reported pain of mild intensity localized in several body areas (ankles, shoulders). Self-reported pain intensity after zoledronic acid infusion did not differ from before treatment at 1 week and 6 months after treatment. Participants' parents perceived an improvement in functioning and quality of life immediately after treatment compared with before, but no significant change was reported by the participants themselves.

Another prospective observational study evaluated pain and functioning in 22 children and adolescents with osteogenesis imperfecta over two bisphosphate infusion cycles (*11*). Participants received pamidronate (*n* = 16) or zoledronic acid (*n* = 6). Pain was assessed using a visual analogue scale and physical functioning was assessed using the Peds QL Generic Core inventory. The results showed that cyclic intravenous bisphosphonate therapy transiently reduced pain until 4 weeks postinfusion. Physical functioning scores improved 4 weeks after infusion. Both pain and physical functioning had returned to pretreatment levels by the time of the second infusion.

A 2016 Cochrane systematic review (14 trials, 819 participants) evaluated the effectiveness and safety of oral and intravenous bisphosphonate therapy in increasing bone mineral density, reducing fractures and improving clinical function in people with osteogenesis imperfecta. One trial compared intravenous bisphosphonate (pamidronate) with placebo for the outcome of bone pain in children and did not find a difference in bone pain reduction scores between the two groups. The mean difference (MD) favoured bisphosphonate treatment but was not statistically significant (MD −0.11, 95% confidence interval (CI) −0.83 to 0.61) (*12*).

Bone mineral density

The observational study using pamidronate at a standard dose of maximum 9 mg/kg a year reported a marked increase in bone mineral density over several years (*7*).

The Cochrane systematic review included three trials comparing of intravenous bisphosphonates (neridronate or pamidronate) with placebo for

changes in bone mineral density (*12*). Mean percentage changes from baseline in spine bone mineral density favoured bisphosphonate treatment but were not statistically significant at 6 months (MD 9.96, 95% CI –2.51 to 22.43) and 12 months (MD 14.68, 95% CI –6.08 to 35.45). Mean percentage changes (z score) in spine bone mineral density significantly favoured bisphosphonate treatment at 6 months (MD 21.59, 95% CI 5.79 to 37.39) and 12 months (MD 25.6, 95% CI 11.48 to 39.72). Mean percentage changes in total hip bone mineral density favoured bisphosphonate treatment but they were not statistically significant at 6 months (MD 6.16, 95% CI –3.57 to 15.9) and 12 months (MD 11.27, 95% CI –3.69 to 26.22).

Fractures

The application remarked that it was difficult to assess the data of the effects of bisphosphonates on fracture rates in patients with osteogenesis imperfecta, given that when there is a decrease in pain and an increase in mobility, a higher risk of fractures is not unexpected.

The Cochrane systematic review concluded that although multiple studies reported decreases in fracture rates independently and no studies reported an increased fracture rate with bisphosphonate treatment, the effect of bisphosphonate treatment in consistently decreasing fractures was unclear (*12*). In the comparison of intravenous bisphosphonates versus placebo, the difference in fracture rates favoured bisphosphate treatment but was not statistically significant (risk ratio 0.53, 95% CI 0.30 to 1.06).

A retrospective study assessed the effects of long-term intravenous bisphosphonate treatment during growth in 37 children with osteogenesis imperfecta who had started treatment before 5 years of age, had subsequent follow-up of at least 10 years and had received treatment for at least 6 years (*13*). All the children had had long-bone or vertebral compression fractures before intravenous bisphosphonate treatment was started but the number of fractures could not be determined with certainty due to lack of radiographic documentation. All the children initially received pamidronate and 30 eventually received zoledronic acid. During the observation period, the children had a median of six and five radiologically documented femur and tibia fractures, respectively. The mean rate of fracture in lower extremity long bones decreased during the first 2 years of treatment and thereafter remained stable. Visible compression fractures decreased markedly between the pretreatment and last follow-up or final (before spinal fusion) radiographs. The number of vertebral compression fractures was significantly lower ($P < 0.01$) at the time of the last bisphosphonate infusion compared with a control group of patients who were matched for age, sex and osteogenesis imperfecta type who had not received bisphosphonate treatment.

An observational cohort study evaluated the effects of bisphosphonate treatment on bone mineral density and other health outcomes in type 1

osteogenesis imperfecta (*14*). Logistic regression modelling predicted that with bisphosphonate exposure, a 1-year increase in age would be associated with a significant decrease of 8.2% in fracture probability for preadolescent (age < 14 years) children, compared with no decrease in untreated children. An increase in lumbar spine areal bone mineral density of 0.1 g/cm^2 was associated with a 10.6% decrease in scoliosis probability, compared with a 46.8% increase in the untreated group. For the same changes in age and lumbar spine areal bone mineral density in preadolescent children, bisphosphonate exposure was also associated with significantly higher mobility scores.

Summary of evidence: harms

Several risks are associated with treatment with bisphosphonates and require monitoring (*15*). Risks are generally similar in children and adults. However, osteonecrosis of the jaw, a significant clinical problem associated with long-term bisphosphonate use in adults, has not been reported in the paediatric age group (*16*). A systematic review evaluated the literature on the risk of bisphosphonate-related osteonecrosis of the jaw in children and adolescents (*17*). In the seven studies included, no cases of osteonecrosis of the jaw were identified. However, the authors noted weaknesses in the studies (e.g. small sample size and absence of risk factors for development of osteonecrosis of the jaw) and concluded that further studies should be conducted.

Oral and oesophageal ulcerations (and potentially cancer of the oesophagus) have only been reported with oral bisphosphonates (*18*).

Bisphosphonates are reported to be generally well tolerated in paediatric patients and adverse effects are limited and predictable. A recent review (*19*) describes the following adverse events.

- Acute phase reaction (so called flu-like syndrome) is observed with fever, malaise, abdominal pain, vomiting, and muscle or bone pain within 1–3 days of starting either intravenous or oral agents, and lasting a few days.
- Asymptomatic hypophosphatemia, and hypomagnesaemia and hypocalcaemia causing tetany are rare and can be prevented with supplementation with calcium and vitamin D.
- More serious side-effects seen in adults including uveitis and thrombocytopenia are rare in children. One case of uveitis was reported among 19 children with Langerhans cell histiocytosis treated with bisphosphonates in Japan (*20*) although histiocytosis itself has also been associated with uveitis (*21*).
- Avascular necrosis of the jaw seen in adults is not seen in paediatric patients.

- A severe case of respiratory distress syndrome was reported with the start of pamidronate in an infant with a history of airway disorders (*22*).
- Osteomalacia (and marked decrease in bone pain) was seen in an adolescent with fibrous dysplasia after intravenous cyclic pamidronate therapy (*23*).

Bisphosphonates are contraindicated during pregnancy. Bisphosphonates stay in bone for a long time. They can be released during bone remodelling. Whether this would cause problems, for instance, during pregnancy is unclear. In two infants delivered to mothers treated with bisphosphonates, asymptomatic hypocalcaemia without any skeletal anomaly was reported in the newborns (*24*).

WHO guidelines

WHO guidelines for the management of osteogenesis imperfecta are not currently available.

Costs/cost–effectiveness

No cost–effectiveness studies on bisphosphonates in osteogenesis imperfecta were identified in the application.

Prices for intravenous zoledronic acid formulations per vial from different countries were reported in the application as: US$ 270 in Argentina, US$ 254 in Canada, US$ 35 in India and US$ 30 in Mexico.

For the management of four 20 kg patients at a dose 0.05 mg/kg every 6 months, the annual cost per patient (assuming vial sharing) would be US$ 135 in Argentina, US$ 127 in Canada, US$ 18 in India and US$ 15 in Mexico.

Availability

Zoledronic acid injection is available globally in both innovator and generic brands.

Committee recommendations

The Expert Committee noted that osteogenesis imperfecta is a rare genetic disease and that bisphosphonates are commonly used in the treatment of moderate-to-severe forms in children and adolescents.

The Committee noted that available evidence suggests that bisphosphonates may increase bone mineral density in children and adolescents with moderate-to-severe osteogenesis imperfecta. However, the Committee considered that the benefits associated with bisphosphonates were unclear for other important outcomes including fracture risk, bone pain, physical functioning and health-related quality of life.

In particular, the Committee noted that the effects of bisphosphonates in reducing fracture risk were not consistent across trials and that it was not clear to what extent fracture risk might be reduced.

The Committee noted that serious harms associated with bisphosphonate treatment in osteogenesis imperfecta were rare and clinically manageable.

Based on these considerations, the Expert Committee did not recommend inclusion of zoledronic acid on the EML and EMLc for the new indication of osteogenesis imperfecta.

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Ketoconazole – addition – EML

Ketoconazole	ATC code: H02CA03

Proposal

Addition of ketoconazole tablets to the complementary list of the EML for use in the management of patients with endogenous Cushing syndrome.

Applicant

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WHO technical department

The technical team for Screening, Diagnosis and Treatment in the Department of Noncommunicable diseases reviewed and provided comments on the application. The technical team advised that it did not support the application, highlighting its views that the data included appeared to be selective, omitting systematic reviews on the topic that could have been included and critically appraised (*1–3*), and there was risk of bias in the included case series, and retrospective observational and cohort studies. The technical unit also noted that the application did not address difficulties in low- and middle-income countries in monitoring liver enzymes and the availability of endocrinologists to monitor treatment effects, nor did it provide any estimation of costs associated with measuring urinary free cortisol levels, monitoring liver enzymes and other possible adverse events.

EML/EMLc

EML

Section

18 Medicines for endocrine disorders

Dose form(s) & strengths(s)

Tablet: 200 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Ketoconazole was added to the EML in 1987 for the treatment of systemic fungal infections. A square box was added to the listing in 1989 to indicate that other azole antifungals could serve as suitable therapeutic alternatives. In 1999, ketoconazole was replaced by fluconazole as the representative medicine on the basis of better cost–effectiveness and fewer adverse events. Ketoconazole remained a therapeutic alternative to fluconazole under the new square box listing until 2019, when the square box was removed from the listing for fluconazole, following the addition of the new azole antifungals itraconazole and voriconazole.

Ketoconazole tablets have not previously been evaluated for inclusion on the Model Lists for use in Cushing syndrome.

Public health relevance

Cushing syndrome is caused by the excessive secretion of cortisol from the adrenal glands. About 80% of cases of Cushing syndrome are due to adrenocorticotropic hormone (ACTH)-secreting pituitary tumours and 20% are due to cortisol-producing adrenal adenomas and carcinomas. ACTH-secreting tumours represent about 5% of clinically identified pituitary adenomas. The annual incidence of ACTH-secreting tumours is about 2–3 per million. About 90% of ACTH-secreting pituitary adenomas are less than 10 mm in maximum diameter (microadenomas) and 10% are more than 10 mm (macroadenomas); malignant ACTH-secreting tumours are rare (*4,5*).

Excess cortisol may cause considerable morbidity, including hypertension, diabetes, heart disease, muscle weakness, fatigue, depression, osteoporosis, weight gain, easy bruising, facial plethora and skin striae due to excessive cortisol levels and hirsutism due to excessive adrenal androgen levels (*6–10*). In children, weight gain with decreased growth velocity is often the presenting feature (*7,9*). Mortality in patients with Cushing syndrome is also two to five times higher than that of the general population (*11–14*). Macroadenomas can continue to grow and cause mass effects, such as visual field defects, hypopituitarism, cranial nerve palsies and headaches. Adrenal lesions also usually present with symptoms and signs related to excessive cortisol and androgen secretion (*6–10*).

Almost all patients with Cushing syndrome due to benign adrenal adenomas or bilateral nodular hyperplasia can be cured surgically by adrenalectomy (*9*). Those not controlled by surgery are treated medically with the goal of achieving hormonal control. Medical treatment may be the only option in some settings where availability of neurosurgeons is limited.

Summary of evidence: benefits

Early studies using ketoconazole to treat Cushing syndrome suggested a normalization rate of urinary-free cortisol levels of over 90% (*15,16*).

A retrospective, multicentre study reviewed data on 200 patients with Cushing disease (78% females, 106 microadenomas, 36 macroadenomas, 58 with no visible tumour) treated with ketoconazole in doses ranging from 200 mg to 1200 mg a day, with most patients receiving 600 mg and 800 mg a day (*17*). Of 39 patients treated for 4 months before surgery, 19 (48.7%) achieved a normal urinary-free cortisol. In 158 patients treated postoperatively or primarily (when surgery was contraindicated), 78 (49.4%) achieved normal urinary-free cortisol, 37 (23.4%) had a > 50% decrease in urinary-free cortisol and 43 (27.2%) had unchanged urinary-free cortisol. Ketoconazole treatment was stopped in 26.8% of patients due to lack of efficacy and in 25.6% of patients due to adverse effects.

Individual prospective, randomized studies of other medicines for management of Cushing syndrome showed normalization of cortisol levels in 28% of patients treated with cabergoline (*18*), 43% of patients treated with metyrapone (*19*), 20% of patients treated with pasireotide (*20*), 66% of patients treated with osilodrostat (*21*), and 31% of patients treated with levoketoconazole (*22*). In the SEISMIC study, 88% of patients treated with mifepristone were judged to have progressive clinical improvement (*23*,*24*). Because mifepristone blocks the cortisol receptor and does not interfere with cortisol synthesis, measurement of cortisol levels cannot be used as a measure of efficacy.

A 2018 systematic review and meta-analysis of 35 randomized trials and cohort studies (1520 participants) evaluated the effectiveness of medical treatment for Cushing syndrome (*25*). The review reported the percentage of patients with pituitary Cushing disease who achieved normalization of cortisol levels as 81.8% (95% confidence interval (CI) 75.4% to 87.6%, four studies) for mitotane, 60.0% (95% CI 31.3% to 83.2%, one study) for metyrapone, 49.0% (95% CI 42.0% to 56.0%, three studies) for ketoconazole, 41.1% (95% CI 32.7% to 49.8%, two studies) for pasireotide and 35.7% (95% CI 24.6% to 47.6%, three studies) for cabergoline. The corresponding percentages for patients with all etiologies of Cushing syndrome, including adrenal carcinoma were 78.9% (95% CI 73.3% to 85.7%, four studies) for mitotane, 75.9% (95% CI 57.5% to 90.9%, two studies) for metyrapone, 71.1% (95% CI 51.6% to 87.5%, seven studies) for ketoconazole, 41.1% (95% CI 32.7% to 49.8%, two studies) for pasireotide and 35.7% (95% CI 24.6% to 47.6%, three studies) for cabergoline. The authors concluded that medication induces cortisol normalization in a large percentage of patients with Cushing disease and would be a reasonable option for patients who chose not to have surgery or in whom surgery was contraindicated, and for patients with recurrence following surgery.

Summary of evidence: harms

The main adverse effect of ketoconazole is liver toxicity. In a retrospective study of 200 patients treated with ketoconazole for Cushing syndrome, liver enzyme

elevations of up to five-fold of normal were reported in 15.8% of patients, four patients experienced five- to 10-fold elevations and one patient experienced a 40-fold increase (*17*). These increases occurred within 4 weeks of starting treatment or with dose increments. All increases returned to normal after treatment withdrawal or dose reduction. Other reported adverse effects of ketoconazole were gastrointestinal symptoms (13.1%), adrenal insufficiency (5.4%) and pruritus (3.7%).

Ketoconazole is a strong CYP3A4 inhibitor and therefore may affect dosing of other medicines that are substrates for this enzyme (e.g. amiodarone, carbamazepine, amitriptyline, selective serotonin reuptake inhibitors, benzodiazepines, calcium channel blockers, statins and colchicine).

In 2013, the United States Food and Drug Administration issued a drug safety communication on ketoconazole use because of potentially fatal liver injury, risk of drug interactions and adrenal gland problems (*26*).

In 2013, the European Medicines Agency's Committee on Medicinal Products for Human Use recommended marketing authorizations of oral ketoconazole be suspended throughout the European Union due to the risk of liver toxicity outweighing the benefits in the treatment of fungal infections. This recommendation was subsequently endorsed by the European Commission. However, it was noted by the European Medicines Agency that ketoconazole was used off-label for the treatment of patients with Cushing syndrome and indicated that national regulatory authorities may make ketoconazole available for these patients under controlled conditions (*27*).

WHO guidelines

WHO guidelines for the management of Cushing syndrome are not currently available.

Costs/cost–effectiveness

A retrospective cohort study compared costs for treatment of 877 patients with Cushing syndrome compared with 2631 matched controls without this disease using a United States insurance administrative claims database to assess the economic burden of Cushing syndrome (*28*). The study found that the mean number of health care visits (ambulatory, emergency department and inpatient) was two-to-four times higher for patients with Cushing syndrome than for control patients. The total mean all-cause health care costs were also higher for patients with Cushing syndrome than for control patients, driven primarily by medical costs, which accounted for 87% and 79% of total costs for patients with Cushing syndrome and controls, respectively. On average, medical costs were nearly seven times higher for patients with Cushing syndrome than for control patients.

The costs of treatment for Cushing syndrome (including drug cost, treatment, complications, adverse events, comorbidity and monitoring) were

reported in a 2014 study that assessed the budget impact of pasireotide in the United States (*29*). The annual cost per patient for treatment with ketoconazole was US$ 25 475 (of which monthly drug costs were US$ 127). Corresponding figures for other medicines were US$ 144 280 (US$ 14 583) for pasireotide, US$ 207 562 (US$ 15 140) for mifepristone, US$ 32 179 (US$ 719) for cabergoline and US$ 40 893 (US$ 1364) for mitotane.

Costs of treatment for Cushing syndrome using ketoconazole and other medicines reported in the application are shown in Table 24.

Table 24
Costs of medicines used to treat Cushing syndrome

Medicine	Unit cost[a], US$/ dose	Average effective dose	Cost for 30 days, US$
Ketoconazole	1.43/200 mg	800 mg/day	172
Cabergoline	46/0.5 mg	3.6 mg/week	1325
Metyrapone	32/250 mg	1375 mg/day	5280
Pasireotide	15 255/30 mg	30 mg/30 day	15 255
Osilodrostat	553/10 mg	10 mg/day	16 590
Mifepristone	603/300 mg	734 mg/day	44 260
Levoketoconazole	313/150 mg	563 mg/day	35 244

[a] Retail cost as of January 2022.

Costs for a 30-day course of ketoconazole were reported in the application as US$ 36 in Argentina, US$ 6 in Bolivia (Plurinational State of), US$ 36 in Brazil, US$ 6–22 in India and US$ 25 in Mexico.

Availability

Ketoconazole (200 mg tablets) has regulatory approval from the European Medicines Agency for use in the treatment of adults and children aged 12 years and older with Cushing syndrome.

Ketoconazole (200 mg tablets), produced by three manufacturers, has regulatory approval from the United States Food and Drug Administration for use in the treatment of fungal infections.

The regulatory status of ketoconazole 200 mg tablets in Australia, Canada and Japan, as presented in the application, was unable to be verified.

Committee recommendations

The Expert Committee noted that ACTH-secreting pituitary tumours are responsible for 80% of cases of Cushing syndrome and are relatively rare, with a reported annual incidence of 2–3 cases per million people. The Committee noted that neurosurgery can cure most cases and is the recommended treatment intervention for this condition. Pharmacological treatment may be required in some patients who are not candidates for surgery, or in settings where experienced neurosurgeons and surgical facilities are not available.

The Committee noted that the evidence presented in the application suggested that a significant proportion of patients had a good response to treatment with ketoconazole as measured by normalization of urinary-free cortisol levels, however, the certainty of evidence was low and drawn from retrospective observational studies and a single meta-analysis. Data from individual randomized studies of other medicines suggested alternative treatments were associated with better outcomes, however direct comparisons were not available.

The Committee expressed grave concerns about the safety profile associated with systemic use of ketoconazole, including serious liver toxicity requiring monitoring with regular liver function tests, QT prolongation and the potential for numerous drug–drug interactions as a result of CYP3A4 inhibition by ketoconazole.

Based on these considerations, the Committee did not recommend the inclusion of ketoconazole on the EML for use in the management of patients with Cushing syndrome.

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Glucagon-like peptide-1 receptor agonists – addition – EML

Liraglutide	ATC code: A10BJ02

Proposal

Addition of glucagon-like peptide-1 (GLP-1) receptor agonists to the core list of the EML for treatment of obesity.

Applicant

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Department of Nutrition and Food Safety

EML/EMLc

EML

Section

18 Medicines for endocrine disorders

Dose form(s) & strengths(s)

Injection: 6 mg/mL in 3 mL prefilled pen

Core/complementary

Core

Individual/square box listing

Square box listing for liraglutide as representative of the class of GLP-1 receptor agonists. Specific alternative medicines were not indicated in the application.

Background

Medicines for the treatment of obesity are currently not included on the WHO Model Lists and have not been assessed by previous Expert Committees.

In 2017, the Expert Committee considered a review of medicines for second-line therapy for type 2 diabetes, including (but not limited to) GLP-1 receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors, based on an update of the 2013 review by the Canadian Agency for Drugs and Technologies in Health. The Committee did not recommend the inclusion of second-line medicines for type 2 diabetes on the EML and confirmed the role of sulfonylureas as one of the most cost-effective treatments for intensification therapy of type 2 diabetes. However, the Committee noted that SGLT2 inhibitors had shown a relevant clinical benefit as second-line therapy in patients at high risk of cardiovascular events, with a reduction in overall mortality. The Committee considered that this finding needed to be confirmed with data from other trials before this class of medicines could be supported for inclusion on the EML (1).

In 2021, the Expert Committee reviewed an application presenting new evidence which confirmed the positive effect of SGLT2 inhibitors compared with placebo on all-cause mortality, cardiovascular outcomes (cardiovascular mortality, non-fatal myocardial infarction and hospital admission for unstable angina), renal outcomes (kidney failure, end-stage renal disease and renal death), body weight and haemoglobin A1c (HbA1c). The Committee noted that the situation was less clear when comparing SGLT2 inhibitors with GLP-1 receptor agonists, although the SGLT2 inhibitors seemed to be the preferred option as they were consistently associated with favourable results for most cardiovascular outcomes and were administered orally in contrast to GLP-1 receptor agonists that needed to be injected. For SGLT2 inhibitors, the Committee considered that there was high-quality evidence showing clinically beneficial effects in patients with type 2 diabetes who had not achieved appropriate glycaemic control with metformin or a sulfonylurea, particularly in those at high risk of cardiovascular events and/or diabetic nephropathy, and there was a reasonable safety profile. The Expert Committee therefore recommended the inclusion of SGLT2 inhibitors on the core list of the EML as a second-line therapy. GLP-1 receptor agonists were not recommended for inclusion for second-line therapy for type 2 diabetes at that time (2).

Public health relevance

Obesity is associated with numerous complications such as ischaemic heart disease, stroke, diabetes mellitus, chronic kidney disease, hypertensive heart disease and lower back pain. Obesity is also associated with increased health care-related costs both for society as well as for people with obesity and their families. The overall medical cost due to obesity in adults in the United States was estimated to be US$ 260.6 billion in 2016 (3).

Obesity was once considered to be a problem of high-income countries but has now become an increasingly important problem in low- and middle-income

countries The global age-standardized prevalence of obesity increased from 0.7% (95% credibility interval (CrI) 0.4% to 1.2%) in 1975 to 5.6% (95% CrI 4.8% to 6.5%) in 2016 in girls aged 5–19 years, and from 0.9% (95% CrI 0.5% to 1.3%) in 1975 to 7.8% (95% CrI 6.7% to 9.1%) in 2016 in boys aged 5–19 years (*4*). A high prevalence of obesity (> 20%) was not only observed in high-income countries but also in several countries in Polynesia and Micronesia, the Middle East and north Africa, and the Caribbean. Overall, it was estimated that in 2016 more than 1.9 billion adults were overweight, of whom 650 million were obese (i.e. with a body mass index (BMI) of at least 30 kg/m^2) (*5*).

The increase in the global prevalence of overweight and obesity has been accompanied by a substantial increase in global deaths attributable to a high BMI ($\geq$ 25 kg/m^2) between 1990 and 2017. According to an analysis of the Global Burden of Disease study, the global deaths attributable to high BMI have increased from 1.2 million (95% uncertainty interval (UI) 0.7 to 1.8 million) in 1990 to 2.4 million (95% UI 1.6 to 3.4 million) in 2017 for females, and from 1.0 million (95% UI 0.5 to 1.6 million) in 1990 to 2.3 million (95% UI 1.4 to 3.4 million) in 2017 for males. Over the same time, the global number of high BMI-related disability-adjusted life years (DALYs) has more than doubled for both sexes (*6*).

Summary of evidence: benefits

GLP-1 is one of two main incretin hormones (the other one being gastric inhibitory polypeptide). GLP-1 is secreted by the gastrointestinal tract on ingestion of glucose or other nutrients. GLP-1 stimulates insulin secretion from pancreatic beta cells and inhibits gastric emptying and release of the hormone glucagon. Liraglutide is a long-acting analogue of GLP 1 and mimics the effects of the naturally occurring hormone, stimulating the secretion of insulin, decreasing glucagon secretion, slowing gastric motility and decreasing appetite via an anorectic effect in the arcuate nucleus of the brain (*7*).

Liraglutide was first approved as a medicine for the treatment of type 2 diabetes in 2009 in Europe and in 2010 in the United States (*8*). In 2014, the United States Food and Drug Administration approved liraglutide for the treatment of obese adults (BMI $\geq$ 30 kg/m^2) and overweight adults (BMI $\geq$ 27 kg/m^2) with at least one weight related condition. The European Medicines Agency approved a similar indication in 2015. Both regulatory authorities emphasize that liraglutide should be used in addition to a reduced-calorie diet and physical activity.

Several phase III studies of liraglutide in the treatment of type 2 diabetes showed that liraglutide treatment was associated with weight loss in diabetic patients (*9–12*). In these studies, the mean reduction in body weight was 1–3 kg with the 1.2 mg daily dose and 2–3.4 kg with a 1.8 mg daily dose (*7*).

The first study to assess the efficacy of liraglutide for the treatment of obesity in patients without type 2 diabetes was an industry-sponsored randomized,

placebo-controlled, double-blind study in 19 sites in eight European countries in 2007 (*13*). Patients were randomized 1:1:1:1:1:1 to one of four doses of liraglutide (1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg subcutaneously once a day), placebo or open-label orlistat (an orally administered lipase inhibitor). Participants in all groups were also assigned to a 500 kcal energy-deficient diet and an increase in physical activity. The primary outcome was weight change during the 20-week study period. Overall, the group on liraglutide lost significantly more weight than patients in the placebo or orlistat groups, specifically losing on average 2.1 kg (95% confidence interval (CI) 0.6 to 3.6 kg) to 4.4 kg (CI 6.9 to 6.0 kg) more weight than the placebo group. The weight loss experienced with liraglutide was dose dependent with the highest weight loss occurring in the highest dose group (3 mg once a day).

A 2022 systematic review and meta-analysis of 12 randomized trials (8249 participants) assessed the efficacy of liraglutide versus placebo on BMI and weight loss in obese adults without diabetes (*14*). Overall, liraglutide showed a statistically larger effect on BMI (mean difference (MD) -1.45 kg/m^2, 95% CI -1.98 to -0.90 kg/m^2) and body weight (MD -3.35 kg, 95% CI -4.65 to -2.05 kg) than placebo. Liraglutide also reduced systolic and diastolic blood pressure compared with placebo (MD -3.07 mmHg, 95% CI -3.66 to -2.48 mmHg and MD -1.01 mmHg, 95% CI -1.55 to -0.47 mmHg, respectively). Seven randomized controlled trials were judged to be of high risk of bias and the quality of evidence was assessed as low or very low for most outcomes.

Another 2022 systematic review and meta-analysis of 12 randomized trials assessed the effect of GLP-1 receptor agonists (semaglutide 2.4 mg weekly (two trials, 2262 participants); semaglutide 0.05 0.4 mg daily (one trial, 957 participants); liraglutide 3.0 mg daily (five trials, 7306 participants); liraglutide 1.8 mg daily (one trial, 68 participants); exenatide 10 micrograms twice daily (two trials, 193 participants); and efpeglenatide 6 mg weekly (one trial, 295 participants)) on weight loss in obese adults without diabetes (*15*). The overall MD in weight loss between GLP-1 receptor agonist and control groups was -7.1 kg (95% CI -9.2 to -5.0 kg). Secondary outcomes assessed showed improved glycaemic control without hypoglycaemic events and improved blood pressure and lipid levels (low-density lipoprotein, high-density lipoprotein and triglycerides) with GLP-1 receptor agonists compared with control. Subgroup analyses compared once-weekly semaglutide 2.4 mg with once-daily liraglutide 3 mg. The treatment effect comparison showed greater weight loss with semaglutide (overall MD -12.4 kg, 95% CI -13.2 to -11.5 kg) than with liraglutide (overall MD -5.3 kg, 95% CI -5.9 to -4.7 kg).

A 2012 systematic review and meta-analysis of 25 randomized trials assessed the effect on weight loss of GLP-1 receptor agonists compared with placebo, third-generation sulphonylureas, insulin, dipeptidyl peptidase 4

inhibitors, thiazolidinediones, or metformin in overweight and obese adults with and without diabetes (*16*). The included trials evaluated exenatide 5 to 10 micrograms twice daily (13 trials, 3566 participants), liraglutide 1.2 or 1.8 mg daily (eight trials, 5512 participants) and exenatide 2 mg once weekly (four trials, 1052 participants). Two trials directly compared exenatide twice daily with exenatide once weekly, and one trial directly compared twice daily exenatide with liraglutide. A statistically significant greater weight loss was seen with GLP-1 receptor agonists than in the control groups (weighted MD −2.9 kg, 95% CI −3.6 to −2.2 kg). The mean reduction of body weight for those on a GLP-1 receptor agonist ranged from −7.2 to −0.2 kg. Subgroup analysis showed that weight loss was greater with higher doses of GLP-1 receptor agonists. Weight loss was seen both in patients with diabetes (−2.8 kg, 95% CI −3.4 to −2.3 kg) and without diabetes (−3.2 kg, 95% CI −4.3 to −2.1 kg).

Another 2022 systematic review and meta-analysis of 14 randomized trials assessed the efficacy of liraglutide 3 mg compared with placebo in overweight (BMI ≥ 27 kg/m2) and obese (BMI ≥ 30 kg/m2) adult patients (with and without diabetes) (*17*). Liraglutide therapy resulted in a significant change in body weight from baseline compared with placebo (MD −4.91 kg, 95% CI −5.43 to −4.39 kg) both in patients without diabetes (MD −5.04 kg, 95% CI −5.60 to −4.49 kg) and in those with diabetes (MD −4.14 kg, 95% CI −4.95 to −3.32). Liraglutide therapy also resulted in a significant reduction in waist circumference from baseline in both groups (MD −3.64 cm (95% CI −4.43 to −2.85 cm) in patients without diabetes and −3.11 cm (95% CI −3.88 to −2.34 cm) in patients with diabetes). BMI was also significantly reduced from baseline in the liraglutide group both in patients without diabetes (MD −1.95 kg/m^2, 95% CI −2.22 to −1.68 kg/m^2) and in those with diabetes (MD −1.40 kg/m^2, (95% CI −1.73 to −1.07 kg/m^2). Liraglutide therapy resulted in a higher proportion of patients with a weight loss of at least 5% (risk ratio (RR) 2.23, 95% CI 1.98 to 2.52) or 10% (RR 3.28, 95% CI 2.23 to 4.83) from baseline compared to placebo in patients with or without diabetes.

A 2016 systematic review and meta-analysis evaluated the effect on weight loss of five pharmacological treatments approved by the United States Food and Drug Administration (including liraglutide) for obese (BMI > 30 kg/m^2) and overweight (BMI > 27 kg/m^2) adult patients (*18*). The review included 28 randomized controlled trials (all considered at high risk of bias) of which three trials (about 4500 participants) assessed the effects of liraglutide: two versus placebo and one versus orlistat, a lipase inhibitor. In the network meta-analysis, compared with placebo, liraglutide was associated with an odds ratio (OR) of 5.54 (95% CrI 4.16 to 7.78) of achieving at least 5% weight loss and OR 4.99 (95% CrI 3.67 to 7.48) of achieving at least 10% weight loss. Among patients treated with liraglutide, a weight loss of at least 5% was achieved in 63% of participants (23% with placebo) and at least 10% in 34% of participants (9% with placebo).

Liraglutide was also associated with an excess weight loss compared with placebo of 5.3 kg (95% CrI –6.06 to –4.52 kg). In the direct meta-analysis, liraglutide was associated with higher odds of 5% weight loss compared with placebo (OR 5.09, 95% CI 4.07 to 6.37) and orlistat (OR 3.66, 95% CI 1.79 to 7.46) and higher odds of 10% weight loss compared with placebo (OR 4.36, 95% CI 3.61 to 5.26) and orlistat (OR 3.87, 95% CI 1.65 to 9.04).

A 2021 systematic review and meta-analysis of 64 randomized trials (27 018 participants) assessed the effectiveness on weight loss of seven GLP-1 receptor agonists (including liraglutide) compared with placebo in obese or overweight adults with a BMI > 25 kg/m^2 (or > 23 kg/m^2 in Asian patients) (19). Liraglutide was assessed in 29 of the included trials. Adults with or without diabetes or with non-alcoholic fatty liver disease were included. For liraglutide, the meta-analysis showed a statistically significant greater weight reduction over placebo with liraglutide ≤ 1.8 mg (20 trials) (weighted MD –2.72 kg, 95% CI –3.35 to –2.09 kg) and with liraglutide > 1.8 mg (nine trials) (weighted MD –4.49 kg, 95% CI –5.26 to –3.72 kg). Across all included GLP-1 receptor agonists, treatment with liraglutide > 1.8 mg (and semaglutide 2.4 mg and < 2.4 mg) were associated with the highest weight losses over placebo.

Summary of evidence: harms

The safety of liraglutide 3 mg versus placebo was assessed in a 2022 systematic review and meta-analysis in overweight and obese adults with (12 trials) and without (2 trials) type 2 diabetes (17). The safety outcome measures looked at the proportion of adults who experienced adverse events, serious adverse events and treatment discontinuation due to adverse events (TDAEs). Of the 14 studies, 11 included the proportion of participants with adverse events or serious adverse events and five included TDAEs. In adults without diabetes, the pooled estimate of nine studies showed a significantly higher proportion in the liraglutide group experienced adverse events compared with the placebo group (RR 1.11, 95% CI 1.04 to 1.18). For serious adverse events, liraglutide 3.0 mg had a similar risk of compared with placebo (RR 1.12, 95% CI 0.89 to 1.40). Of the five studies including TDAEs, the risk of TDAEs was similar in both treatment groups (RR 1.14, 95% CI 0.50 to 2.60).

A 2019 systematic review and meta-analysis of five randomized trials (4754 participants) investigated the safety of liraglutide in obese individuals without diabetes (20). Four trials (4703 participants) reported the proportion of participants who had withdrawn due to adverse events: 202/2972 in the liraglutide group and 36/1731 in the placebo group (OR 2.85, 95% CI 0.84 to 9.62). In addition, nausea was significantly more common in the liraglutide group than the placebo group (1189/2982 and 236/1731 patients, respectively, OR 5.04, 95% CI 3.34 to 7.60).

A 2016 systematic review and meta-analysis assessed adverse events of multiple pharmacological treatments for obesity (orlistat, lorcaserin, naltrexone bupropion, phentermine-topiramate or liraglutide) in overweight and obese adults who were being treated for at least 1 year (*18*). Compared with placebo, liraglutide (OR 2.95, 95% CI 2.11 to 4.23; surface under the cumulative rankings score 0.20) and naltrexone-bupropion (OR 2.64, 95% CI 2.10 to 3.35; surface under the cumulative ranking (SUCRA) score 0.23) had the highest probability of TDAEs. SUCRA scores (from 0 to 1) determined the probability of each agent having the fewest TDAEs, with higher scores indicating a lower probability.

A 2021 systematic review and network meta-analysis of 64 randomized trials (27 018 participants) also assessed adverse events of GLP-1 receptor agonists in obese participants (*19*). Compared with placebo, taspoglutide (relative risk (RR) 3.87 (95% CI 1.44 to 10.35; SUCRA score 15.1) and liraglutide > 1.8 mg (RR 2.32, 95% CI 1.49 to 3.63; SUCRA score 28.3) had the highest probability of TDAEs. SUCRA scores (from 0 to 100) determined the probability of each agent having the fewest TDAEs, with higher scores indicating a lower probability. GLP-1 agonists or analogues were associated with significantly increased risks of nausea (RR 2.75, 95% CI 2.44 to 3.09) and vomiting (RR 3.22, 95% CI 2.74 to 3.78).

WHO guidelines

WHO guidelines for the management of overweight and obesity are not currently available.

Costs/cost–effectiveness

Several studies on the cost–effectiveness of liraglutide and semaglutide for the treatment of obesity are available. This literature is, however, smaller than the literature examining the cost–effectiveness of GLP-1 receptor agonists for the treatment of type 2 diabetes. Furthermore, the available cost–effectiveness analyses are limited to high-income countries.

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) published a technology appraisal of liraglutide for managing obesity, focusing on the subgroup of patients with BMI ≥ 35 kg/m^2, prediabetes (non-diabetic hyperglycaemia) and a high risk of cardiovascular disease (*21*). At the chosen threshold of £20 000 per quality-adjusted life year (QALY) gained, the report concluded that liraglutide was cost-effective for the management of obesity. Specifically, the base-case incremental cost–effectiveness ratio for liraglutide plus diet and exercise compared with diet and exercise alone was £13 569 per QALY gained. NICE also published a technology appraisal on semaglutide for managing obesity (*22*). For the population of people with a BMI ≥ 30 kg/m^2 with at least one weight-related comorbidity, the base-case incremental cost–effectiveness ratio for semaglutide plus diet and exercise was £16 337 per QALY gained compared to

diet and exercise alone. In comparison with liraglutide, the base-case incremental cost–effectiveness ratio was £600 per QALY gained.

A report by the Canadian Agency for Drugs and Technologies in Health (CADTH) found that compared with standard care, the incremental cost–effectiveness ratio for liraglutide compared with diet and exercise was Can$ 196 876 per QALY gained, and that the price of liraglutide would need to decrease by at least 62% to achieve cost–effectiveness at a Can$ 50 000 per QALY threshold (23).

In the United States context, the Institute for Clinical and Economic Review published a report on the effectiveness and value of medications for obesity management (24). The report concluded that prices would need to decrease for semaglutide and liraglutide to meet cost–effectiveness benchmarks. Specifically, to achieve incremental cost–effectiveness ratios between US$ 100 000 and US$ 150 000 per QALY or equal value life year gained, the health-benefit price benchmark range for semaglutide would require a discount of 28-45% from the current wholesale acquisition cost.

A cost–effectiveness analysis of GLP-1 receptor agonists for treatment of obesity in a United States setting, using a willingness-to-pay threshold of US$ 195 000 found that exenatide, dulaglutide and semaglutide were not cost-effective (25). Compared with exenatide as the reference strategy, semaglutide was the most cost-effective strategy with an incremental cost–effectiveness ratios of US$ 135 467 per QALY gained.

A manufacturer-sponsored cost–effectiveness analysis reported that semaglutide 2.4 mg was cost-effective at a willingness-to-pay threshold of US$ 150 000 compared with no treatment, diet and exercise alone, and other anti-obesity medicines (liraglutide 3 mg, phentermine-topiramate and naltrexone-bupropion) over a 30-year time horizon, with the incremental cost per QALY gained ranging from US$ 23 556 to US$ 144 296 (26).

Cost–effectiveness studies to date have been based on prices of the branded product without generic competition. Patents for liraglutide have begun to expire (see next section on availability) and biosimilar versions of liraglutide are expected to lead to price reductions and improve cost–effectiveness.

Availability

Liraglutide has been approved by the United States Food and Drug Administration as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. As of the date of the application at the end of 2022, liraglutide was also available in Canada, Denmark, France, Germany, Indonesia, Italy, Japan, Malaysia, the Netherlands (Kingdom of the), Singapore, Sweden, and the United States.

According to a report released by the manufacturer, the drug compound patent for liraglutide has expired in China and Japan as of February 2022 and is set to expire in 2023 in the United States and Germany. The manufacturer reports that generic versions of liraglutide could be available in the United States from June 2024 (*27*).

Committee recommendations

The Expert Committee noted that the prevalence of overweight and obesity continues to increase in adults and children and has grown to epidemic proportions, with more than 4 million people having died in 2017 because of being overweight or obese according to the Global Burden of Disease Study. Overweight and obesity, as well as their associated noncommunicable diseases such as arterial hypertension, type 2 diabetes, hyperlipidaemia and breathing problems, are largely preventable. The Committee recognized however that when lifestyle modifications such as reduced calorie diet and regular physical activity are not sufficient, people with obesity may require pharmacological or surgical treatments.

The Committee noted that GLP-1 receptor agonists have been shown to reduce weight and BMI in the short term compared with placebo. However, evidence about the efficacy in different populations (e.g. with regard to ethnicity and age) is lacking. The optimal duration of treatment has also not been defined since maintenance of weight reduction once the therapy is stopped seems to be rare. Furthermore, to date, it is unclear whether treatment of overweight and obesity with GLP-1 receptor agonists affects long-term clinically important outcomes such as hypertension, hyperglycaemia, osteoarthritis and mortality.

The Committee also noted that the use of GLP-1 receptor agonists was associated with an increased frequency of adverse events such as nausea, vomiting, constipation and diarrhoea compared with placebo, although these were usually manageable and self-limiting. The Committee stressed the importance of long-term safety data, which are currently lacking, given the potential need for long-term administration of these medicines to maintain weight loss.

The Committee noted that prices of these medicines were currently high and treatments were unlikely to be cost-effective in several regions of the world.

The Committee also noted that the current application focused on weight loss in people with obesity, while GLP-1 receptor agonists are licensed and widely used for the treatment of type 2 diabetes. In that context, the Committee noted that the applicant already proposed to submit a new application in 2025 to evaluate GLP-1 receptor agonists for the treatment of type 2 diabetes.

The Expert Committee therefore did not recommend inclusion of GLP-1 receptor agonists to the core list of the EML for weight loss in people with obesity because of uncertain long-term clinical benefit and safety in this population.

The Committee noted the advice from the applicants of a planned submission to the 2025 Expert Committee meeting for consideration of GLP-1 receptor agonists for use in the treatment of type 2 diabetes.

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18.3 Estrogens

Estradiol – addition – EML

17-β-estradiol	ATC code: G03CA03

Proposal

Addition of 17-β-estradiol tablets to the complementary list of the EML for the management of pubertal development in adolescents with primary or secondary ovarian failure.

Applicant

Latin American Society for Pediatric Endocrinology

Global Pediatric Endocrinology and Diabetes

WHO technical department

The sexual health and reproductive cancers unit within the WHO Department of Sexual and Reproductive Health and Research reviewed the application. The technical unit supported the inclusion of 17-β-estradiol on the EML as an option to enable induction of puberty in: adolescents with certain relevant differences in sex development, including Turner syndrome; adolescent females who have undergone certain oncology treatments resulting in primary failure; and other adolescent females with primary ovarian failure.

The technical unit highlighted that use of the medicine could support the prevention of bone loss, and noted the potential harm related to estrogen therapy delivered to adolescents at too high a dose and expressed concern about the current availability of adolescent-appropriate dosage forms in tablets or as transdermal patches.

The technical unit noted the importance of holistic care for individuals with differences of sex development throughout the life course, including during adolescence. This care includes interdisciplinary support for mental and emotional well-being and development in addition to physical health and development.

The technical unit highlighted that WHO did not currently have clinical guidelines on induction of puberty in adolescents and advised that the comments provided in relation to this application should be taken as a WHO recommendation.

The technical unit also advised that it would welcome external appraisal of the current evidence about estrogen-only and combined estrogen–progestogen hormone replacement therapy for menopause to determine whether it warranted inclusion in the EML for relief of menopausal symptoms.

EML/EMLc

EML

Section

18.3 Estrogens

Dose form(s) & strengths(s)

Tablet: 0.5 mg, 1 mg, 2 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

17-β-estradiol has not previously been considered for inclusion on the EML for management of pubertal development.

Ethinylestradiol as hormone replacement therapy was included on the EML from 1977 until 2011, when it, and progestogens medroxyprogesterone acetate and norethisterone, were recommended for deletion. At that time, after consideration of a review of the available evidence, the Committee noted that long-term hormone replacement treatment of menopause was no longer considered appropriate, notwithstanding possible individual need for the treatment of symptoms. The Committee recommended deletion of these medicines and signalled the need for a review of the short-term symptomatic management of menopause and the development of guidelines in this regard (1).

Public health relevance

The global prevalence of primary ovarian failure or primary ovarian insufficiency varies in different ethnic populations (2,3). It is characterized by elevated levels of gonadotropins and low levels of estradiol, and lack of spontaneous pubertal development and pubertal growth spurt, accompanied by symptoms including reduction in ovarian function and primary amenorrhoea/oligomenorrhoea. The prevalence of primary ovarian failure according to etiology is 5/10 000 females for Turner syndrome (4), 5/10 000 for oncological treatments (5), 6/100 000 for 46,XY dysgenetic disorders of sex development (6) and 1/10 000 for other etiologies of primary ovarian failure in females younger than 20 years (7). Long-term consequences of primary ovarian failure include increased lifetime risk of cardiovascular disease, osteoporosis, earlier mortality, and neurocognitive disorders (8).

Secondary ovarian insufficiency (hypogonadotropic hypogonadism) is caused by multiple pituitary hormone deficiency in 1/10 000 newborns (*9*) or isolated gonadotropin hormone-releasing hormone deficiency in 1/125 000 females (*10*). It can also occur as a result of structural abnormalities, such as pituitary tumours or craniopharyngiomas and their treatments.

The application defined absent pubertal development in girls as the absence of breast development by 13 years or the absence of menarche by 15 years. Accumulating data show that initiation of puberty at an age comparable with peers is essential for normal physiological development, including secondary sex characteristics, bone and muscle, and social, sexual and psychologic development. Delayed pubertal induction, which is often the case in individuals without pubertal development, may have longstanding consequences (*11*).

Summary of evidence: benefits

The application presented a narrative summary of the benefits of estrogen therapy for induction of puberty in girls with hypogonadism. Estrogens are recommended as first-line treatment for inducing puberty in girls with hypogonadism (*12,13*), with the aim of mimicking normal puberty and allowing girls to achieve normal final adult height and healthy bone mass accrual, and avoiding adverse physical and metabolic consequences of hypogonadism (e.g. lack of breast development, infertility, cardiovascular disease, bone loss/osteoporosis) (*14,15*).

The 2022 guidelines of the European Reference Network on rare endocrine conditions (*11*) recommend the use of bioidentical human estrogens (estradiol/17-β-estradiol E2) for pubertal induction or to sustain puberty in girls (low-quality evidence). The optimal type, route and administration, however, are not well established, and no advantage was observed for one type over another. From studies evaluated in the guideline development process, it was noted that transdermal forms were associated with estradiol, estrone and bioestrogen concentrations closer to normal in the high-dose transdermal group compared with oral forms, and normalization of gonadotropins was comparable between treatments when high-dose transdermal treatment was used (*16*). Oral 17-β-estradiol at a dose of 4 mg daily for 5 years immediately after pubertal induction was associated with more girls with Turner syndrome achieving a normal uterine size than those receiving a dose of 2 mg daily (*17*). For metabolic endpoints, including effects on bone mineralization, body composition, body mass index, lipids, glucose, insulin tolerance, protein turnover and lipolysis, there was very low-quality evidence that transdermal and oral routes of estrogen delivery had similar effects (*18–20*).

The application acknowledged that the use of transdermal formulations was promising. However it did not propose inclusion of transdermal formulations for a number of reasons including: the need to change patches regularly which

may not be acceptable to adolescents; the need to cut/manipulate adult patches; the limited availability in resource-constrained settings; stability concerns at different temperatures; and lack of comparative studies.

Summary of evidence: harms

There is no evidence of liver toxicity (*21*) or increased risk of cancer before the age of natural menopause in women with primary ovarian failure (*22*) given estrogen replacement therapy. The evidence of potential harm related to estrogen therapy in girls with hypogonadism is dose related: high-dose estrogen treatment early in puberty or rapid dose escalation may result in reduced final height and poor breast development, such as prominent nipple development with poor supporting breast tissue. This effect can be minimized by a gradual start with low-dose estrogen regimens. There are also concerns that supraphysiological supplementation may adversely affect uterine development and bone mass accrual (*23*).

Non-specific adverse events that have been reported include nausea, vomiting, fluid retention, hypertension, ankle oedema, headache, depression, nervousness, insomnia, leg cramps, decreased high-density lipoprotein cholesterol, acne, itching, dry skin, dysmenorrhoea and irregular vaginal bleeding.

WHO guidelines

WHO guidelines for management of pubertal development in adolescents with primary or secondary ovarian failure are not currently available.

Costs/cost–effectiveness

The application reported the monthly cost of treatment with 17-β-estradiol to be US$ 2.70 and US$ 4.50 for doses of 1 mg and 2 mg a day, respectively. Individual tablet costs were reported as US$ 0.15 for 2 mg tablets in Argentina, US$ 0.11 for 1 mg tablets in India and US$ 0.09 for both 1 mg and 2 mg tablets in New Zealand.

No cost–effectiveness data were presented in the application.

Availability

Estradiol tablets are available globally in branded and generic formulations. Child-appropriate formulations are lacking for younger children, with the available formulations requiring manipulation to obtain appropriate doses.

Committee recommendations

The Expert Committee noted that management of delayed pubertal development with estradiol aims to mimic normal puberty to allow achievement of final adult height and healthy bone mass accrual, and to avoid adverse physical and metabolic

consequences in adolescents with primary or secondary ovarian failure. The Committee noted that the global prevalence of primary or secondary ovarian failure and primary ovarian insufficiency varies in different ethnic populations but was generally low.

The Committee considered that the application reported insufficient information on the evidence supporting the efficacy and safety of estradiol for the proposed indications. The Committee also considered that information on the optimal dosage and formulations for use in the proposed population was inadequate.

The Committee advised that any future consideration of estradiol therapy for inclusion on the Model Lists should also address its use in the management of other indications for which it is commonly used, such as hormone replacement therapy in menopause or after hysterectomy.

The Expert Committee therefore did not recommend the inclusion of 17-β-estradiol on the complementary list of the EML for the management of pubertal development in adolescents with primary or secondary ovarian failure.

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18.5 Medicines for diabetes
18.5.1 Insulins
Human insulin – new formulation – EML and EMLc

Human insulin, fast-acting	ATC code: A10AB01
Human insulin, intermediate-acting	ATC code: A10AC01

Proposal

Inclusion of prefilled pen and cartridge formulations of human insulin (fast- and intermediate-acting) on the EML and EMLc.

Applicant

Kim Donaghue, The Children's Hospital at Westmead, Westmead, Australia

Jean-Pierre Chanoine, British Colombia Children's Hospital, Vancouver, Canada

Salllianne Kavanagh, University of Huddersfield, Huddersfield, United Kingdom

Mark E. Molitch, Northwestern University Feinberg School of Medicine, Chicago, IL, United States of America

Carine de Beaufort, Centre Hospitalier de Luxembourg, Luxembourg

Sanjay Kalra, Bharti Hospital, Karnal, India

WHO technical department

The technical team in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical team did not support the application highlighting the following reasons.

- The body of evidence provided was insufficient and selective, with some systematic reviews on the topic omitted.
- A substantial percentage of the included studies in the application were observational studies, with a risk of confounding bias.
- No distinction was made between data on human and analogue insulin.
- No adequate cost–effectiveness/utility/benefit analyses on the topic were provided.
- Environmental impact concerns exist with plastic prefilled pens.
- The evidence table provided was biased, with few data on people with type 1 diabetes, and the results on the advantages of human insulin were not reported.

EML/EMLc

EML and EMLc

Section

18.5.1 Insulins

Dose form(s) & strengths(s)

Injection: 100 IU/mL in 3 mL cartridge or prefilled pen

Core/complementary

Core

Individual/square box listing

Individual

Background

Human insulin in vials has been available on the EML since 1977 and on the EMLc since 2007. In 2021, long-acting insulin analogues, in cartridge and prefilled pen delivery systems, were added to the Model Lists (*1*).

Public health relevance

Diabetes mellitus (type 1 and type 2) affected almost 460 million people worldwide in 2019, most of whom (about 95%) had type 2 diabetes (*2*). Proper management and treatment are crucial to prevent vascular complications and avoid adverse outcomes of hypoglycaemia.

Insulin treatment is crucial for people with type 1 diabetes and for many with type 2 diabetes. It is typically administered through injections, with the preferred method being the basal bolus approach (*3*,*4*). This involves using intermediate or long-acting insulin once or twice a day and short-acting insulin three to five times a day before meals, adjusted based on factors such as blood glucose levels, growth, activity, illness and stress. Regular dose adjustments are necessary for effective diabetes management.

The proper administration of insulin is essential for diabetes management. If the dose is too high, it can lead to hypoglycaemia, which may cause unconsciousness, seizures or death. If the dose is too low, glucose levels are poorly controlled, increasing the risk of diabetic ketoacidosis and long-term vascular complications, which can also result in morbidity and death if not treated appropriately.

Reuse of needles for insulin administration is common in low-income countries and has been associated with infection (*5*).

Summary of evidence: benefits

The application identified two systematic reviews that compared insulin cartridge or pen devices with vials and syringes.

A 2016 systematic review and meta-analysis evaluated the efficacy of insulin pen devices compared with vial and syringe administration in patients with type 1 and type 2 diabetes (6). The review included 17 studies (10 retrospective cohort studies, six crossover randomized controlled trials and a parallel non-randomized clinical trial). Six of the 17 studies included people with type 1 diabetes. Data were reported for glycosylated haemoglobin (HbA1c) outcomes, hypoglycaemia, adherence (assessed using the medication possession ratio, which estimates the proportion of days the patient has medication available during the observation period), persistence (defined as the number of days until discontinuation of the medication), patient preference and quality of life. Meta-analyses were performed where possible. The following results were reported in the application.

- For mean change in HbA1c at 12 months, there was very low-certainty evidence that cartridge/pen delivery systems improve HbA1c compared to vial and syringe administration (mean difference (MD) –0.28%, 95% CI –0.49% to –0.07%; four randomized controlled trials, 5079 participants).

- For mean change in HbA1c at 12 months in insulin-naïve patients, there was low-certainty evidence that cartridge/pen delivery systems improve HbA1c compared to vial and syringe administration (MD –0.35%, 95% CI –0.50% to –0.19%; three randomized controlled trials, 2973 participants).

- For percentage of patients with at least one episode of hypoglycaemia after 12 months, there was low-certainty evidence of fewer patients with hypoglycaemia with cartridge/pen delivery systems compared to vial and syringe administration (risk ratio (RR) 0.78, 95% CI 0.66 to 0.91; four randomized controlled trials, 7822 participants).

- For mean change in medication possession ratio after 12 months, there was low-certainty evidence of improved adherence with cartridge/pen delivery systems compared with vial and syringe administration (MD 0.10, 95% CI 0.04 to 0.16; four randomized controlled trials, 6860 participants).

- For percentage of persistent patients after 12 months, there was low-certainty evidence of more patients persistent at 12 months with cartridge/pen compared to vial and syringe administration (RR 1.31, 95% CI 1.15 to 1.48; six studies, 10 753 participants).

The systematic review also reported a non-statistically significant trend favouring cartridge/pen delivery systems for the percentage of patients who achieved HbA1c < 7% (RR 1.12, 95% CI 0.99 to 1.27). Patient preference was measured in different studies using several non-validated questionnaires and different time horizons (*7–11*). These studies showed a tendency favouring cartridge/pen delivery systems. A single, small study used a short-form health survey (SF-36) to assess quality of life in 32 and 33 patients assigned to use cartridge/pen or vial and syringe administration, respectively (*12*). Cartridge/pen delivery systems were associated with statistically significant differences over vial and syringe administration in change from baseline scores for three sub-scales of the SF-36: physical component scores (+3.9 standard deviation (SD) 1.9 versus −1.0 SD 1.3, *P* = 0.037); physical role scores (+16.4 SD 9.4 versus −18.2 SD 8.4, *P* = 0.008); and general health status score (+9.8 SD 4.0 versus −2.5 SD 3.3, *P* = 0.021). Significant differences were not observed for the other sub-scales.

A 2013 systematic review of 17 studies aimed to identify real-world factors affecting adherence to insulin therapy in patients with type 1 and 2 diabetes (*13*). Six studies used self-reported measures and 11 studies used calculated measures of adherence. Six of the studies reported adherence by delivery system: three in patients starting insulin therapy and three in patients switching from vial and syringe administration to a pen device. Five of these studies showed significantly higher adherence with a pen device than vial and syringe administration, measured using either medication possession ratio or proportion of days covered. The application pooled data from these studies and found low-certainty evidence of higher adherence with pen devices compared with vial and syringe administration (RR 1.16, 95% CI 1.12 to 1.21; six studies, 10 630 participants).

Two recent studies conducted in North India (*14*) and Lebanon (*15*) showed that patients preferred insulin pens/cartridges to vials and syringes for several reasons. Patients reported that the injections using pens/cartridges were less painful, more convenient and simpler, leading to fewer instances of missed insulin injections. Moreover, using pens/cartridges allowed patients to easily administer insulin for meals outside their homes or during vacations. Additionally, patients experienced less social stigma with the use of pens/cartridges compared with vials and syringes.

Summary of evidence: harms

No data were presented in the application on harms associated with insulin administered using cartridge/pen delivery systems. The application stated that the alternate delivery method has been in use for more than 20 years in some countries and no harmful effects have been documented.

WHO guidelines

The 2018 WHO guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes include a strong recommendation for the use of human insulin to control blood glucose levels in adults with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated, without reference to a particular delivery system (*16*).

Costs/cost–effectiveness

The cost of insulin pens/cartridges for diabetes management is higher than vials and syringes in most cases, particularly in low- and middle-income countries (*17*). However, when considering the total cost of diabetes care, claims data in the United States show cost savings with the use of pens/cartridges, primarily due to reduced hypoglycaemia compared to VaS (*18,19*). A retrospective observational study of individuals with type 2 diabetes enrolled in Medicaid in the United States, followed for 2 years, found significantly lower annualized health care costs in those people using pen therapy compared with those using syringes (US$ 14 857 versus US$ 31 765). This difference was mainly due to reduced hospital, diabetes-related and outpatient costs. However, prescription costs of syringes were significantly lower and prescription costs of pens significantly higher in patients who were switched from syringes to pens versus those who remained on syringes (*18*).

A longitudinal, retrospective analysis of two claims' databases in the United States of individuals with type 1 or 2 diabetes who started insulin aspart therapy using pens ($n = 10\ 577$) or vials/syringes ($n = 9305$) found that vial/syringe use was associated with a 35% and 44% higher risk of hypoglycaemia compared with using pens/cartridges (*19*). Vial/syringe use was associated with 89% and 63% greater health care costs related to hypoglycaemic events compared with pen/cartridge use.

A study on the price and availability of insulin in 13 low- and middle-income countries found that the median prices for short-acting, intermediate-acting and rapid-acting insulin and mixed human insulin were lower for vials than for pens/cartridges. For example, the median price for 10 mL of 100 IU/mL mixed human insulin was US$ 6.76 for vials, US$ 14.42 for cartridges and US$ 18.16 for pens (*20*).

A cross-sectional survey evaluated price, availability and affordability of insulin products in eight cities in Pakistan (*21*). This study included a comparison of median prices and affordability of all types of insulin products combined (including originator and biosimilar products) in vial, pen and cartridge forms in the private sector. The median prices for 10 mL of 100 IU/mL insulin in vials, pens and cartridges were 735, 3070 and 1313 Pakistani rupees, respectively. The number of days' wages of the least-paid, unskilled public sector worker required to obtain a 30-day supply of human insulin in Pakistan was reported as 1.2 days

for vials, 5.2 for pens and 2.2 for cartridges. In comparison, the number of days' wages for a 30-day supply of insulin was 3.3 days for vials and 6.9 for cartridges in Nepal, and 1.4 for vials, 5.1 for pens and 3.5 for cartridges in Bengaluru, India.

In a survey in 2019 in leading diabetes centres in 37 low- and middle-income countries supported by the Life for a Child Program, 16.7% of people with diabetes younger than 25 years were using insulin pens. Additionally, 74% of respondents preferred insulin pens as their method of insulin delivery (*5*).

Availability

Human insulin in prefilled pens and cartridges have wide global regulatory approval.

Current insulin prices and availability are a barrier to treatment in most low- and middle-income countries, and some subpopulations in higher-income countries cannot reliably access insulin because it is unavailable and/or unaffordable. To address this problem, in 2019 WHO issued a first invitation for expressions of interest for prequalification of human insulin. In 2022, a second invitation was issued (*22*). Products included in the second invitation included:

- human insulin injection (soluble) 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial and cartridge;
- human intermediate-acting insulin 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial and cartridge (as compound insulin zinc suspension or isophane insulin);
- long-acting insulin analogue solution for injection 100 U/mL vial and 100 U/mL in 3 mL cartridge.

Human insulin solution 100 IU/mL and human insulin suspension 100 IU/mL in 10 mL vials and 3 mL cartridges manufactured by Novo Nordisk were prequalified by WHO in September 2022 (*23*).

Committee recommendations

The Expert Committee recognized insulin as a life-saving essential medicine for which a strong public health need existed and acknowledged that affordable and equitable access to insulin products continued to be a global health priority. The Committee was encouraged by the progress made by WHO through its prequalification programme to address this challenge with the prequalification of both human insulin and long-acting insulin analogue products in the recent past.

The Committee recalled the recommendation in 2021 to include long-acting insulin analogues on the Model Lists in prefilled pen and cartridge delivery systems and considered that inclusion of human insulin in the same delivery systems would be consistent with that recommendation. The Committee

considered that cartridges and prefilled pens may offer advantages for patients over vials and syringes in terms of ease of use, greater accuracy of dosing and improved adherence.

The Expert Committee therefore recommended that the current listings for human insulin on the EML and EMLc be extended to include cartridge and prefilled pen delivery systems.

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18.6 Medicines for hypoglycaemia

Somatropin – addition – EMLc

Somatropin	ATC code: H01AC01

Proposal

Inclusion of somatropin (recombinant human growth hormone, rhGH) on the complementary list of the EMLc for the management of hypoglycaemia secondary to growth hormone deficiency in neonates, infants and young children.

Applicant

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WHO technical department

Not applicable

EML/EMLc

EMLc

Section

18.6 Medicines for hypoglycaemia

Dose form(s) & strengths(s)

Injection: 5 mg in cartridge or prefilled pen

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Somatropin has not been previously considered for inclusion on the Model Lists for the proposed nor any other indication.

Diazoxide and glucagon were recommended for inclusion on the EMLc in 2021 and 2011, respectively, for use in the treatment of hypoglycaemia in children. Diazoxide was recommended specifically for management of hypoglycaemia secondary to prolonged hyperinsulinism (*1*).

Public health relevance

The prevalence of idiopathic growth hormone deficiency in the United Kingdom and United States of America is estimated to be between 1 in 3400 and 4000 (*2*). Other estimates report a worldwide prevalence of growth hormone deficiency of between 1 in 4000 to 1 in 10 000 (*3*).

Growth hormone deficiency occurs when the pituitary gland fails to produce enough growth hormone. This deficiency is typically associated with medical conditions that affect the pituitary gland, such as congenital brain abnormalities (e.g. septo-optic dysplasia), and in rare cases, gene deletions in the hormonal pathway responsible for growth hormone production. These conditions are usually present at birth and often diagnosed in infancy. Additionally, growth hormone deficiency can be caused by brain tumours and their treatment, including radiation therapy, which typically affects older children. Growth hormone deficiency is frequently linked to short stature throughout childhood, adolescence and adulthood.

The presentation, diagnosis, and management of growth hormone deficiency differ substantially between neonates and older children or adolescents (*4–7*). Neonatal growth hormone deficiency is associated with severe hypoglycaemia in 30–85% of cases and can be managed with recombinant human growth hormone treatment (*8,9*). Neonatal growth hormone deficiency is rarely observed beyond 2 years of age, although there have been occasional reports in children up to the age of 7 years (*8,10–12*). Long-term consequences of moderate and severe neonatal hypoglycaemia include irreversible neurological damage and delayed psychomotor development (*13–16*).

Summary of evidence: benefits

No evidence for the benefits of rhGH in the treatment of hypoglycaemia secondary to growth hormone deficiency was presented in the application. The application stated that randomized, placebo-controlled trials evaluating the effectiveness of rhGH therapy on hypoglycaemia in neonates were lacking because it is ethically unreasonable not to treat patients diagnosed with growth hormone deficiency with growth hormone replacement therapy.

Several case reports, case series and cohort studies have reported the effectiveness of rhGH therapy in addressing hypoglycaemia in neonates and infants with human growth hormone deficiency (*10*).

No evidence was presented in the application on potential alternative treatments for hypoglycaemia in neonates and infants, such as dextrose, diazoxide and glucagon.

Summary of evidence: harms

In the absence of long-term randomized trials, evaluation of the potential harms and toxicity of rhGH has been conducted through various registries mandated by health authorities worldwide.

When used as replacement therapy in children and adolescents side-effects of rhGH include rash and pain at injection site, transient fever, prepubertal gynaecomastia, arthralgia, oedema, benign intracranial hypertension, insulin resistance, progression of scoliosis and slipped capital femoral epiphysis (*17*). A review of data from two observational studies of the long-term safety of growth hormone treatment in children found no indication of an increased risk of mortality or adverse events related to the dose of growth hormone in any risk group (*18*). The application stated that short- and long-term adverse effects associated with rhGH reported in older children and adolescents have not been reported in neonates or infants (*19*).

Because rhGH stimulates cell proliferation, concerns exist that treatment might be associated with an increased risk of malignancies.

A 2017 cohort study of 23 984 patients treated with rhGH in eight European countries since 1984 found a significantly increased incidence in bone and bladder cancer in rhGH-treated patients without previous cancer. For patients treated with rhGH after previous cancer, cancer mortality risk was significantly increased with increasing rhGH dose. The incidence of Hodgkin lymphoma increased significantly with longer follow-up in all patients and in patients without previous cancer (*20*).

The United States National Cooperative Growth Study evaluated the safety and efficacy of rhGH in 54 996 children between 1985 and 2006. No increased risk in the development of leukaemia was observed in children treated with rhGH compared with an age-matched general population. Intracranial and extracranial malignancies were not significantly more frequent in patients without risk factors. An increased risk of secondary malignancies in patients previously treated with radiation was observed (*21*).

The Childhood Cancer Survival Study followed up 13 539 survivors of childhood cancer. A nested cohort of 361 cancer survivors treated with rhGH showed no significantly increased risk of disease recurrence (relative risk (RR) 0.83, 95% confidence interval (CI) 0.37 to 1.86). An increased risk of development of secondary neoplasms (all solid tumours and no secondary leukaemias) was observed (RR 3.21, 95% CI 1.88 to 5.46) (*22*).

Additional evidence

The evidence provided by the applicants was incomplete and was supplemented by the reviewers and Secretariat.

WHO guidelines

WHO guidelines for the management of hypoglycaemia secondary to growth hormone deficiency are not currently available.

Costs/cost–effectiveness

Data specifically addressing the cost–effectiveness of rhGH treatment in neonates and infants with hypoglycaemia secondary to growth hormone deficiency are lacking.

The application reported the cost of growth hormone (per mg) as US$ 46.50 to 62.10 in Argentina, US$ 20.67 to 34.20 in Canada, US$ 6.55 in India and US$ 26.30 in Mexico. The monthly treatment costs (assuming a price of US$ 25/mg and approximate weight of the 50% centile of 3.5 kg for neonates, 7.5 kg for 6-month-old infants and 15 kg for 24-month-old infants) were estimated in the submission to be US$ 56, US$ 120 and US$ 240, respectively.

Availability

Somatropin is manufactured and distributed by several pharmaceutical companies around the world. Manufacturers differ by the appearance and quality of the injection devices and by the different strengths and concentrations of the cartridges to suit all ages.

The availability of and financial support for rhGH treatment in low- and middle-income countries are generally limited compared with high-income countries, potentially leading to disparities in access to this therapy for individuals with growth hormone deficiency in those regions.

Other considerations

Treatment with rhGH requires specialized diagnostic and monitoring facilities as well as medical care by a paediatric endocrinologist or, if not available, by a paediatrician knowledgeable in paediatric endocrine diseases.

The misuse of rhGH for performance enhancement is a serious concern. This is primarily due to the hormone's anabolic properties, which can potentially lead to unauthorized off-label use.

Committee recommendations

The Expert Committee noted that growth hormone deficiency, both congenital and acquired, has been reported to affect between 1 in 4000 to 10 000 people globally. However, the incidence and prevalence of hypoglycaemia due to growth hormone deficiency, the indication for which listing of somatropin is requested, was not reported in the application. The Committee acknowledged that management of hypoglycaemia, of any etiology, in neonates and infants was critical to prevent permanent neurological sequelae.

The Committee noted that the application did not identify specific evidence from clinical trials of the efficacy and harms of somatropin in the management of hypoglycaemia due to growth hormone deficiency, but acknowledged limited evidence from case reports and cohort studies that have reported the effectiveness of rhGH therapy for this indication.

The Committee noted that the Model Lists currently include diazoxide, glucagon and glucose for use in the management of hypoglycaemia. The Committee considered that comparative evidence for somatropin versus these medicines, including information on the comparative costs and cost–effectiveness would be necessary to inform any future consideration of somatropin for this indication

The Expert Committee therefore did not recommend the inclusion of somatropin on the complementary list of the EMLc for the management of hypoglycaemia secondary to growth hormone deficiency in neonates, infants and young children.

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18.8 Medicines for disorders of the pituitary hormone system
Bromocriptine and cabergoline – addition – EML

Bromocriptine	ATC code: G02CB01
Cabergoline	ATC code: G02CB03

Proposal

Addition of bromocriptine and cabergoline to the core list of the EML and EMLc for treatment of hyperprolactinaemia due to prolactinomas.

Applicant

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WHO technical department

The Contraception and Fertility Care unit within the Department of Sexual and Reproductive Health and Research reviewed the application. The technical unit supported the inclusion of bromocriptine and cabergoline on the EML, highlighting that these medicines are important for the management of hyperprolactinaemia, a condition with consequences that affect a wide variety of people globally.

Evidence suggests that compared to no treatment, oral bromocriptine is effective in normalizing prolactin levels in people with hyperprolactinaemia (*1–3*), may have some effect on return of ovulatory cycles (*2,3*) and may have a limited effect on live births in women with idiopathic hyperprolactinaemia (*4*).

Evidence suggests that cabergoline is effective in normalizing prolactin levels (*1,2*). In addition, based on a de novo systematic search of data from randomized controlled trials published between 1990 and June 2019 by the sexual and reproductive Health department, there was low-quality evidence showing that cabergoline may increase pregnancy assessed at 6–7 weeks of gestation compared with bromocriptine. Data on live births are not available from these randomized controlled trials (unpublished data).

EML/EMLc

EML and EMLc

Section

18.8 Medicines for disorders of the pituitary hormone system (new subsection)

Dose form(s) & strengths(s)

Bromocriptine
Tablet: 2.5 mg, 5 mg
Capsule: 5 mg

Cabergoline
Tablet: 0.5, 1 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Bromocriptine, cabergoline and other oral dopamine agonists were evaluated in 2015 for inclusion on the EML for use in the treatment of Parkinson disease. At that time, the Expert Committee did not recommend inclusion due to insufficient evidence for clinically relevant efficacy or safety advantages of oral dopamine agonists over the existing medicines already included in the EML for treatment of Parkinson disease (*5*).

Oral dopamine agonists have not previously been evaluated for addition to the EML for treatment of hyperprolactinaemia/prolactinoma. Currently, the Model Lists do not include any medicines for use in this indication.

Public health relevance

Prolactinomas (also called lactotroph adenomas) are pituitary adenomas that secrete prolactin and are the most common cause of pathological hyperprolactinaemia. Hyperprolactinaemia can cause amenorrhoea in women, erectile dysfunction in men and loss of libido, galactorrhoea and infertility in both sexes. Hyperprolactinaemia occurs in 5% to 17% of women with secondary amenorrhoea, which is an important cause of infertility (*6–8*).

The prevalence of prolactinomas ranges from 25 to 63 per 100 000. The prevalence of symptomatic microprolactinomas and macroprolactinomas is about 40 per 100 000 and 10 per 100 000, respectively. The annual incidence of prolactinomas ranges from 2 to 5 new cases per 100 000, and the value is three times higher in women than in men (*9*).

About 10% of unselected pituitaries examined at autopsy contain pituitary adenomas and magnetic resonance imaging scans of normal volunteers show a similar proportion of the tumours. Immunohistochemical staining shows that about 50% are prolactinomas (*10*). Patients may be symptomatic either from

the effects of the hyperprolactinaemia or from the mass effect of the tumour (headache, hypopituitarism, visual field defects) and these symptomatic patients require treatment.

An alternative to pharmacological treatment with dopamine agonists is trans-sphenoidal surgery performed by pituitary neurosurgeons. A survey in low- and middle-income countries published in 2018 showed that individuals living in 11 countries (of 68 countries with complete responses) did not have access to any neurosurgical care (*11*). Radiation therapy is usually reserved for patients not responding to pharmacological and/or surgical treatment or with invasive tumours and is also unavailable in many settings.

Summary of evidence: benefits

Medical therapy with bromocriptine and trans-sphenoidal surgical removal of prolactinomas have been in clinical use since the 1970s, and with cabergoline since the 1980s.

Dopamine agonists versus no treatment

A 2012 systematic review and meta-analysis compared the efficacy and adverse effects of different treatment modalities (medications, surgery and radiotherapy) for hyperprolactinaemia (not specifically prolactinomas) (*3*). Three observational studies and one randomized controlled trial that compared dopamine agonists to no treatment were identified. Aggregated results showed that dopamine agonists significantly reduced prolactin levels (weighted mean difference (WMD), –45 ng/mL, 95% confidence interval (CI) –77 to –11 ng/mL) and the risk of persistent hyperprolactinaemia (risk ratio (RR) 0.90, 95% CI 0.81 to 0.99). No significant effect on clinical outcomes was demonstrated in this meta-analysis, however, the number of assessable patients was small for each outcome.

Cabergoline versus bromocriptine

A 2011 systematic review and meta-analysis of four randomized controlled trials (743 participants) compared cabergoline with bromocriptine for the treatment of patients with idiopathic hyperprolactinaemia and prolactinomas (*2*). Cabergoline was superior to bromocriptine for normalization of serum prolactin levels (RR 0.67, 95% CI 0.57 to 0.80), and normalization of menstruation with return of ovulatory cycles (RR 0.74, 95% CI 0.67 to 0.83).

Dopamine agonists versus trans-sphenoidal surgery

A 2021 systematic review and meta-analysis compared the outcomes of patients treated with dopamine agonists and patients treated with surgery as initial therapy for microprolactinomas (*12*). Overall, 16 case series and 2 retrospective cohort studies published between 1999 and 2018 (661 participants) were identified. At ≥ 12 months of follow-up, the medical treatment group achieved higher remission

rates of hyperprolactinaemia (96% versus 86%, *P* = 0.02; absolute numbers not provided) but surgery showed a higher remission rate after treatment withdrawal of dopamine agonists (78% versus 44%, *P* = 0.003). No data comparing bromocriptine with cabergoline were provided. Given the non-randomized nature of these studies, the results need to be interpreted with caution.

In a 2006 review of 50 surgical series (years not reported) including 2137 patients with microadenomas and 2226 with macroadenomas, normalization of prolactin levels was achieved in 74.7% (1596/2137) of those with microadenomas and 33.9% (755/2226) of those with macroadenomas by 1–12 weeks after surgery (*13*).

Summary of evidence: harms

Commonly reported adverse effects of dopamine agonists include nausea, vomiting, headache, nasal stuffiness, orthostatic dizziness and Reynaud phenomenon. In studies comparing cabergoline and bromocriptine, adverse effects were reported less frequently and were less severe with cabergoline than bromocriptine (*2,3*).

A 2011 systematic review and meta-analysis of four randomized controlled trials comparing cabergoline and bromocriptine in patients with idiopathic hyperprolactinaemia and prolactinomas found that the bromocriptine group experienced a significantly higher number of adverse effects compared with the cabergoline group (RR 1.43, 95% CI 1.03 to 1.98). Patients receiving cabergoline had significantly fewer occurrences of nausea (RR 1.66, 95% CI 1.33 to 2.06) and vomiting (RR 2.02, 95% CI 1.13 to 3.59). However, no notable differences were seen between the treatment groups for constipation, headache, dizziness, vertigo, abdominal pain, dyspepsia, gastritis, fatigue, mastalgia, depression, hot flashes, somnolence or postural hypotension (*2*).

Impulse control disorders have been found to be common in patients treated with dopamine agonists when used in high doses for the treatment of Parkinson disease. The mechanism of action behind impulse control disorders seems to be an interaction between the dopamine agonists and the D3 receptors in the mesolimbic system, known to be responsible for the processes governing behaviour, pleasure and addiction (*14*). Clinical experience and studies show that impulse control disorders also occur in patients with prolactinomas and are, in part, dose related. A cross-sectional multicentre study of 308 patients with prolactinomas (289 treated with cabergoline, 19 treated with bromocriptine) followed in 11 referral centres in Türkiye found that 16.6% (51 patients) developed an impulse control disorder (hypersexuality alone in 6.5% (20 patients), pathological gambling alone in 0.6% (2 patients), compulsive eating alone in 2.9% (9 patients), compulsive shopping alone in 1.0% (3 patients), and more than one impulse control disorder in 5.5% (17 patients); hypersexuality was more common in men and compulsive eating more common in women (*15*).

Cardiac valve abnormalities, usually valvular insufficiency, have been reported with dopamine agonists used for treatment of Parkinson disease, and led to market removal of pergolide for the treatment of Parkinson disease in the United States in 2007 (*16*). Doses of dopamine agonists for the treatment of hyperprolactinaemia are lower than those used for the treatment of Parkinson disease (3–5 mg per day). Only 15–20% of patients treated with cabergoline for hyperprolactinaemia require doses higher than 2 mg/week and very few patients require doses approaching 1–2 mg/day.

A 2018 meta-analysis of 13 case–control studies (836 cases and 1388 controls) published between 2008 and 2013 assessed the association between the use of cabergoline for the treatment of hyperprolactinaemia and clinically significant cardiac valvulopathy (*17*). Significantly more cases of mild tricuspid regurgitation without clinical relevance were found in patients treated with cabergoline for more than 1 year (20% versus 11%; odds ratio (OR) 1.91, 95% CI 1.28 to 2.87). Clinically significant tricuspid regurgitation (reported as moderate or severe) was also more common in patients using cabergoline (5% versus 1%; OR 3.74, 95% CI 1.79 to 7.80) but the overall frequency was low (33 moderate and no severe instances among 693 cases with available data) and strongly influenced by a single study that contributed 27 instances of moderate tricuspid regurgitation alone (54% versus 18%) (*18*).

A subsequent prospective study by the group reporting the 27 instances of moderate tricuspid regurgitation did not show an increased risk of significant cardiac valve regurgitation in 40 patients with newly diagnosed hyperprolactinaemia treated with cabergoline and followed up for 60 months (*19*).

The mechanism for the valve abnormalities described with high-dose cabergoline is thought to be the action of the cabergoline at serotonin 5-HT$_{2B}$ receptors, which are present in human cardiac valves and are necessary for normal cardiac development. Excess stimulation of these receptors is thought to result in activation of mitogenic pathways with the development of a plaque-like process that extends along leaflet surfaces and encases the chordae tendinae (*20*). Bromocriptine does not seem to be associated with an increased risk of valvulopathy as evidenced in a nationwide Danish registry study including 3035 female bromocriptine users and 15 175 controls matched on age, sex and year of inclusion (*21*).

Because the valve abnormalities are seen relatively commonly in people with Parkinson disease treated with 3–5 mg/day of cabergoline and not in cabergoline-treated patients in whom the dose is usually less than 2 mg/week, it is uncertain at what dose level these valve effects may occur if doses of cabergoline greater than 2 mg/week are needed to control prolactin levels and tumour growth. Therefore, it has been recommended that all patients receiving cabergoline doses greater than 2 mg/week have an annual echocardiogram. In 30–50% of patients who develop abnormities, reversal of abnormalities can occur if cabergoline is discontinued (*22*).

Additional evidence

The evidence provided by the applicants was incomplete and was supplemented by the reviewers and Secretariat.

WHO guidelines

WHO is currently developing guidelines on the prevention, diagnosis and treatment of infertility. The guidelines will compare the effectiveness of cabergoline and bromocriptine for the management of infertility due to ovulatory dysfunction secondary to hyperprolactinaemia. The guidelines are expected to be published in late 2023 or early 2024.

Costs/cost–effectiveness

Representative costs for 1 month of treatment with bromocriptine 5 mg/day and cabergoline 1 mg/week from different countries, as reported in the application, are shown in Table 25.

Table 25
Monthly treatment costs for dopamine agonists (US$)

Country	US$	
	Bromocriptine 5 mg/day	**Cabergoline 1 mg/week**
Argentina	Not available	24
Bolivia (Plurinational State of)	Not available	17
Brazil	46	18
India	12	6
Mexico	20	40
United States	360	392

A 2016 cost–effectiveness study compared medical therapy with either bromocriptine or cabergoline to trans-sphenoidal surgery (either microsurgical or endoscopic) (*23*). The analysis was conducted from the perspective of the United States third-party health care payer. In the base-case scenario, using a 5-year time horizon (medical therapy continued for 5 years or surgery followed for 5 years), the incremental cost–effectiveness ratios of microscopic trans-sphenoidal surgery and endoscopic trans-sphenoidal surgery were US$ 2797 per quality-adjusted life year (QALY) gained and US$ 3151 per QALY, respectively, compared with US$ 4380 per QALY for cabergoline and US$ 3901 per QALY for

bromocriptine. Using a 10-year time horizon, the respective incremental cost–effectiveness ratios were US$ 1530 per QALY for microscopic surgery, US$ 1683 per QALY for endoscopic surgery, US$ 2876 per QALY for bromocriptine and US$ 3514 per QALY for cabergoline. The authors concluded that surgery was more cost-effective than therapy with bromocriptine or cabergoline at 10 years, assuming a "cure" rate of 90% and a complication rate of < 1% with surgery. Under these assumptions surgery was dominant compared with treatment with dopamine agonists. However, the application highlighted that the study did not account for the fact that a 90% cure rate is achievable only for microprolactinomas in highly specialized surgical settings and that hyperprolactinaemia recurs after surgery in 10–20% of cases which then require treatment with dopamine agonists.

A 2017 cost–effectiveness analysis compared surgery to treatment with dopamine agonists in the United States (*24*). The study used a third-party payer perspective and was based on data from 108 patients with prolactinomas seen by neurosurgeons at a single centre in the United States between 2010 and 2015. The base case assumed an 80% response to dopamine agonists and a 60% response to surgical treatment. For patients diagnosed with prolactinoma at 40 years of age, the analysis suggested that surgery had the lowest lifetime cost (US$ 40 473), followed by bromocriptine (US$ 41 601) and cabergoline (US$ 70 696). The analysis also suggested that surgery generated more QALYs. The authors concluded that surgery was a more cost-effective treatment than dopamine agonists for prolactinomas across a range of ages, medical/surgical costs and medical/surgical response rates if surgical cure rates are > 30%.

A 2017 study used retrospective data from 126 patients with prolactinoma treated in a single centre in China between 2008 and 2009 to compare the cost–effectiveness of medical therapy with bromocriptine and trans-sphenoidal surgery. For microadenoma, the estimated costs of bromocriptine and surgical treatment were ¥20 555 and ¥22 527, respectively. For macroadenoma, the costs of bromocriptine therapy were ¥31 461 and ¥27 178 in males and females, respectively, while the costs of surgery were ¥42357 and ¥44 094 in males and females, respectively (*25*).

Availability

Bromocriptine and cabergoline are available in most countries in branded and generic forms.

Committee recommendations

The Expert Committee noted that prolactinomas were relatively rare, but were associated with important clinical sequelae from both hyperprolactinaemia (e.g. infertility) and physical mass effects of the tumour itself (e.g. headache, hypopituitarism and visual field defects). The Committee also noted that

prolactinomas may be treated medically or surgically but recognized that the availability of specialized neurosurgeons was limited or even non-existent in some low- and middle-income settings.

The Committee noted that dopamine agonist therapy was a preferred first-line intervention for medical management of hyperprolactinaemia and prolactinomas and may be the only option in settings where specialist neurosurgery is not available, or in patients for whom surgery is not feasible.

The limitations of the application notwithstanding, the Committee considered that overall, the available evidence suggested that medical therapy with dopamine agonists could achieve prolactin normalization in most patients, while treatment was continued. Analyses suggest that cabergoline may be moderately more effective and have fewer adverse effects than bromocriptine but overall both have a favourable risk–benefit balance.

The Expert Committee therefore recommended the inclusion of cabergoline on the core list of the EML for the medical management of hyperprolactinaemia associated with prolactinomas as the representative dopamine agonist for this indication based on a more favourable risk–benefit balance, albeit at a potentially higher cost. Listing was recommended with bromocriptine as therapeutic alternative under a square box listing.

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Lanreotide and octreotide – addition – EML

Lanreotide	**ATC code: H01CB03**
Octreotide	**ATC code: H01CB02**

Proposal

Inclusion of lanreotide and octreotide on the complementary list of the EML for management of gigantism and acromegaly in adults with growth hormone-producing tumours.

Applicant

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WHO technical department

Not applicable

EML/EMLc

EML

Section

18.8 Medicines for disorders of the pituitary hormone system (new subsection)

Dose form(s) & strengths(s)

Lanreotide
Injection (modified-release): 60 mg/0.2 mL, 90 mg/0.3 mL, 120 mg/0.5 mL in prefilled syringe

Octreotide
Injection (immediate-release): 0.05 mg/mL, 0.1 mg/mL, 0.5 mg/mL (as acetate) in 1 mL vial
Injection (modified-release): 20 mg (as acetate) in vial plus diluent

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Lanreotide and octreotide have not previously been considered for the inclusion on the Model Lists for the management of gigantism and acromegaly in adults with growth hormone-producing tumours. The EML does not currently include any medicines for this indication.

Public health relevance

Pituitary adenomas are relatively common tumours found in the pituitary gland. They are detected in about 10% of unselected pituitary samples during autopsies and in magnetic resonance imaging scans of healthy individuals at a similar rate. The prevalence is about 50 cases per million population with an annual incidence of new diagnoses of about 3–4 per million. However, not all these tumours cause noticeable symptoms. Clinical studies have shown that the overall prevalence of pituitary adenomas is about 1 in 1420 individuals, with 10% of these tumours secreting growth hormone (*1*). Most patients with pituitary adenomas experience symptoms due to excessive growth hormone secretion, resulting in acromegaly or gigantism. In addition, symptoms may arise from the size of the tumour itself, such as visual field defects, hypopituitarism, cranial nerve palsy and headache. Symptomatic patients are the primary target for treatment with medications, such as octreotide or lanreotide, if surgery fails to control the symptoms (*2–5*). Clinical complications of acromegaly include musculoskeletal abnormalities, hypopituitarism, sleep apnoea, cardiovascular abnormalities, reproductive system abnormalities and colon neoplasms. Risk factors for cardiovascular disease and diabetes have also been reported. Mortality is also two- to three-fold higher than the general population (*6*).

Trans-sphenoidal surgery is the primary treatment for pituitary tumours and offer a chance for cure. Even if a complete cure is not achieved, surgery can significantly reduce growth hormone levels and improve clinical symptoms. The success of the surgery depends on factors such as tumour size and baseline growth hormone levels, with better outcomes seen in smaller tumours and lower growth hormone levels. Maintaining growth hormone levels lower than 2 ng/mL after surgery can reduce mortality and reverse much of the associated morbidity. Relapses occur in about 5% of patients who initially achieve growth hormone levels lower than 2 ng/mL, but in fewer than 2% when the threshold is 1 ng/mL The risks of surgery for small tumours are minimal when performed by experienced pituitary neurosurgeons. However, larger tumours have a higher risk of complications such as cerebrospinal fluid leak, meningitis and permanent diabetes insipidus (*2–5*).

About one third of patients have microadenomas, of whom 20–40% do not respond to surgery. Among patients with macroadenomas, surgical control rates are even lower, with 50–75% of patients not achieving successful outcomes.

For patients who are not effectively treated through surgery, medical therapy is the next option. Somatostatin receptor ligands such as lanreotide and octreotide are the primary medications used in such cases and can achieve hormonal control in about 30–40% of patients (*2–5,7*)

In many low-income countries, access to specialized pituitary neurosurgeons is limited. A survey conducted in 2018 showed that 16% of these countries did not have any practicing neurosurgeons at all (*8*). In such situations, medical treatment with somatostatin receptor ligands may be the primary and most effective form of treatment, rather than a secondary option after surgery.

Summary of evidence: benefits

Hormonal control, by surgical and/or pharmacological means, has been associated with lower rates of morbidity and mortality in patients with acromegaly.

An analysis of three multicentre clinical trials investigated the biochemical efficacy of long-acting lanreotide in patients with acromegaly previously untreated with somatostatin analogues (*9*). Efficacy endpoints were normalized insulin-like growth factor-1 (IGF-1) levels, and growth hormone < 2.5 ng/mL + normalized IGF-1 at study end/last value available. Pooled analyses found that in patients treated with lanreotide, 42% achieved normalized IGF-1 levels (46% post-surgery and 40% de novo) and 35% achieved growth hormone plus IGF-1 control (39% post-surgery and 33% de novo).

A 2018 systematic review and meta-analysis of 26 observational studies (10 770 participants) compared acromegaly mortality rates with those of the general population (*10*). Of note, somatostatin analogues were introduced for treatment of acromegaly in the 1980s. From 17 studies published before 2008, the standardized mortality ratio (SMR) for patients with acromegaly was significantly higher than in the general population (1.76, 95% confidence interval (CI) 1.52 to 2.04). From nine studies published after 2008, no significant difference was found between patients with acromegaly and the general population (SMR 1.35, 95% CI 0.99 to 1.85). From six studies in which somatostatin analogues were used as adjuvant treatment to surgery and/or radiotherapy, mortality was not increased in acromegaly patients (SMR 0.98, 95% CI 0.83 to 1.15), while studies that investigated only patients treated with surgery and/or radiotherapy, mortality in acromegaly patients was significantly higher (SMR 2.11, 95% CI 1.54 to 2.91).

An analysis of clinically available somatostatin analogue formulations for the treatment of acromegaly investigated the relative efficacy of lanreotide and octreotide preparations and concluded that lanreotide depot and octreotide long-acting formulations were equivalent in the control of symptoms and biochemical markets in patients with acromegaly (*11*).

The application stated that due to the rarity of gigantism cases, evidence was derived from uncontrolled reports or case series, but it did not reference or elaborate these data.

Summary of evidence: harms

Gastrointestinal symptoms such as diarrhoea, bloating, nausea and abdominal discomfort occur in 50–75% of patients receiving somatostatin analogues. Hepatobiliary disorders (e.g. cholelithiasis, gallstones and biliary sludge) and injection-site reactions have also been reported frequently (*12–15*).

A study of patient reported outcome data from 105 patients with acromegaly treated with somatostatin analogues in routine clinical practice found that more than 80% reported experiencing joint pain, forgetfulness and memory loss, soft tissue swelling, and fatigue/weakness (*16*).

WHO guidelines

WHO guidelines for the treatment of pituitary adenomas, acromegaly and gigantism are not currently available.

Costs/cost–effectiveness

The prices for somatostatin analogues vary considerably across countries and settings. Representative retail costs for lanreotide depot injection and octreotide long-acting injection from different countries, as reported in the application, are shown in Table 26.

Table 26
Retail costs for somatostatin analogues

Country	US$ per month (dosage)	
	Lanreotide depot	**Octreotide long-acting**
Argentina	2260 (120 mg)	1100 (20 mg)
Brazil	800 (90 mg)	1200 (20 mg)
India	267 (90 mg)	213 (20 mg)
Mexico	1293 (120 mg)	Not reported
United States of America	8029 (90 mg)	4360 (20 mg)

The application stated that cost–effectiveness studies comparing the two medicines have not been conducted. The application described the costs associated with managing the complications of untreated acromegaly (e.g. cardiovascular disease, diabetes, musculoskeletal effects) as being considerable, although cost differentials were not assessed.

Availability

The application highlighted that the availability of expert pituitary neurosurgeons in many low-income countries is limited, with a 2018 survey showing that 16% of such countries have no practising neurosurgeon at all (*8*). In such circumstances, medical treatment with somatostatin analogues may be the only effective treatment and would be considered the primary treatment rather than a secondary treatment.

Lanreotide and octreotide have wide regulatory approval and are available globally. Generic brands of octreotide are reported to be available in some markets.

Octreotide, and to a lesser extent lanreotide, is included on multiple national essential medicines lists, including in low- and middle-income countries.

Committee recommendations

The Committee noted that pituitary adenomas were relatively common but usually non-malignant. About 10% of clinically identified adenomas are associated with excessive growth hormone secretion and are responsible for acromegaly and gigantism. The Committee noted that trans-sphenoidal surgery to remove the adenoma was the treatment of first choice for this condition but accepted that pharmacological treatment with somatostatin analogues was an effective alternative in situations where surgery is not effective, possible or available.

The Committee wished to highlight that the application did not adequately elaborate on the evidence identified to describe the benefits and harms of somatostatin analogues in the treatment of acromegaly and gigantism.

The Committee noted that several studies support the benefits of optimal hormonal control (by means of surgery and/or pharmacological intervention) in reducing mortality rates in patients with acromegaly. The Committee also noted evidence of the effectiveness of somatostatin analogues in normalizing growth hormone and IGF-1 levels. The Committee considered that the frequency of adverse effects associated with somatostatin analogues was relatively high, and that the burden of treatment was considerable. However, given the reported mortality benefit, the Committee considered the overall benefit-to-harm profile to be favourable for the intervention.

The Committee noted that there appeared to be no differences in efficacy between lanreotide and octreotide, however no head-to-head studies had been conducted. The Committee also noted that no comparative cost–effectiveness data were available, but lanreotide was reported to be more expensive than octreotide in most settings reported in the application.

Based on these considerations, the Expert Committee recommended the inclusion of octreotide immediate-release and modified-release injections on the complementary list of the EML for use in the management of acromegaly and

gigantism in adults with growth hormone-producing pituitary adenomas. The Committee did not recommend the inclusion of lanreotide depot injection either as an individual medicine or as a therapeutic alternative to octreotide, because it was not shown to be superior to octreotide, is more expensive and, unlike octreotide, generic forms are not widely available.

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Section 21: Ophthalmological preparations

Hypromellose – addition – EML and EMLc

Hypromellose	ATC code: S01KA02

Proposal

Addition of hypromellose eye drops to the core list of the EML and EMLc for the treatment of dry eye disease (keratoconjunctivitis sicca).

Applicant

International Council of Ophthalmology

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

21. Ophthalmological preparations

21.7 Artificial tears (new subsection)

Dose form(s) & strengths(s)

Solution (eye drops): 0.3%

Core/complementary

Core

Individual/square box listing

Square box listing for hypromellose as the representative artificial tears agent, with carmellose (eye drops 0.5%) and sodium hyaluronate (eye drops 0.18%) as therapeutic alternatives.

Background

Artificial tears preparations for the treatment of dry eye disease have not previously been considered for inclusion on the Model Lists.

Public health relevance

Dry eye disease is a multifactorial disease of the ocular surface that is characterized by a loss of homeostasis of the tear film. It is accompanied by ocular symptoms,

such as visual disturbance and discomfort (*1*,*2*). The negative impact on vision can limit education and work productivity by interfering with patients' daily activities, such as sustained visual attention when reading, writing, driving and using digital display monitors (*3*,*4*). Patients with dry eye disease also report psychological concerns and higher levels of anxiety and depression compared with those without dry eyes (*5*).

Risk factors for dry eye disease include age 50 years or older (*6*,*7*), female sex (*8*,*9*), wearing contract lenses or a history of refractive surgery (*10*), exposure to environments with low relative humidity and extremes of temperature (*10*), certain chronic and autoimmune conditions (*10*,*11*), medication use (*9*,*12*) and prolonged engagement in visual tasks (*13*,*14*).

Dry eye disease has a global prevalence ranging from about 5% to 50%, corresponding to 385 million to 3.85 billion people worldwide (*15*). The highest prevalence of dry eye disease has been reported in the WHO's African region, followed by the Eastern Mediterranean Region, South-East Asia Region, Western Pacific Region, European Region, and Region of the Americas (*16*).

Summary of evidence: benefits

A Cochrane systematic review published in 2016 of 43 randomized controlled trials (3497 participants) evaluated the effectiveness of over-the-counter artificial tear applications in treating dry eye disease compared with no treatment, placebo or another class of over-the-counter artificial tears (*17*). The authors considered participant symptoms (subjective) to be the primary outcome for the review. Secondary outcomes included objective measures of effectiveness (e.g. tests of vision or tear stability). Overall, the review found uncertainty with regard to whether different over-the-counter artificial tears provided similar relief of dry eye disease compared with each other or placebo, with most of the included studies producing contradictory between-group results, or no between-group differences. The quality of the evidence was judged as low due to high risks of bias and poor reporting of outcome measures. The authors concluded that over-the-counter artificial tears may be a safe and effective treatment for dry eye disease, with the literature indicating that most products have similar efficacy.

A systematic review published in 2009 of 33 studies (1293 participants) assessed the efficacy of dry eye treatments with artificial tears or ocular lubricants using scoring of rose bengal stains as the outcome measure (*18*). Mean baseline and 30-day post-treatment scores were calculated, along with the net change and the percentage change in the rose bengal scores. A statistically significant reduction in mean rose bengal scores was observed from baseline to 30-days post-treatment with any type of artificial tears or ocular lubricant from 4.2 (standard deviation (SD) 1.6) to 2.8 (SD 1.2). The net reductions in mean rose bengal scores were −1.1 (SD 0.8) for traditional artificial tears (e.g. hypromellose), −1.2 (SD 0.7) for

carbomer gels and −2.1 (SD 0.9) for hyaluronic acid-based products. No significant difference was found between traditional artificial tears and carbomer gels, but there was a significant difference between traditional artificial tears and hyaluronic acid-based products. A multiple analysis of variance (ANOVA) test, comparing outcomes using the different treatments, found no significant difference between the three groups. Across all studies, the overall net reduction in rose bengal staining after 4 weeks of treatment was 33%. The authors noted heavily skewed data for some treatments, so determined a 25% improvement in rose bengal staining scores with 1 month of treatment was more reasonable. No information was provided in the application on what constituted a clinically meaningful improvement.

The application also presented brief summaries of findings of individual clinical trials comparing hypromellose artificial tears with other artificial tears, placebo or no treatment (*19–27*). The outcome assessed to evaluate the effectiveness of hypromellose tears was the relief of dry eye symptoms. Both hypromellose and comparator artificial tears products were generally found to be effective in relieving symptoms of dry eye disease. Most of these studies were included in the above-mentioned Cochrane systematic review (*17*).

Summary of evidence: harms

The application stated that overall the clinical evidence surveyed suggested that hypromellose was generally safe, with occasional transient burning and stinging of the eyes. Similar levels of adverse effects were observed when hypromellose was compared with other types of artificial tears and dry-eye treatments.

The Cochrane systematic review found that the use of artificial tears was relatively safe, although not without adverse events. The most common adverse events were blurred vision, ocular discomfort and foreign body sensation (*17*).

WHO guidelines

WHO guidelines for treatment of dry eye disease are not currently available. The 2019 WHO *World report on vision* recognizes that eye conditions that do not typically cause vision impairment, such as dry eye disease and conjunctivitis, are frequently among the leading reasons for patients to present to eye care services globally, and should not be overlooked (*28*).

Costs/cost–effectiveness

The application stated that hypromellose has been found to be cost-effective in several national studies (not referenced in the application) as it is a relatively cheap and effective treatment with considerable potential to reduce the burden on society from dry eye disease.

In the United Kingdom, the price for a 10 mL bottle of preserved hypromellose 0.3% artificial tears (about 200 drops of 0.05 mL) was reported as

US$ 1.79, equivalent to an annual treatment cost of US$ 18.37 assuming average usage of 5.7 drops per day. Similar costs were reported in Singapore and the United States, with a price per bottle of US$ 1.52.

Non-preserved and single unit-dose preparations of artificial tears are more costly to manufacture and to purchase. They may be less convenient to use than preserved and bottled preparations (*29*). In Singapore, the mean unit cost of preservative-containing lubricants was around US$ 5.50, meanwhile that for preservative-free lubricants was US$ 12.96 (*30*).

Availability

Artificial tears preparations, including hypromellose, are available on the market globally. They are produced by multiple manufacturers and are often available over the counter.

Committee recommendations

The Committee noted that dry eye disease was a chronic and progressive condition and a common reason for ophthalmic outpatient visits. Severe dry eye disease, if untreated, can lead to ocular infection and inflammation, corneal abrasions, corneal ulcers and vision loss.

Based on the evidence presented, the Committee accepted that hypromellose was a generally safe and effective ocular surface lubricant for reducing the signs and symptoms of dry eye disease for patients with mild to moderate disease. Its effectiveness and safety are comparable to other artificial tears preparations. However, the Committee noted that the available data were limited by the variable definition of dry eye disease applied in published studies and the disease severity examined, and that compliance with treatment was rarely quantified. As a result, the optimal composition, dose, formulation or formulations for artificial tears preparations for the treatment of dry eye disease have not been demonstrated.

The Committee also considered that the sight-threatening complications of dry eye disease were primarily associated with severe forms of the condition. Limited evidence was available of the effectiveness of hypromellose for in improving relevant clinical outcomes compared with other artificial tear preparations, including combinations, specifically in patients with severe dry eye disease.

The Expert Committee therefore did not recommend inclusion of hypromellose on the EML and EMLc for the treatment of dry eye disease in adults and children.

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Section 22: Medicines for reproductive health and perinatal care
22.2 Ovulation inducers
Letrozole – addition – EML

Letrozole	ATC code: L02BG04

Proposal

Addition of letrozole to the complementary list of the EML for the treatment of anovulatory infertility associated with polycystic ovary syndrome or unexplained infertility in adults.

Applicant

WHO Sexual and Reproductive Health and Research Department

WHO technical department

Sexual and Reproductive Health and Research

EML/EMLc

EML

Section

22.2 Ovulation inducers

Dose form(s) & strengths(s)

Solid oral dosage form: 2.5 mg

Core/complementary

Complementary

Individual/square box listing

Square box listing with letrozole as the representative aromatase inhibitor, with anastrozole specified as a therapeutic alternative.

Background

Aromatase inhibitors for the treatment of anovulatory infertility have not previously been considered for inclusion in the EML.

Anastrozole (with a square box specifying other aromatase inhibitors classified at the fourth level ATC chemical subgroup L02BG as therapeutic alternatives) is included on the EML for use in the treatment of early-stage and metastatic breast cancer.

Public health relevance

Infertility affects millions of people worldwide, often with serious consequences. In 2010, up to 48.5 million couples were estimated to be affected by infertility globally (*1*). Although a large proportion of adults express a desire for children (*2,3*), nearly one in six experience infertility, which is defined as a disease of the reproductive system characterized by the failure to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse (*4*).

Fertility care is an important component of sexual and reproductive health and rights, but in most countries, infertility policies and services are inadequate. The Universal Declaration of Human Rights (Article 16) states that "men and women of full age, without any limitation due to race, nationality or religion, have the right to marry and found a family" (*5*). Treating infertility is part of realizing the human right to the enjoyment of the highest attainable standard of physical and mental health, as well as the right to decide the number, timing and spacing of children (*6*). Addressing infertility is also central to achieving Sustainable Development Goal (SDG) 3 (ensure healthy lives and promote well-being for all at all ages) and SDG 5 (achieve gender equality and empower all women and girls). However, fertility care services are unavailable or unaffordable in many countries, particularly in low- and middle-income countries (*7*).

Although uncertainty exists, ovulatory disorders may account for up to 25% of infertility (*8,9*), with 70% of ovulatory dysfunction due to polycystic ovary syndrome. Similarly, although uncertainty exists, up to a further 15% of couples are thought to have so-called unexplained infertility (*8*). These are the two causes of infertility for which aromatase inhibitors can be used as part of treatment. Therefore, up to 40% of infertility cases, or 19 million couples globally, could benefit from fertility treatment with ovulation induction medicines, including aromatase inhibitors.

Summary of evidence: benefits

Note on concerns about data integrity

The application highlighted that some clinical evidence in this area has been affected by concerns of potential research fraud. Several manuscripts by Badawy and Abu Hashim have been retracted or are the subject of editorial expressions of concern (*10–15*). Some systematic reviews that provided data to support this application had included data from the above research group. To mitigate this issue, the applicants conducted a re-analysis excluding potentially fraudulent data, where these data had been included. Conclusions are based on analyses that excluded these studies.

Infertility due to polycystic ovary syndrome

A 2022 Cochrane systematic review and meta-analysis evaluated the effectiveness and safety of aromatase inhibitors compared with clomifene citrate (a selective

oestrogen receptor modulator) for ovulation induction in infertile women with polycystic ovary syndrome (*16*). This review did not include studies by Badawy and Abu Hashim. The review found moderate-certainty evidence for a moderate increase in live births (risk ratio (RR) 1.52, 95% confidence interval (CI) 1.29 to 1.80; absolute difference 104 more live births per 1000 (95% CI 58 to 160 more); eight randomized controlled trials, 1646 participants) and clinical pregnancies (RR 1.41, 95% CI 1.25 to 1.58; absolute difference 94 more clinical pregnancies per 1000 (95% CI 58 to 133 more); 17 randomized controlled trials, 2516 participants) with letrozole compared with clomifene in patients with infertility due to polycystic ovary syndrome.

Unexplained fertility

As part of developing a new guideline for the treatment of infertility, WHO commissioned an analysis by a team at McMaster University, Canada, to adapt the 2019 systematic review by Eskew and colleagues (*17*) of letrozole use in unexplained infertility by excluding potentially fraudulent data from the analysis. The result of the as-of-yet unpublished analysis by McMaster University is presented in the application as the best available meta-analysis.

Results of this analysis found no significant difference between letrozole and clomifene citrate when used for ovarian stimulation followed by intrauterine insemination for couples with unexplained infertility for: live births (RR 1.00, 95% CI 0.81 to 1.22; absolute difference 0 more live births per 1000 (95% CI 125 fewer to 145 more; one randomized controlled trial, 191 participants, low-certainty evidence); or pregnancy (RR 1.32, 95% CI 0.83 to 2.09; absolute difference 80 more pregnancies per 1000 (95% CI 43 fewer to 272 more; five randomized controlled trials, 1266 participants).

Anastrozole

The Cochrane systematic review (*16*) included one trial (40 participants) comparing letrozole and anastrozole (*18*). No data were available for live births and there was insufficient evidence of a difference between treatments for the outcome of clinical pregnancy rate (odds ratio (OR) 1.88, 95% CI 0.40 to 8.88).

Summary of evidence: harms

In the context of using aromatase inhibitors for ovulation induction, the main serious adverse events are ovarian hyperstimulation syndrome, a rare but serious syndrome associated with treatments that stimulate ovulation, and multiple pregnancy. Less serious adverse effects that can occur with letrozole treatment include hot flashes, headache, fatigue, dizziness and irritability.

Infertility due to polycystic ovary syndrome

The above-mentioned Cochrane systematic review included data on miscarriage, ovarian hyperstimulation syndrome and multiple pregnancies in the meta-

analysis (*16*). It found that compared with clomifene citrate, the risk of miscarriage was slightly increased with letrozole (RR 1.36, 95% CI 0.98 to 1.89; absolute difference 22 more miscarriages per 1000 (95% CI 1 fewer to 53 more); 10 randomized controlled trials, 1752 participants, moderate-certainty evidence), with no difference in the risk of multiple pregnancies (RR 0.69, 95% CI 0.34 to 1.41; absolute difference 6 fewer per 1000 (95% CI 13 fewer to 8 more); 12 randomized controlled trials, 1971 participants, low-certainty evidence) and ovarian hyperstimulation syndrome (risk difference (RD) 0.00, 95% CI –0.01 to 0.00; absolute difference 0 fewer cases of ovarian hyperstimulation syndrome per 1000 (95% CI 10 fewer to 0); eight randomized controlled trials, 1572 participants, low-certainty evidence).

Unexplained fertility

For letrozole versus clomifene citrate followed by intrauterine insemination in unexplained infertility, the McMaster University re-analysis found a small reduction in miscarriage (RR 0.52, 95% CI 0.20 to 1.38; absolute difference 134 fewer miscarriages per 1000 (95% CI 224 fewer to 106 more); four randomized controlled trials, 324 participants, low-certainty evidence) and no differences in multiple pregnancies (RR 0.76, 95% CI 0.22 to 2.64; absolute difference 17 fewer multiple pregnancies per 1000 (95% CI 55 fewer to 116 more); four randomized controlled trials, 323 participants, low-certainty evidence) or ectopic pregnancies with letrozole compared with clomifene citrate.

Another systematic review and meta-analysis of 45 studies (17 randomized controlled trials with 776 participants, 21 comparative cohorts with 2453 participants and seven non-comparative cohorts) analysed the risk of fetal harm after letrozole use for ovulation induction/ovarian stimulation in couples with infertility of different causes (*19*). Studies of concern were excluded from that analysis. The review found no difference in the risk of congenital malformations with letrozole versus clomifene citrate (RD from randomized controlled trials: 0.00, 95% CI –0.02 to 0.02; RD from cohort studies: –0.02, 95% CI –0.04 to –0.01).

In the above-mentioned study comparing letrozole and anastrozole, no data were available for ovarian hyperstimulation syndrome. No multiple pregnancies were reported with either treatment (*30,31*).

WHO guidelines

WHO guidelines on the prevention, diagnosis and treatment of infertility are currently being developed and are expected to be published by the end of 2023. Based on the evidence reviewed so far, the Guideline Development Group intends to suggest the use of letrozole as the preferred agent for ovulation induction in women with infertility caused by polycystic ovary syndrome, and the use of either letrozole or clomifene citrate in women with unexplained infertility undergoing intrauterine insemination.

Costs/cost–effectiveness

The application presented comparative prices of aromatase inhibitors and clomifene citrate as shown in Table 27. In most comparisons, letrozole and anastrozole were more expensive than clomifene citrate. However, the absolute cost was not high, and the medicines were likely to only be used for 5 days per cycle, so their total cost, relative to the overall cost of treatment including stimulated intrauterine insemination, would also not be high.

Table 27
Prices of anastrozole, letrozole and clomifene in selected countries

Country	US$ per tablet/capsule		
	Anastrozole 1 mg	Letrozole 2.5 mg	Clomifene 50 mg
Bangladesh	0.39	0.39	0.10
Brazil	2.70	2.48	0.36
El Salvador	7.72	6.78	1.49
India	0.13	0.03	0.07
Indonesia	0.21	0.12	No data
Morocco	1.19	1.44	No data
South Africa	0.36	0.97	0.33
Ukraine	0.51	0.45	No data
United Kingdom	0.04	0.08	0.38
United States of America	17.77	17.45	0.67

No relevant studies were identified in the application that assessed the cost–effectiveness of aromatase inhibitors for the proposed indications.

Availability

Letrozole and anastrozole are available globally as originator and generic brands.

Other considerations

Neither letrozole nor anastrozole are approved for the treatment of infertility by the United States Food and Drug Administration or by the European Medicines Agency; their use for this indication is off label.

Committee recommendations

The Expert Committee acknowledged that the availability of and access to effective treatments for infertility was important as part of sexual and reproductive health and for achieving targets of the SDGs.

The Committee noted evidence that letrozole was associated with a moderate increase in live births and clinical pregnancies compared with clomifene (a medicine currently included in the EML) in patients with infertility due to polycystic ovary syndrome, and had similar efficacy to clomifene for live births or biochemically tested pregnancy in couples with unexplained infertility. The Committee considered the safety profile of letrozole to be acceptable and, on balance, the medicine to have a favourable benefit-to-harm profile.

The Committee noted that WHO guidelines for the prevention, diagnosis and treatment of infertility were in development and were expected to include recommendations for use of letrozole for ovulation induction in women with infertility caused by polycystic ovary syndrome, and women with unexplained infertility undergoing intrauterine insemination.

Based on these considerations, the Expert Committee therefore recommended inclusion of letrozole on the complementary list of the EML for the treatment of anovulatory infertility associated with polycystic ovary syndrome or unexplained infertility. Listing was recommended with anastrozole as a therapeutic alternative under a square box listing.

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22.3 Uterotonics

Mifepristone – misoprostol – new indication – EML

Mifepristone – misoprostol	ATC code: G03XB51

Proposal

Extension of the indication for combination regimen of mifepristone and misoprostol on the core list of EML to include medical management of intrauterine fetal demise (IUFD).

Applicant

WHO Department of Sexual and Reproductive Health and Research

WHO technical department

Sexual and Reproductive Health and Research

EML/EMLc

EML

Section

22.3 Uterotonics

Dose form(s) & strengths(s)

Tablet: 200 mg – Tablet: 200 micrograms

Copackage containing mifepristone 200 mg tablet [1 tablet] and misoprostol 200 micrograms tablet [4 tablets]

Core/complementary

Core

Individual/square box listing

Individual

Background

Mifepristone and misoprostol have not been previously considered for inclusion on the EML for medical management of IUFD. No other medicines are currently included on the EML for use in medical management of this indication.

The combination of mifepristone and misoprostol has been included on the EML since 2005 for medical abortion. Misoprostol 200 microgram tablets are also listed individually for the management of incomplete abortion and

miscarriage, and prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used.

Public health relevance

About 1% of all pregnancies are complicated by IUFD (*1*). IUFD refers to the clinical condition where the fetus is no longer alive, but the uterus has not yet started to expel its contents and the cervix remains closed. Some of the clinical findings suggestive of IUFD include vaginal bleeding, absent fetal heartbeat on electronic auscultation, a failure to feel fetal movements or a uterus that is significantly smaller than the expected size (*2*). Although the exact incidence of IUFD is not known, about 50% occur between 20 and 27 weeks of gestation (mainly from 20 to 23 weeks) (*3*). Management options include expectant, surgical abortion with dilation and evacuation, or medical management.

Several studies have demonstrated that IUFD can be associated with haemorrhage and sepsis leading to increased morbidity and mortality. After an IUFD, the need for a blood transfusion and blood products ranges from 18% to 28% (*4,5*). IUFD can also lead to a rare but unique complication of disseminated intravascular coagulation (*6,7*). The presence of disseminated intravascular coagulation was a substantial risk for haemorrhage (*8,9*). Evidence of disseminated intravascular coagulation was observed in 10% of IUFD cases within 4 weeks of fetal demise. Timely management of IUFD has been shown to decrease the risk of severe coagulation abnormalities (*7,10*).

Summary of evidence: benefits

Studies that assessed medical management of IUFD consistently showed that the combination regimen of mifepristone and misoprostol had a high success rate of fetal expulsion with a short induction to abortion interval (*11–13*).

A randomized controlled trial that compared combination regimen of mifepristone and misoprostol with misoprostol alone for IUFD showed that the combination regimen was significantly more successful in achieving fetal expulsion within 24 hours (92.5% versus 71.2%; relative risk (RR) 1.3, 95% confidence interval (CI) 1.1 to 1.6) (*11*). In addition, the study demonstrated a significantly shorter mean fetal expulsion time with the combination regimen (9.8 versus 16.3 hours; mean difference (MD) 6.5 hours, 95% CI 4.5 to 8.5 hours). This finding has clinical and health system implications in terms of shorter facility stay, bed occupancy and patient turnover rate.

Another study compared two dose regimens of misoprostol (200 micrograms and 400 micrograms) for second-trimester termination of viable and non-viable pregnancies (*12*). This study showed that in the combination regimen of mifepristone and misoprostol, 400 microgram misoprostol dosing achieved a shorter expulsion time compared with a 200 microgram dosing (9.3 versus 11.6 hours).

A cohort study assessed the effect of pretreatment with mifepristone 24–48 hours before misoprostol compared with misoprostol alone. Women with IUFD who received mifepristone had a shorter fetal expulsion time than those treated with misoprostol alone (10.6 hours versus 16.2 hours; $P = 0.04$). In addition, mifepristone pretreatment significantly reduced the risk of infection ($P = 0.049$) and lowered the need for pain relief ($P = 0.022$) (*13*).

A recent systematic review assessed the effectiveness, safety and acceptability of medical management of IUFD at ≥ 14 to ≤ 28 weeks of gestation (*14*). The review included 16 randomized controlled trials that compared: regimens of mifepristone used in combination with misoprostol versus misoprostol alone; different doses of misoprostol after administration of mifepristone; different doses of misoprostol with or without a loading dose; different routes of administration of misoprostol; and different preparations of misoprostol. The trials included were conducted in 17 countries providing information on the varying country contexts in which such services may be provided. Of these 17 countries, six were lower middle-income economies, seven were upper middle-income economies and four were high-income economies. Treatment with combination regimen of mifepristone and misoprostol had higher rates of complete abortion within 24 hours (RR 1.18, 95% CI, 0.91 to 1.53; very low-certainty evidence) and a shorter expulsion time (6.3 hours shorter (95% CI –9.3 to –3.4 hours; very low-certainty evidence) than misoprostol alone. Serious adverse events such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete removal of products, or death were not reported. Treatment with 400 micrograms misoprostol in the combination regimen showed higher rates of complete abortion within 24 hours (RR 0.90, 95% CI 0.74 to 1.10; low-certainty evidence) and lower rates of serious adverse events (RR 1.40, 95% CI 0.32 to 6.05; very low-certainty evidence) than 200 microgram misoprostol dosing. Overall, women were satisfied with their treatment and found the pain associated with the induction less than or the same as they expected.

Over the past 2 decades, a number of clinical studies have been conducted to assess the clinical effectiveness and safety of medical abortion in different settings (*15–19*). Systematic reviews of these studies have led to refined regimens of medical abortion using a combination of mifepristone and misoprostol (*20–22*). The WHO guidelines have included recommendations for the use of this combination regimen for medical abortion since 2012 (*23*). The clinical effectiveness of this regimen was as high as 95%. Serious adverse events such as transfusion or hospitalization were reported rarely (*21,22,24*). Such findings were consistently reported in several individual clinical trials and systematic reviews. Although these studies focused on induced abortion, given the same mechanism of action, a similar outcome can be reasonably inferred on the use of the combination regimen in similar clinical contexts. As such, these findings can

serve as indirect evidence to demonstrate the applicability of the combination regimen for medical management of IUFD.

Summary of evidence: harms

Although it is difficult to estimate the total number of medical abortions using mifepristone and misoprostol that have taken place globally, research published in 2017 reported that more than 3 million people in the United States have had a medical abortion using a regimen containing mifepristone since approval by the Food and Drug Administration in 2000 (*25*). More recently, a study by the Guttmacher Institute estimated that 12.7 million medical abortions occur annually in India (*26*).

Abdominal pain and cramping are expected side-effects of medical abortion, but their incidence is not systematically reported in clinical studies. Treatment with mifepristone and misoprostol is intended to induce uterine bleeding and cramping and as such, bleeding and cramping are expected consequences of the abortion process (*27*). These side-effects are minor and can be managed with widely available analgesic medications such as non-steroidal anti-inflammatory drugs (*24*). WHO's 2022 abortion care guideline states that women requesting abortion should always be offered medication for pain management. Pain medications can be offered by various cadres of health care providers (*28*). All women seeking abortion should be counselled about common side-effects after mifepristone and misoprostol medical abortion and told how they can be managed. In deciding on a course of treatment, some pregnant women may choose regimens with routes of misoprostol that may be associated with more side-effects but may be more consistent with their wishes and expectations of acceptability and overall satisfaction.

The most commonly reported adverse reactions (> 15%) for mifepristone and misoprostol include nausea, weakness, fever/chills, vomiting, headache, diarrhoea and dizziness. The frequency of adverse reactions varies between studies and depends on many factors, including the patient population and gestational age (*11,12*).

Uterine rupture is a rare complication and is usually associated with a prior uterine scar and/or very high doses of misoprostol. A systematic review of second-trimester abortion with misoprostol showed the risk of uterine rupture was 0.28% in women with prior caesarean birth, whereas the risk was 0.04% in those without prior caesarean delivery (*29*). WHO guidelines highlight the need for sound clinical judgement and health system preparedness for emergency management of uterine rupture in these very rare events (*28*).

Analysis of clinical studies involving 30 966 participants who used a combination regimen for medical abortion up to 70 days gestation showed serious adverse events to be very low (reported in < 0.5% of women). No differences were

seen in the rate or type of serious adverse reaction by geographical location. A summary of the reported serious adverse reaction is shown in Table 28 (*30*).

Table 28
Serious adverse reactions reported following administration of mifepristone (oral) and misoprostol (buccal) in clinical studies

Country	United States studies			Other studies		
	No. of studies	No. of evaluable women	Frequency, %	No. of studies	No. of evaluable women	Frequency, %
Transfusion	4	17 774	0.03–0.5	3	12 134	0-0.1
Sepsis	1	629	0.2	1	11 155	<0.01
Emergency room visit	2	1 043	2.9–4.6%	1	95	0
Hospitalization related to medical abortion	3	14 339	0.04-0.6	3	1 286	0–0.7
Infection without sepsis	1	216	0	1	11 155	0.2
Haemorrhage	NR	NR	NR	1	11 155	0.1

NR: Not reported.
Source: United States Food and Drug Administration, 2016 (*30*).

Safety data published in the United States 16 years after mifepristone's approval found an estimated mifepristone-associated mortality rate of 0.00063% (*25*,*30*). Studies involving mifepristone and misoprostol among more than 423 000 women globally reported very low rates (0.01% to 0.7%) of non-fatal serious adverse events such as hospital admission, blood transfusion or serious infection after the use of mifepristone. These events were almost always treatable without permanent sequelae (*25*).

WHO guidelines

Medical management of IUFD with mifepristone and misoprostol has been a recommendation in the WHO guidelines since 2018 (*31*) and was recently updated in 2022 (*28*). This updated guideline recommends medical management of IUFD at gestational ages ≥ 14 to ≤ 28 weeks using a combination of 200 mg of mifepristone administered orally followed 1–2 days later by repeat doses of 400 micrograms misoprostol administered sublingually or vaginally every

4–6 hours. Misoprostol can be repeated at the noted interval as needed to achieve success of the abortion process. This regimen was shown to have a higher rate of complete abortion within 24 hours and a shorter induction time (*14*). The certainty of the evidence was low to very low, downgraded due to imprecision arising from a small sample size. Difficulties in reaching large sample sizes have been a limitation of abortion-related studies and these studies may fall short of statistically significant findings. In such circumstances, it is important to consider outcomes in their totality taking into account other important parameters such as the value and preference of end-users and implications to the health system (*28*).

The WHO guideline on abortion care recognizes medical management of IUFD with combination regimen can be performed by a wide range of health care providers including midlevel (non-physician) health care providers (*28*).

Studies have been done on medical abortion for pregnancies at gestational ages ≥ 12 weeks as a facility-based procedure. Based on extrapolation from these studies, the WHO recommends women undergoing medical management of IUFD with the combination regimen should remain under observation until the process is complete (*28*).

Recommendations in other current clinical guidelines

The clinical recommendation from the United States Society of Family Planning for interruption of nonviable pregnancy between 24 and 28 weeks includes the administration of a mifepristone and misoprostol regimen. This regimen is noted to have a shortened expulsion time (*32*). The American College of Obstetricians and Gynecologists also recommends the use of mifepristone plus misoprostol for IUFD. Either 200 mg or 600 mg of oral mifepristone 24–48 hours before misoprostol reduces the time to delivery compared with misoprostol alone (*33*). These are grade B recommendations as per the United States Preventive Services Task Force (there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial). Similarly, the Royal College of Obstetricians and Gynaecologists recommends a combination of a single dose of 200 mg of mifepristone with misoprostol for the management of IUFD. This is a grade B recommendation, which was developed from high-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal (*34*).

Costs/cost–effectiveness

The price of mifepristone and misoprostol, individually and copackaged, varies widely by geographical location. The legal status of abortion, willing marketers and distributors, and a perceived sustainable market all affect the cost to the buyer. Market flexibility is being regulated by the increasing number of new products entering markets.

The United Nations Population Fund (UNFPA) product catalogue contains different commodities related to sexual and reproductive health. All products included in this catalogue are WHO prequalified or authorized for use by a stringent regulatory authority. The UNFPA product catalogue currently lists mifepristone 200 mg at a price of US$ 16 per tablet and misoprostol 200 micrograms at US$ 13.92 for a pack of 40 tablets (*35*).

A large study on the price of medical abortion commodities in different settings showed unit prices of mifepristone, misoprostol and combi-packs varied greatly (*36*). The median price of mifepristone per tablet was US$ 11.78 (range US$ 1.77 to 37.83). The price was highest in Latin America and the Caribbean (US$ 24.47) and lowest in South and South-east Asia (US$ 5.20). In Africa, mifepristone prices ranged from US$ 6.00 to 21.86. The most commonly identified mifepristone brand had a median price to the consumer of US$ 10.35 per tablet (range US$ 3.02 to 17.91). The median price per misoprostol tablet was US$ 0.63 (range US$ 0.09 to 27.63). The price of misoprostol also showed great variation within and between countries and regions, with a similar pattern for mifepristone (highest in Latin America and the Caribbean and lowest in South and South-east Asia). The median price of copackaged mifepristone and misoprostol was US$ 11.14 (range US$ 3.50 to 35.86) per pack (36). The price range for the most frequently identified brand was also wide (US$ 4.02 to 20.05); this product had a median price per pack of US$ 15.44.

Availability

Mifepristone and misoprostol, both individually and copackaged, are widely and increasingly available globally (36,37). Branded and generic products are available. Misoprostol and copackaged mifepristone + misoprostol are included on the WHO List of Prequalified Finished Pharmaceutical Products.

Committee recommendations

The Expert Committee noted the evidence from a randomized controlled trial and systematic review that assessed medical management of IUFD that showed the combination regimen of mifepristone and misoprostol was associated with a higher proportion of complete fetal expulsion at 24 hours as well as with lower time to complete expulsion compared with misoprostol alone, without increased severe adverse events or requirement for surgery. While the Committee noted that the available evidence was graded low certainty, indirect evidence on the use of mifepristone and misoprostol in the management of medical abortion showed high effectiveness. The Committee also noted side-effects associated with the regimen were minor and that uterine rupture was very rare.

Additionally, the Committee noted that medical management of IUFD with mifepristone and misoprostol has been recommended in the WHO guidelines

on abortion care since 2018. The Committee also noted that mifepristone and misoprostol were widely available and were prequalified by WHO.

The Committee emphasized the importance of providing patients and health care providers with multiple choices for the management of IUFD.

The Expert Committee therefore recommended that the listing for mifepristone – misoprostol on the core list of the EML be extended to include the new indication of medical management of IUFD.

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Section 24: Medicines for mental and behavioural disorders
24.1 Medicines used in psychotic disorders

Chlorpromazine and haloperidol – deletion – EMLc

Chlorpromazine	**ATC code: N05AA01**
Haloperidol	**ATC code: N05AD01**

Proposal

Deletion of chlorpromazine and haloperidol from the EMLc for treatment of psychotic disorders in children.

Applicant

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy

WHO technical department

Mental Health and Substance Use

EML/EMLc

EMLc

Section

24.1 Medicines used in psychotic disorders

Dose form(s) & strengths(s)

Chlorpromazine
Injection: 25 mg/mL (hydrochloride) in 2 mL ampoule
Oral liquid: 25 mg/5 mL (hydrochloride)
Tablet: 10 mg, 25 mg, 50 mg, 100 mg

Haloperidol
Injection: 5 mg in 1 mL ampoule
Oral liquid: 2 mg/mL
Solid oral dosage form: 0.5 mg, 2 mg, 5 mg

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Chlorpromazine and haloperidol have been included in the EMLc for treatment of psychotic disorders in children since the first list was published in 2007.

In 2013, a request for deletion of these medicines was made by the WHO Department of Mental Health and Substance Use. The Expert Committee recognized that the indications for use for chlorpromazine and haloperidol were very rare in children and that adverse events from these medicines may be more frequent in children than in adults. However, the Committee recognized the importance of ensuring that treatment was available for severe psychiatric disorders in children and noted that the application did not fully review all treatment options. The Committee therefore requested a review of the evidence for the benefits and risks of each medicine in the paediatric population and decided to make no changes to the list until such reviews had been considered (*1*).

Public health relevance

Psychotic disorders are very rare in childhood. The prevalence of the onset of psychotic symptoms before 13 years of age has been estimated to be 100 times lower than the adult form of the disorder (*2*). Due to the scarcity of definitive epidemiological studies, the true prevalence is likely to be even less (*3,4*). Two studies investigating rates of childhood neuropsychiatric disorders in Sweden and North Dakota (United States) found the prevalence of childhood-onset schizophrenia to be 1.6 per 100 000 children and 1.9 per 100 000 children, respectively (*5–7*). The largest study on childhood-onset schizophrenia to date, involving 1400 national referrals to the United States National Institute of Mental Health over 10 years, identified 260 children with psychosis of whom only 71 met the criteria for childhood-onset schizophrenia at study entry (*8*).

Beyond schizophrenia, psychotic symptoms often represent an ancillary manifestation of other psychiatric conditions (e.g. major depression, bipolar disorder or psychosis not otherwise specified). A study comprising all types of psychiatric and child-guidance services in three large clinics in Germany subdivided childhood psychoses into four diagnostic groups: schizophreniform disorder, affective psychosis, typical non-schizophrenic child and adolescent psychosis and atypical psychosis. The analysis of the distribution of age at onset defined by age at first contact for the four diagnostic categories until the age of 15–18 years showed that first contacts for schizophrenia, affective psychoses or unspecified psychoses become visible in the age group of 12–15 years, followed by a steep increase in the next age group (*9*).

Major depression may occur in 1% of children (*10,11*), whereas bipolar disorder occurs in 1% to 2% of adolescents (*12,13*). Mood disorders with psychosis are considerably rarer in children. The prevalence of psychosis not otherwise specified and bipolar disorder in children is hard to ascertain because of controversy

about validity. More generally, transitory psychotic experiences may be triggered by various psychiatric conditions. Finally, psychotic symptoms have been associated with, or are secondary to, a wide variety of medical disorders. Studies on adults show that about 3% of new-onset presentations of psychosis can be attributed to a medical condition (*14*). Therefore, before making a diagnosis of a primary psychotic disorder, secondary causes should be ruled out or, if necessary, adequately treated.

Subclinical psychotic experiences may be more common and are usually benign, as in 75–90% of cases they spontaneously remit over time (*13*).

Summary of evidence: benefits

The application presented the results of a comprehensive literature search for systematic reviews on the efficacy, acceptability and tolerability of antipsychotic medicines in children with schizophrenia and related psychoses. No systematic reviews were found on the efficacy of antipsychotics specifically focused on children aged 12 years or younger. Existing reviews included a mixed population of children and adolescents, largely composed of individuals between 14 and 18 years of age. Eleven systematic reviews were included (*15–25*), from which data from five randomized controlled trials (four for haloperidol and one for chlorpromazine) were extracted and reanalysed using standard Cochrane methodology. Data from a further three randomized controlled trials involving second-generation antipsychotics were also extracted and reanalysed (*26–28*). Of note, the data reviewed accounted only for oral administration of haloperidol, chlorpromazine or other antipsychotics; no evidence from randomized controlled trials was available on the efficacy of these compounds administered by intramuscular injection. The findings from trials of chlorpromazine and haloperidol are described below. For second-generation antipsychotics, as no trials have been conducted versus placebo, no information is available on the potentially beneficial role of these medications in children.

Chlorpromazine

A single randomized controlled trial (60 participants) evaluated the efficacy of chlorpromazine in comparison with risperidone in children and adolescents aged 7 to 16 years with a diagnosis of childhood-onset schizophrenia (*29*). Psychotic symptomatology at 8 weeks was evaluated using the Brief Psychiatric Rating Scale. Results showed a trend favouring risperidone over chlorpromazine (mean difference (MD) 1.80, 95% confidence interval (CI) –1.14 to 4.74). The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) certainty of evidence was judged to be very low.

Haloperidol

A single placebo-controlled randomized controlled trial of haloperidol in children with schizophrenia (12 participants) was not included in the meta-

analysis because it had a crossover design and the results before crossing over were not available (*30*).

Two double-blind randomized controlled trials (90 participants) compared haloperidol with fluphenazine in children with schizophrenia (*31,32*). Pooling the two studies for the outcome "showing moderate or marked improvement" at study endpoint showed a non-significant trend favouring fluphenazine (risk ratio (RR) 0.91, 95% CI 0.72 to 1.14).

One double-blind randomized controlled trial (42 participants) compared haloperidol with risperidone in children with childhood-onset schizophrenia (*33*). For the outcome of psychotic symptomatology at 6 weeks as measured by the Brief Psychiatric Rating Scale, no significant difference was seen between treatments (MD 1.39, 95% CI –0.93 to 3.71).

Summary of evidence: harms

Chlorpromazine

From the randomized controlled trial of chlorpromazine versus risperidone, there was very low-certainty evidence of no difference between treatment arms in extrapyramidal symptoms (RR 2.0, 95% CI 0.2 to 20.9), drowsiness (RR 11.0, 95% CI 0.64 to 190.53) or anticholinergic effects (RR 2.0, 95% CI 0.40 to 10.11). No data were available for the outcomes of drop-outs for any reason or drop-outs due to adverse events (*29*).

Haloperidol

From the randomized controlled trials involving haloperidol (*31–33*), there was very low-certainty evidence of no differences between haloperidol and other antipsychotics overall for any side-effects (RR 1.39, 95% CI 0.61 to 3.15; two randomized controlled trials, 72 participants). In one study (42 participants), there was very low-certainty evidence that haloperidol caused fewer side-effects than risperidone (RR 2.05, 95% CI 1.32 to 3.19). There was very low-certainty evidence of a trend favouring haloperidol over other antipsychotics overall for extrapyramidal symptoms (RR 1.82, 95% CI 0.33 to 10.06; three randomized controlled trials, 132 participants). There was very low-certainty evidence that haloperidol caused significantly more extrapyramidal side-effects than risperidone (RR 8.60, 95% CI 2.67 to 27.68; one randomized controlled trial, 42 participants). For weight gain, there was very low-certainty evidence of no difference between haloperidol and fluphenazine (RR 1.17, 95% CI 0.88 to 1.55; one randomized controlled trial, 30 participants). There was very low-certainty evidence that haloperidol caused significantly more drowsiness than risperidone (RR 6.50, 95% CI 1.67 to 25.33; one randomized controlled trial, 42 participants), and of no difference between treatment arms for anticholinergic side-effects (RR 7.00, 95% CI 0.38 to 127.69; one randomized controlled trial, 42 participants) (*33*).

First-generation antipsychotics are associated with extrapyramidal side-effects (dystonia, tardive dyskinesia and parkinsonian symptoms), hyperprolactinaemia and neuroleptic malignant syndrome. Evidence indicates that side-effects may be more severe in children than in adults (*34–36*).

No safety data are available in children exposed to long-term use of antipsychotics.

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders do not include any treatment recommendations for psychotic disorders in children (*37*). Similarly, other national and international guidelines do not include specific treatment recommendations for children, with most referring only to the adolescent population.

Costs/cost–effectiveness

No cost–effectiveness analyses are available for antipsychotics in children with psychosis. Chlorpromazine and haloperidol are available as generics, mostly at low purchase prices.

Availability

Chlorpromazine and haloperidol are available globally, however specific data on availability are not considered relevant for the proposal to delete them from the EMLc.

Committee recommendations

The Expert Committee recommended the deletion of chlorpromazine and haloperidol (all dosage forms) from the complementary list of the EMLc. The Committee noted that schizophrenia and other chronic psychotic disorders were rare in children younger than 12 years. The Committee agreed that the available evidence for these medicines in the treatment of psychoses in children was inconclusive and insufficient to support their ongoing inclusion on the EMLc.

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Chlorpromazine injection – deletion/olanzapine injection – addition – EML

Chlorpromazine injection (deletion)	**ATC code: N05AA01**
Olanzapine injection (addition)	**ATC code: N05AH03**

Proposal

Deletion of chlorpromazine intramuscular injection for treatment of adults with schizophrenia and related psychotic disorders from the core list of the EML.

Addition of olanzapine intramuscular injection to the core list of the EML for the acute treatment of adults with schizophrenia spectrum disorders.

Applicant

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy

WHO technical department

Mental Health and Substance Use

EML/EMLc

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Section

24.1 Medicines used in psychotic disorders

Dose form(s) & strengths(s)

Chlorpromazine – Injection: 25 mg/mL (hydrochloride) in 2 mL ampoule

Olanzapine – Powder for injection (immediate-release): 10 mg in vial

Core/complementary

Core

Individual/square box listing

Individual

Background

Chlorpromazine, with a square box, has been included on the EML since the first list was published in 1977. Listed formulations include the injection being proposed for removal, as well as oral liquid and tablets. Haloperidol is the only other immediate-release injectable antipsychotic currently included on the EML.

In 2021, as part of a comprehensive review of square box listings on the EML and EMLc, the Expert Committee requested that the therapeutic alternatives for chlorpromazine under the square box listing be reviewed.

In addition to the current application, a separate application considered at the 2023 Expert Committee meeting provided a review of therapeutic alternatives among first-generation antipsychotics.

Public health relevance

About 24 million people in the world are estimated have schizophrenia (*1*). The prevalence of schizophrenia ranges from 0.2% to 0.4% across countries, while its incidence is reported to be 18.7 per 100 000 person-years (*2*). Globally, 129 million disability-adjusted life-years are attributable to mental health disorders, 11.7% of which are attributable specifically to schizophrenia spectrum disorders. Schizophrenia is also associated with direct and indirect health care costs, and it is considered the costliest mental health condition per person globally (*1,3*).

Acute psychomotor agitation is a multifactorial clinical manifestation that can occur in a broad spectrum of psychiatric and neurological syndromes. Although data on the epidemiology of acute agitation are lacking, up to 20% of psychiatric emergency visits in the United States might involve agitated individuals with schizophrenia (*4*). Other studies report an overall prevalence of between 4% and 10% in emergency settings (*5*). In psychiatric inpatient settings, a literature review estimated an overall incidence of episodes of violence of about 32% (*6*).

Acute agitation might include heterogeneous manifestations, including highly disorganized behaviours, verbal or physical hostility and overt aggressiveness towards oneself, objects or other individuals. Paranoid delusional thoughts, hallucinations and substance abuse or withdrawal, along with social and environmental triggers, are among the most common underlying cause of acute agitation in people with chronic psychoses (*5*). Although non-pharmacological management can be effective in many cases, more invasive or coercive measures are sometimes required, particularly when: the insight of disease is poor; there is immediate risk to personal safety; and effective environmental measures cannot be promptly applied.

Summary of evidence: benefits

Chlorpromazine

A 2017 Cochrane systematic review and pairwise meta-analysis included four randomized controlled trials that compared injectable chlorpromazine and injectable haloperidol for rapid tranquilization in adults with psychosis-induced aggression or agitation (*7*). These trials provided heterogeneous measures of efficacy and could not be all pooled for any efficacy outcomes. Although a number of outcomes were reported in the meta-analysis, the applicants selected

only those pooling at least two randomized controlled trials. For the outcome "not marked improvement", no significant differences were found between injectable haloperidol and chlorpromazine, although the point estimate favoured haloperidol (risk ratio (RR) 0.79, 95% confidence interval (CI) 0.61 to 1.02; two randomized controlled trials, 89 participants, very low-certainty evidence). Results for the outcome "not any improvement" significantly favoured haloperidol (RR 0.15, 95% CI 0.05 to 0.49; two randomized controlled trials, 89 participants, very low-certainty evidence).

Olanzapine

A systematic review and network meta-analysis of 10 randomized controlled trials (1964 participants) compared short-acting intramuscular second-generation antipsychotics (aripiprazole, olanzapine and ziprasidone), haloperidol and placebo in acutely agitated individuals with schizophrenia spectrum disorders (*8*). For the primary outcome of response 2 hours after the injection, all included second-generation antipsychotics were found to significantly outperform placebo, while no significant differences emerged in comparison with intramuscular haloperidol. Olanzapine was significantly more effective than aripiprazole for reducing agitation at 2 hours (RR 1.24, 95% CI 1.05 to 1.45; low-certainty evidence), but not haloperidol (RR 1.13, 95% CI 0.99 to 1.28; low-certainty evidence) or ziprasidone (RR 1.26, 95% CI 0.76 to 2.09; very low-certainty evidence). For the outcome of treatment response at 24 hours, no significant differences were found between olanzapine and haloperidol or olanzapine and aripiprazole.

Summary of evidence: harms

Chlorpromazine

A meta-analysis of four randomized controlled trials (153 participants) compared injectable haloperidol and injectable chlorpromazine for acceptability outcome "leaving the study early". The analysis found very low-quality evidence of significant benefit in favour of haloperidol (RR 0.21, 95% CI 0.07 to 0.71). Analysis of adverse events generally found no difference between treatments (*7*).

A revision of psychotropic medicines included in the interagency emergency health kit was conducted in 2011 (*9*). Injectable chlorpromazine was removed from the kit and was replaced by injectable haloperidol based on concerns of the risk of cardiovascular side-effects with chlorpromazine and its local irritation when administered intramuscularly (*10*).

Olanzapine

A systematic review and pairwise meta-analysis of randomized controlled trials compared side-effects of intramuscular olanzapine with those of any other antipsychotic or placebo for treatment of acute agitation in people with

schizophrenia spectrum disorders (*11*). Compared with placebo, there was very low-certainty evidence of no significant difference for intramuscular olanzapine in terms of serious adverse events (RR 0.48, 95% CI 0.05 to 5.18) or other specified adverse events with the exception of QT prolongation, which significantly favoured placebo (RR 0.34, 95% CI 0.16 to 0.70). Compared with haloperidol, no significant differences were found with olanzapine for study discontinuation for any reason (RR 1.02, 95% CI 0.47 to 2.23) or other specified undesirable outcomes with the exception of the use of anticholinergic medicines, extrapyramidal effects and dystonia, for which results favoured olanzapine.

WHO guidelines

The proposed deletion of chlorpromazine intramuscular injection and inclusion of olanzapine intramuscular injection are aligned with recommendations in the 2023 WHO Mental Health Gap Action Programme (mhGAP) guidelines (*12*).

Costs/cost–effectiveness

A 2022 cost–effectiveness analysis using data from a randomized clinical trial in Hong Kong between December 2014 and September 2019 compared the costs associated with intramuscular midazolam, haloperidol and olanzapine for the management of acute agitation in an emergency department (*13*). The main cost driver was labour costs for agitation management; the cost of the medicine was a minor contributor to total expenditure. Midazolam was the most cost–effective intervention, while no difference was found between haloperidol and olanzapine.

A 2009 retrospective study compared the medical records of 27 patients who received intramuscular haloperidol for the treatment of acute agitation episodes with those of 26 patients who received intramuscular olanzapine (*14*). No differences were found between the two treatments for mean number of repeated medication doses per episode of agitation and the proportion of patients requiring the use of seclusion and restraints. The authors concluded that, with equal effectiveness, haloperidol was the less expensive option.

In a 2011 retrospective cohort study based on a review of electronic medical records, 136 patients with a diagnosis of schizophrenia or schizoaffective disorder treated with different short-acting intramuscular antipsychotics (haloperidol, aripiprazole, olanzapine and ziprasidone) were compared for duration of hospital stay, number of injections received and associated costs (*15*). No difference in the length of hospitalization was found between the group of patients treated with haloperidol and those treated with second-generation antipsychotics. Treatment with haloperidol was associated with a significant reduction in the number of required injections and with lower costs compared to second-generation antipsychotics. Among the second-generation antipsychotics, ziprasidone was associated with a shorter duration of hospital stay compared with olanzapine.

The costs of chlorpromazine, haloperidol, olanzapine and aripiprazole intramuscular injections in different countries presented in the application are shown in Table 29.

Table 29
Costs of intramuscular antipsychotics

Country	US$ per unit			
	Chlorpromazine IM, 50 mg/2 mL	Haloperidol IM, 5 mg/mL	Olanzapine IM, 10 mg in vial	Aripiprazole IM, 9.75 mg/1.3 mL
Australia	1.74	1.82	NA	NA
India	0.34	0.08	0.43	NA
Italy	0.95	0.69	29.74	4.65
South Africa	1.08	2.51	8.39	5.82
United Kingdom	0.84	6.56	NA	3.85
United States	8.88	1.07	34.15	NA

IM: intramuscular; NA: not available.

Availability

Olanzapine intramuscular injection is available globally in branded and generic forms.

Committee recommendations

The Expert Committee noted that injectable, intramuscular immediate-release formulations of antipsychotic medicines were relevant for the management of people with schizophrenia and related psychotic disorders, especially for short-term treatment of acute psychomotor agitation when treatment cannot be administered orally.

The Committee noted that the most updated and high-quality scientific literature showed that evidence supporting chlorpromazine injection was quantitatively and qualitatively poor (no evidence against placebo, and low/very low-certainty evidence against haloperidol injection). The Committee also noted that chlorpromazine injection may be associated with an increased risk of adverse effects and was not included in current WHO guidelines.

The Committee noted that the evidence presented in the application showed injectable haloperidol, olanzapine and aripiprazole had similar efficacy profiles, but that olanzapine and aripiprazole generally had a more tolerable

safety profile in terms of motor symptoms (including acute dystonia and other extrapyramidal symptoms) than injectable haloperidol. The Committee noted that olanzapine was available in generic forms in many countries, while generic forms of aripiprazole were currently not available.

Based on these considerations, the Expert Committee recommended the removal of chlorpromazine immediate-release injection from the core list of the EML. The Committee also recommended the addition of olanzapine immediate-release injection on the core list of the EML for treatment of adults with schizophrenia and related psychotic disorders.

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Chlorpromazine, fluphenazine decanoate/enantate and haloperidol – review of square box alternatives – EML

Chlorpromazine	**ATC code: N05AA01**
Fluphenazine	**ATC code: N05AB02**
Haloperidol	**ATC code: N05AD01**

Proposal

Review of therapeutic alternatives under the square box listings for chlorpromazine, fluphenazine and haloperidol on the EML for use in the treatment of schizophrenia and related psychotic disorders.

The application proposed:

- oral chlorpromazine formulations be listed as a therapeutic alternative to oral haloperidol; and
- haloperidol decanoate and zuclopenthixol deaconate be listed as therapeutic alternatives to fluphenazine.

Applicant

WHO Department of Mental Health and Substance Use

WHO technical department

Mental Health and Substance Use

EML/EMLc

EML

Section

24.1 Medicines used in psychotic disorders

Dose form(s) & strengths(s)

Dose forms and strengths included on the 2021 EML

Chlorpromazine
Injection: 25 mg/mL (hydrochloride) in 2 mL ampoule
Oral liquid: 25 mg/5 mL (hydrochloride)
Tablet: 100 mg (hydrochloride)

Fluphenazine
Injection: 25 mg (decanoate or enantate) in 1 mL ampoule

Haloperidol
Injection: 5 mg in 1 mL ampoule
Tablet: 2 mg, 5 mg.

Core/complementary

Core

Individual/square box listing

Square box listing

Background

Chlorpromazine, fluphenazine and haloperidol have all been included on the EML for use in the treatment of schizophrenia and related psychotic disorders since the first EML was published in 1977.

At its meeting in 2021, the Expert Committee considered a review of square box listings on the EML and EMLc and recommended that all square box listings be qualified to explicitly indicate the recommended therapeutic alternatives. The Committee requested that the therapeutic alternatives for chlorpromazine, fluphenazine and haloperidol be reviewed and updated in 2023 (*1*). Thus, the EML Secretariat invited the WHO Department of Mental Health and Substance Use to submit an application reviewing the therapeutic alternatives for these medicines.

In a separate application to the 2023 Expert Committee meeting, the WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation at the University of Verona, Italy, proposed the deletion of chlorpromazine intramuscular injection from the EML.

Public health relevance

About 24 million people in the world are estimated to have schizophrenia (*2*). The prevalence of schizophrenia ranges from 0.2% to 0.4% across countries, while its incidence is reported to be 18.7 per 100 000 person-years (*3*). Globally, 129 million disability-adjusted life-years are attributable to mental health disorders, 11.7% of which are attributable specifically to schizophrenia spectrum disorders. Schizophrenia is also associated with relevant direct and indirect healthcare costs, and it is considered the costliest mental health condition per person globally (*2,4*). People with schizophrenia have a life expectancy about 14 years lower than the general population (*5*).

Summary of evidence: benefits

The application stated that according to the most recent and high-quality meta-analysis evidence on both acute and maintenance treatment of schizophrenia spectrum disorders, differences exist between first-generation antipsychotics in terms of efficacy, tolerability and certainty of evidence.

The applicants examined two recent meta-analyses: a 2019 systematic review and network meta-analysis (402 randomized controlled trials, 53 463

participants) which evaluated the comparative efficacy and tolerability of 32 oral antipsychotics for acute treatment of adults with schizophrenia (*6*); and a 2022 systematic review and meta-analysis (537 randomized controlled trials, 76 382 participants) which investigated the response of subgroups of patients with schizophrenia to different antipsychotic medicines (*7*). The evidence for first-generation antipsychotics was reviewed according to the following criteria.

  ▪ Demonstration of better efficacy in comparison with placebo for acute and/or maintenance treatment, considering the effect size as clinically meaningful when the confidence interval included a standardized mean difference of ≥ 0.3 for continuous outcomes, or a risk ratio of ≤ 0.6 for dichotomous outcomes.

  ▪ A moderate to high certainty of evidence according to grading of recommendations, assessment, development, and evaluations (GRADE)/confidence in network meta-analysis (CINeMA) approach for acute or maintenance treatment, or both.

The first-generation antipsychotics identified as meeting the above criteria were oral chlorpromazine, immediate-acting haloperidol, long-acting haloperidol decanoate, fluphenazine enantate/decanoate and zuclopenthixol decanoate. When compared head-to-head with the first-generation antipsychotics already listed in the EML, no statistically significant differences were found.

Summary of evidence: harms

Different side-effect profiles of the different first-generation antipsychotics were observed, although tolerability outcomes were rarely reported and were likely imprecise. In general, chlorpromazine had a higher risk of weight gain and anticholinergic effects compared with haloperidol, however haloperidol was associated with higher risks of extrapyramidal symptoms, akathisia and hyperprolactinaemia than chlorpromazine.

WHO guidelines

The medicines proposed in the application are recommended in the 2023 WHO Mental Health Gap Action Programme (mhGAP) guidelines (*8*).

Costs/cost–effectiveness

Not applicable

Availability

The proposed medicines are available in branded and generic forms.

Other considerations

In consideration of a separate application at the meeting, the Expert Committee recommended the deletion of chlorpromazine immediate-release injection from the core list of the EML.

Committee recommendations

The Expert Committee recalled the request made by the 2021 Committee for therapeutic alternatives to be reviewed for the square box listings for chlorpromazine, fluphenazine and haloperidol for treatment of schizophrenia and related psychotic disorders. The Expert Committee accepted the rationale applied by the WHO Department of Mental Health and Substance Use in identifying suitable therapeutic alternatives and made the following recommendations.

For immediate-acting first-generation antipsychotics, chlorpromazine (oral formulations only) should be included as a therapeutic alternative to oral haloperidol. This recommendation, coupled with the recommendation to remove chlorpromazine injection, effectively removes the independent listing for chlorpromazine from the EML.

For long-acting first-generation antipsychotics, haloperidol decanoate and zuclopenthixol decanoate should be included as therapeutic alternatives to fluphenazine.

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Paliperidone palmitate – new formulation – EML

Paliperidone palmitate	**ATC code: N05AX13**

Proposal

Addition of paliperidone palmitate 3-month (PP3M) long-acting injection formulation to the core list of the EML for the maintenance treatment of adults with schizophrenia.

Applicant

Janssen Research & Development, LLC, Raritan, NJ, United States of America

WHO technical department

The WHO department of Mental Health and Substance Use reviewed the application. The technical department made the following comments.

- Preliminary findings on the safety profile of PP3M are yet to be substantiated by evidence coming from long-term and pharmacovigilance studies.
- The long half-life of PP3M has implications for the possibility of seeking prompt assistance in the event of treatment-emergent adverse effects in rural settings
- The requirement to use PP3M after at least 4 months treatment with paliperidone palmitate 1-month (PP1M) may hinder its use due to limited or no availability in many low- and middle-income settings.
- Price information is lacking from low- and middle-income countries, and no generics are currently available.
- PP3M is not currently recommended for use in WHO guidelines.

EML/EMLc

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Section

24.1 Medicines used in psychotic disorders

Dose form(s) & strengths(s)

Injection (prolonged-release): 175 mg, 263 mg, 350 mg, 525 mg (as palmitate) in prefilled syringe

Core/complementary

Core

Individual/square box listing

Individual

Background

In 2021, the Expert Committee recommended the addition of PP1M long-acting injection to the core list of the EML for maintenance treatment of schizophrenia in adults stabilized on oral therapy. A square box listing was recommended specifying risperidone long-acting injection as a therapeutic alternative (*1*).

The 2021 Committee considered that long-acting injectable antipsychotic medicines are a valuable treatment option to increase adherence to treatment and reduce relapse in adults with schizophrenia and related psychotic disorders. The Committee also noted with concern the uncertainty of current and future availability of fluphenazine injection, which was the only long-acting injectable antipsychotic medicine included on the EML at that time and considered that the availability of alternative medicines would be important to meet the public health need for such treatments. The Committee noted that long-acting injectable antipsychotic medicines are an established treatment option for schizophrenia and are recommended in existing WHO Mental Health Gap Action Programme (mhGAP) guidelines. In particular, the Committee acknowledged that long-acting injectable antipsychotic medicines are useful in low-resource settings, where many factors might impede regular monitoring and follow-up of patients.

The 2021 Committee noted that the available data suggested benefits of long-acting injectable antipsychotic medicines versus oral antipsychotic medicines in preventing hospitalization or relapse, especially in populations with low treatment adherence. The effectiveness and overall safety of first-generation and second-generation antipsychotic medicines were similar. The availability of agents with different side-effect profiles may support the selection of one treatment over another given a patient's clinical status and vulnerabilities.

In consideration of the application for inclusion of PP1M, the 2021 Committee noted that although PP3M was shown to be effective and acceptable, the applicants decided not to include this formulation in the proposal for the following reasons.

- PP3M had become available only relatively recently, was not yet commonly used in clinical practice and its worldwide availability might be limited.

- Some concerns had been raised about a randomized study comparing PP3M and placebo (*2*) in which study participants underwent a stabilization phase with PP1M before randomization which might have inflated the effect size in favour of paliperidone.

- ▪ More research was needed to rule out possible unintended consequences of PP3M, including the effects of reduced doctors' visits due to the longer dosing interval.
- ▪ The cumulative monthly dosing of PP3M was slighter higher than that of PP1M and this may affect toxicity and tolerability (*3*).

Public health relevance

Schizophrenia is a debilitating mental disorder that typically starts in late adolescence or early adulthood (*4–6*). In 2019, nearly 24 million people worldwide were estimated to have schizophrenia (*7*). The global burden of mental disorders, including schizophrenia, has been increasing over time (*4,7*). Between 1990 and 2019, the number of disability-adjusted life years (DALYs) due to mental disorders rose from 80.8 million to 125.3 million, accounting for almost 5% of all DALYs (*7*). The incident cases and DALYs of schizophrenia also increased during this period, reaching 1.13 million persons and 12.66 million DALYs, a 37% increase in incident cases and a 62% increase in DALYs compared with 1990 (*4*). In low- and middle-income countries, a significant treatment gap exists, with about two thirds of individuals with schizophrenia not receiving adequate treatment (*8*). People with schizophrenia also have a reduced life expectancy of about 15 years compared with the general population, which is partly due to physical diseases such as cardiovascular disease (*9,10*).

Schizophrenia is a significant economic burden and is projected to cost the global economy trillions of dollars by 2030 (*11–13*). The costs include direct expenses of treatment, rehabilitation and social welfare, as well as indirect costs such as reduced productivity, unemployment and the financial impact on families. The burden is exacerbated by the limited global coverage of mental health care (*14–17*).

Long-term treatment is crucial in managing schizophrenia, and long-acting injectable medicines are commonly prescribed for patients who are non-compliant or experience persistent symptoms (*18–21*).

Summary of evidence: benefits

The R092670-PSY-3011 study was a company-sponsored non-inferiority phase III study that compared PP3M with PP1M in adults with schizophrenia (*22*). Participants received PP1M during a 17-week open-label phase before being randomized to receive the same dose of PP1M or the corresponding equivalent dose of PP3M for 48 weeks. The primary efficacy endpoint was the percentage of participants who had not relapsed at the end of the double blind phase based on the Kaplan–Meier 48-week cumulative estimate of survival. The per-protocol analysis showed similar rates of relapse in both treatment groups after 48 weeks (37/458 (8.1%) for PP3M versus 45/490 (9.2%) for PP1M; estimated difference

(PP3M – PP1M) 1.2%, 95% confidence interval (CI) –2.7% to 5.1%). It was concluded that PP3M was non-inferior to PP1M as the lower bound of the CI was larger than the prespecified non-inferiority margin of –15%. The hazard ratio (HR) for risk of relapse when switching from PP1M to PP3M versus remaining on PP1M was 0.87 (95% CI 0.56 to 1.34). Subgroup analyses also supported the non-inferiority of PP3M in different age groups, sexes, races, baseline body mass index groups and geographic regions (*23–25*).

The R092670-PSY-3012 study was a company-sponsored long-term, placebo-controlled phase III randomized withdrawal study with PP3M in adults with schizophrenia (*2*). The study consisted of four phases and evaluated the efficacy of PP3M in delaying relapse of symptoms in adult participants with schizophrenia who had achieved symptom control with PP1M. The study used a randomized withdrawal design to assess whether the discontinuation of PP3M treatment after stabilization with PP1M would affect the course of the disease. The fixed-dose regimen of PP3M was based on the conversion from the effective dose of PP1M. The primary endpoint was the time to relapse during the double-blind phase. At the preplanned interim analysis, conducted after 42 relapse events, 23.0% (31/135) of participants who switched from open-label PP3M to double-blind placebo experienced a relapse event, compared with 7.4% (11/148) of participants who remained on PP3M. Participants who continued treatment with PP3M in the double-blind phase experienced a significantly longer time to relapse compared with those who switched to placebo (*P* < 0.001 based on a log-rank test). The median time to the first relapse was 274 days in the placebo group, while it was not estimable in the PP3M group. At the final analysis, after 56 relapse events, 29.0% (42/145) of participants in the double-blind placebo group experienced a relapse event versus 8.8% (14/160) of participants in the double-blind PP3M group. A significant difference was seen in the time to relapse which favoured PP3M (*P* < 0.001 based on a log-rank test). The median time to the first relapse event was 395 days for the placebo group, while it was not estimable for the PP3M group.

A 2021 systematic review and network meta-analysis of 78 randomized controlled trials (11 505 participants) compared relapse prevention and acceptability of long-acting injectable antipsychotics in the maintenance treatment of non-affective psychoses in adults (*26*). PP1M and PP3M were among the long-acting antipsychotics included in the analysis. The primary outcomes were the proportion of patients who experienced at least one relapse, and the proportion of patients who dropped out of the trial for any reason (acceptability). The ranking probability was assessed by surface under the cumulative ranking curve (SUCRA) and the certainty of evidence was assessed by Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). The primary analysis found that most long-acting injectable antipsychotics evaluated

were significantly more effective than placebo in preventing relapse, including PP3M (relative risk (RR) 0.27, 95% CI 0.17 to 0.42; SUCRA 80.2%, high-certainty evidence) and PP1M (RR 0.39, 95% CI 0.30 to 0.50; SUCRA 46.8%, high-certainty evidence). There was also moderate-certainty evidence of no significant difference for the comparison between PP3M and PP1M (RR 1.44, 95% CI 0.95 to 2.19). Additionally, most long-acting injectable antipsychotics evaluated were significantly more acceptable than placebo, including PP3M (0.60, 95% CI 0.43 to 0.84; SUCRA 62.5%, high-certainty evidence) and PP1M (0.70, 95% CI 0.85 to 0.85; SUCRA 39.5%, moderate-certainty evidence). Exploratory secondary analyses showed significantly lower hospitalization rates for several long-acting injectable antipsychotics including PP3M (RR 0.26, 95% CI 0.10 to 0.65) and PP1M (RR 0.37, 95% CI 0.16 to 0.87). The authors concluded that long-acting injectable formulations of paliperidone (PP3M and PP1M) were among those that demonstrated the highest effectiveness and acceptability in preventing relapse in non-affective psychoses.

A 2022 systematic review and network meta-analysis of 92 randomized controlled trials (22 645 participants) evaluated the differences in the effectiveness and tolerability of oral antipsychotics and long-acting injectable antipsychotics for maintenance treatment of schizophrenia-spectrum disorders (*27*). The two coprimary outcomes were the proportion of participants who experienced at least one relapse, and the proportion of participants who dropped out of the trial due to an adverse event. There was moderate-certainty evidence that PP3M was superior to placebo for the prevention of relapse (RR 0.24, 95% CI 0.13 to 0.42; SUCRA 80.3%).

A more recent 2022 systematic review and network meta-analysis of 100 randomized controlled trials (16 812 participants) compared the efficacy and tolerability of 32 antipsychotics as maintenance treatment for non-treatment-resistant patients with schizophrenia. No clear evidence for the superiority of specific antipsychotics for relapse prevention was observed and the authors concluded that the choice of medicine should be guided mainly by tolerability (*28*).

A retrospective observational study used claims data from the Hungarian National Health Insurance Fund database to compare the effectiveness of long-acting injectable antipsychotics versus oral antipsychotics (*29*). The study included 5400 patients who started treatment with a second-generation antipsychotic as monotherapy (1423 given injectable medicines, and 3977 given oral medicines) including PP1M and PP3M. The primary outcome was the all-cause discontinuation of the antipsychotic medication over a 1-year and 1.5-year period. The results showed that long-acting injectable antipsychotics had higher continuation rates compared with oral antipsychotics. Patients given PP3M (*n* = 627) had the highest continuation rates of all antipsychotics, with 79% and 76% of patients continuing treatment for 1 year and 1.5 years, respectively.

Adjusted analyses showed that the risk of discontinuation was significantly higher for oral antipsychotics compared with PP3M and aripiprazole long-acting injection ($P < 0.01$ for all). Compared with PP1M, the risk of discontinuation was significantly higher for all oral antipsychotics except olanzapine and paliperidone. Risperidone long-acting injection had a lower risk of discontinuation compared with oral risperidone ($P < 0.001$). All other long-acting injectable antipsychotics had a significantly higher risk of discontinuation than PP3M ($P < 0.05$). The study limitations included the lack of randomization and control group, potential misclassification of diagnoses, and selection bias of different treatments (29).

A company-sponsored prospective, multinational, single-arm, open-label phase IIIb study (305 participants) evaluated the efficacy and safety of converting patients with schizophrenia stabilized with PP1M to PP3M in a naturalistic clinical setting over 52 weeks (30). The primary efficacy endpoint was symptomatic remission at last observation carried forward. Symptomatic remission was achieved by 56.8% (172/303) of patients at the last observation carried forward endpoint, while symptomatic remission was achieved by 60.7% (184/303) of patients during the 12-month treatment period. Among these, 4.0% (12/303) patients had met the criteria for symptomatic remission during the treatment period, then subsequently did not. Over the PP3M treatment period, the proportion of patients hospitalized for psychiatric reasons fell from 13.5% at baseline to 4.6%, and the mean number of days of hospitalization fell from 33.2 days to 15.2 days. Additionally, the number of patients visiting the emergency department for psychiatric reasons decreased from 11 to 3 during the PP3M treatment period compared with the 12 months before baseline.

Summary of evidence: harms

PP3M and PP1M have the same active moiety, route of administration and nanoparticle aqueous suspension technology, although they differ in particle size and concentration (31). When used within the recommended dose range, PP3M results in similar exposure to paliperidone as PP1M, without accumulation over time (32).

Safety findings from the long-term PP3M studies R092670 PSY 3011 (22) and R092670 PSY 3012 (2) were comparable to previous studies with PP1M, with no clinically meaningful differences in the safety profile between the two products.

The warnings and precautions for PP3M are in line with those for other second-generation antipsychotics. In the United States, PP3M carries a black box warning on the increased risk of death associated with cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis (33).

The types and incidences of adverse events are consistent between PP3M and PP1M. Weight gain was the most frequently reported treatment-emergent adverse event in both groups. The incidence of adverse events related to tardive

dyskinesia/extrapyramidal symptoms, QT prolongation, hyperglycaemia and diabetes mellitus, weight gain, hyperprolactinaemia and prolactin-related adverse events, as well as injection site reactions and discontinuations due to these events, were generally similar between PP3M and PP1M. Neuroleptic malignant syndrome was not reported. While injection-site adverse events were infrequently reported in completed studies with PP3M, they occurred more frequently than with PP1M. Subgroup analyses based on geographical regions (east Asian, European/non-European and Latin American) did not show any unique safety signals associated with PP3M compared with PP1M (*23–25*).

The 2021 network meta-analysis showed that PP1M had a higher risk of adverse events (RR 1.87, 95% CI 1.02 to 3.40) and weight gain (RR 2.51, 95% CI 1.55 to 4.05) compared with placebo. Point estimates for these outcomes also showed a higher risk for PP3M, however they were not statistically significant. PP3M had a lower risk of QTc prolongation than PP1M (based on results from a single study). Both PP1M and PP3M showed significantly higher risk of hyperprolactinaemia (RR 3.25, 95% CI 1.24 to 8.51 and RR 2.99, 95% CI 1.11 to 8.05, respectively) (*27*).

An observational review of the French pharmacovigilance database found that adverse drug reactions associated with paliperidone palmitate were similar to those reported for other atypical antipsychotics (*34*). Another observational cohort study of 90 patients with schizophrenia spectrum disorders found that increased appetite and weight were more common with PP3M (40.9%) and PP1M (76.5%) compared with haloperidol decanoate (17.6%), but there were no significant differences in sedation, extrapyramidal symptoms, decreased libido or body mass index (*35*). A large retrospective cohort study involving 92 075 patients with schizophrenia or schizoaffective disorder reported no increased risk of all-cause death, completed suicide or suicidal behaviour/attempts in users of various long-acting injectable antipsychotics, including PP3M and PP1M (*36*). Likewise, an observational, cross-sectional study in 431 non-institutionalized patients with schizophrenia, psychosis, and schizoaffective, delusional, bipolar or personality disorders found similar results (*37*). A 12-month cohort study in outpatients with non-affective first episode psychosis found no statistically significant differences in treatment side-effects between PP3M and PP1M (*38*). Studies examining the switch from PP1M or clozapine to PP3M did not report any new safety concerns (*30,39–43*).

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a conditional recommendation that long-acting injection antipsychotic medicines (fluphenazine, haloperidol, paliperidone, risperidone and zuclopenthixol) should

be considered as an alternative to oral antipsychotic medicines for adults with psychotic disorders (including schizophrenia) requiring long-term treatment, carefully balancing effectiveness, side-effects and individual preference (moderate certainty of evidence) (*44*).

Costs/cost–effectiveness

PP3M is available in different dose levels. The cost per patient for PP3M can vary depending on the dose and country. In the Netherlands (Kingdom of the), Portugal and Sweden, the publicly available list prices for PP3M range from €565 to €1868 per prefilled syringe or €2259 to €7471 a year (*45*). These prices can vary based on factors such as country-specific assessments of value, population coverage, local pricing and reimbursement negotiations, and local regulations.

Despite potentially higher drug acquisition costs, PP3M and PP1M have been found to be cost-saving for maintenance treatment in resource-limited settings based on evidence from Rwanda and South Africa. Additionally, compared with standard oral antipsychotics, PP3M and PP1M have the potential for cost offsets. In the context of Rwanda, where health care resources are limited and patients must often travel long distances for treatment, a 1-year cost consequence model study showed that PP3M and PP1M led to longer treatment duration, fewer relapses, and fewer hospital days compared with haloperidol, the standard of care. This resulted in reduced indirect costs by almost 50%, including travel expenses and improved productivity (*46,47*).

Real-world evidence and simulation studies also suggest that early use of long-acting injectable antipsychotics can improve long-term patient outcomes and potentially lead to cost offsets (*48,49*). These include a reduction in hospital admissions, reduced use of disability benefits, and increases in independent living and competitive employment.

An analysis of the R092670-PSY-3012 study found that in terms of direct costs, PP3M decreased the likelihood of hospitalization and emergency room visits, resulting in lower costs (*49*). The odds ratio for hospitalization for psychiatric and social reasons during the double-blind phase for placebo versus PP3M was 7.74 (95% CI 2.39 to 25.05). Total health-related health care resource utilization costs, mental health-related costs and hospitalization/ emergency room visit costs were significantly lower for the PP3M group versus the placebo group.

Availability

PP3M is approved and registered in 90 countries worldwide. It is not currently available on the market in all 90 countries in which it is registered. Generic brands are not currently available, with patent protection for the innovator brand not due to expire until 2036.

Committee recommendations

The Expert Committee recognized that long-acting injectable antipsychotic medicines were an important treatment option for some patients with schizophrenia, and recalled the recommendation made by the 2021 Expert Committee to include PP1M long-acting injection on the EML for this indication, with risperidone long-acting injection as a therapeutic alternative among second-generation antipsychotics. The Committee also noted the separate application to the 2023 meeting proposing therapeutic alternatives to long-acting injections of first-generation antipsychotics.

The Committee noted that compared with the 1-month formulation (PP1M), the 3-month formulation (PP3M) had evidence of similar clinical efficacy and safety and may offer advantages to patients in terms of fewer injections. However, the Committee noted that PP3M was recommended for use only in patients who have been adequately treated with PP1M and demonstrate benefit from and tolerance to it for at least 4 months. The Committee was therefore concerned that both strength formulations would need to be available for appropriate treatment and considered that the more limited availability of PP3M in low- and middle-income countries would be problematic. In addition, the Committee noted that PP3M was more highly priced and was not yet available in generic forms.

The Committee also noted that PP3M long-acting injection was not currently included in WHO mhGAP guidelines.

Based on these considerations, the Expert Committee did not recommend inclusion of PP3M long-acting injection on the EML for maintenance treatment of schizophrenia.

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Risperidone – addition of square box – EML

Risperidone	ATC code: N05AX08

Proposal

Addition of a square box to the listing of risperidone on the EML for treatment of schizophrenia and related chronic psychotic disorders, specifying aripiprazole, olanzapine, paliperidone and quetiapine as therapeutic alternatives.

Applicant

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy

WHO technical department

Mental Health and Substance Use

EML/EMLc

EML

Section

24.1 Medicines used in psychotic disorders

Dose form(s) & strengths(s)

Risperidone
Tablet: 1 mg, 2 mg, 3 mg, 4 mg, 6 mg

Aripiprazole
Tablet: 5 mg, 10 mg, 15 mg, 30 mg

Olanzapine
Tablet: 5 mg, 10 mg, 20 mg
Orodispersible tablet: 5 mg, 10 mg, 20 mg

Paliperidone
Tablet (modified-release): 3 mg, 6 mg, 9 mg

Quetiapine
Tablet (immediate-release): 25 mg, 100 mg, 150 mg, 200 mg, 300 mg
Tablet (modified-release): 50 mg, 150 mg, 200 mg, 300 mg, 400 mg

Core/complementary

Core

Individual/square box listing

Square box

Background

Oral risperidone was added to the EML in 2013 as a treatment for schizophrenia. In making this recommendation, the Expert Committee considered that except for clozapine, the efficacy and safety of the second-generation antipsychotics were comparable but noted that the availability of generics varied considerably. The Expert Committee recommended that risperidone be added to the EML without the square box symbol. However, the Committee indicated that it would welcome further applications for additional second-generation antipsychotics, based on careful consideration of suitable alternatives or additions to risperidone (*1*).

Public health relevance

In 2019, about 24 million people in the world were estimated to have schizophrenia (*2*). The prevalence of schizophrenia ranged from 0.2% to 0.4% across countries, while its incidence was 16.7 per 100 000 person-years (*3*). Globally, 129 million disability-adjusted life-years are attributable to mental health disorders, 11.7% of which are attributable to schizophrenia spectrum disorders. Schizophrenia is also associated with direct and indirect health care costs, and it is considered the costliest mental health condition per person globally (*2*,*4*).

The relationship between schizophrenia and stress-related noncommunicable diseases is well known (*5*). People with schizophrenia have a 15–20 year shorter life expectancy than the general population (*6*,*7*). While suicide explains some of this reduced life expectancy, physical diseases probably account for most of the premature mortality (*7*,*8*).

According to current evidence, regular pharmacological treatment from the early phases of the disease may preserve neurocognitive abilities, prevent structural brain changes and delay progression to chronic functional deterioration, thus resulting in better life conditions and increased survival (*9*). However, treatment adherence is an important problem, with up to half of all individuals with schizophrenia not taking medications as prescribed and only one third fully adhering to antipsychotic treatment. Such non-adherence increases the risk of relapse (*10–13*).

Not all antipsychotics are equally effective and tolerable, and not all are supported by high-quality evidence (*14–19*). Both clinical response and individual vulnerability to adverse events vary widely between individuals, therefore health practitioners treating patients with schizophrenia should tailor the choice of antipsychotic medicine based on individual characteristics, weighing expected benefits and harms (*12*).

The median value for treatment coverage in low- and middle-income countries has been estimated at about 30% (*20*), suggesting that 70% of people with schizophrenia spectrum disorders in these countries do not receive adequate treatment. The treatment gap for schizophrenia disorders was larger in low-income countries (89%) than in lower middle-income (69%) and upper middle-income countries (63%). The size of the treatment gap is negatively associated with the prevalence of schizophrenia disorders in the general population, gross national income, availability of psychiatric hospital beds, number of psychiatrists per 100 000 population and number of nurses in mental health facilities per 100 000 population (*20*). Furthermore, few countries are aligned with the general principle of providing full access to essential psychotropic medicines, with limited availability and high prices being major barriers (*21*).

Summary of evidence: benefits

The application presented the results of a comprehensive literature search for systematic reviews on the efficacy, acceptability, tolerability and safety of antipsychotic medicines in adults with schizophrenia spectrum disorders. Two key systematic reviews and network meta-analyses were identified (*15,16*).

A 2019 network meta-analysis including both placebo-controlled and head-to-head randomized controlled trials compared 32 oral antipsychotics for the acute treatment of adults with multiepisode schizophrenia (*15*). The primary outcome analysis of change in overall symptoms at the end of the study was based on 218 studies (40 815 participants). Most antipsychotics (81%) outperformed placebo, with standardized mean differences (SMD) ranging between –0.89 (clozapine) and –0.26 (brexpiprazole). Effect sizes and 95% credible intervals (95% CrI) were largely overlapping. Certainty of evidence according to the confidence in network meta-analysis (CINeMA) approach was high only for risperidone and paliperidone, and moderate for amisulpride, zotepine, olanzapine, perphenazine, haloperidol and quetiapine. In the head-to-head comparisons, clozapine, amisulpride, zotepine, olanzapine and risperidone were among the best-performing medications. Amisulpride outperformed risperidone (SMD –0.18, 95% CrI –0.33 to –0.02), which in turn outperformed quetiapine (SMD –0.13, 95% CrI –0.23 to –0.04), aripiprazole (SMD –0.14, 95% CrI –0.25 to –0.03), ziprasidone (SMD –0.14, 95% CrI –0.25 to –0.03), sertindole (SMD –0.15, 95% CrI –0.30 to –0.01), asenapine (SMD –0.16, 95% CrI –0.30 to –0.02), lurasidone (SMD –0.19, 95% CrI –0.32 to –0.05), cariprazine (SMD –0.21, 95% CrI –0.36 to –0.05), iloperidone (SMD –0.22, 95% CrI –0.34 to –0.10) and brexpiprazole (SMD –0.29, 95% CrI –0.45 to –0.14). Most of these comparisons barely reached statistical significance and the differences were clinically negligible (Cohen d < 0.2) (*22*), with the exception of cariprazine, iloperidone and brexpiprazole, for which the differences were small (0.2 < Cohen d < 0.5).

A 2022 network meta-analysis including both placebo-controlled and head-to-head randomized controlled trials compared 32 oral and long-acting antipsychotics for the prevention of relapse in adults with schizophrenia or schizoaffective disorder with stable symptoms who were already treated with antipsychotics (*16*). The primary outcome analysis of risk of relapse was based on 100 studies (16 812 participants). All antipsychotics had risk ratios (RR) less than 1 compared with placebo, and all except for oral cariprazine, oral lurasidone and long-acting injectable clopenthixol had 95% CrI excluding no effect. Certainty of evidence according to the CINeMA approach was moderate for most of the best-performing medications, with the exception of oral fluphenazine, oral tiotixene and oral iloperidone oral which were rated as low-certainty of evidence. From the head-to-head comparisons, clozapine, amisulpride, zotepine, olanzapine and risperidone were among the best-performing medications, while in most cases the differences were small or non-significant. No statistically significant differences emerged in head-to-head comparison of risperidone and other oral second-generation antipsychotics.

Two additional network meta-analyses were described which confirmed and expanded the efficacy findings described above (*17,19*).

Summary of evidence: harms

The network meta-analysis on the acute treatment of adults with multiepisode schizophrenia provided data on the acceptability of treatments (all-cause discontinuation) (*15*). The analysis included 226 randomized controlled trials (42 672 participants) and showed that most of the included medications were significantly more acceptable than placebo and none was less acceptable than placebo. Certainty of evidence according to the CINeMA approach was high for olanzapine, paliperidone, risperidone, iloperidone, aripiprazole, quetiapine and asenapine, and moderate for amisulpride, clotiapine, zuclopenthixol, zotepine and levomepromazine. In head-to-head comparisons between risperidone and other second-generation antipsychotics, risperidone was outperformed by olanzapine (RR 0.93, 95% confidence interval (CI) 0.87 to 0.98). However, risperidone outperformed lurasidone (RR 0.90, 95% CI 0.84 to 0.98), ziprasidone (RR 0.88, 95% CI 0.80 to 0.96), brexpiprazole (RR 0.89, 95% CI 0.83 to 0.97), cariprazine (RR 0.87, 95% CI 0.81 to 0.94) and sertindole (RR 0.81, 95% CI 0.70 to 0.90). In all cases, the differences between risperidone and other second-generation antipsychotics were clinically and statistically very small.

The network meta-analysis on the prevention of relapse in adults with schizophrenia or schizoaffective disorder showed that the risk of discontinuation for any reason was significantly lower for most of the included antipsychotics compared with placebo. None of the included antipsychotic medicines was associated with a significantly higher risk of discontinuation for any reason compared with placebo

(*16*). Certainty of evidence according to the CINeMA approach was moderate for most of the medications, with the exception of oral sertindole oral, for which the certainty of evidence was rated as high, and zotepine and cariprazine for which it was rated as low. In head-to-head comparisons between risperidone and other second-generation antipsychotics, risperidone outperformed lurasidone (RR 2.28, 95% CI 1.29 to 3.84) and cariprazine (RR 3.26, 95% CI 1.13 to 7.43), with no significant differences with the remaining second-generation antipsychotics. Results reported in another network meta-analysis (87 randomized controlled trials, 21 772 participants) were generally consistent with these findings for clinically stable adults with schizophrenia spectrum disorder (*19*).

A 2017 network meta-analysis of 19 randomized controlled trials (2669 participants) on acute treatment of first-episode schizophrenia showed a significantly lower risk of all cause discontinuation for oral aripiprazole, quetiapine, risperidone and olanzapine compared with haloperidol (*17*). The certainty of evidence according to CINeMA was low due to the relatively small number of participants included.

A 2018 meta-analysis of 352 randomized controlled trials (84 988 participants) compared the risk of short-term mortality between second-generation antipsychotics and placebo for multiple diagnoses (*23*). No significant differences were found between antipsychotics and placebo for mortality by any cause in the subgroup of people with schizophrenia (odds ratio (OR) 0.69, 95% CI 0.35 to 1.35).

A 2019 meta-analysis of 314 randomized controlled trials (67 642 participants) compared the risk of somatic serious adverse events between second-generation antipsychotics and placebo for multiple diagnoses (*24*). Subgroup analyses of the individual antipsychotics showed a significantly higher risk of serious adverse events for haloperidol (OR 1.61, 95% CI 1.07 to 2.43), olanzapine (OR 1.35, 95% CI 1.04 to 1.74) and risperidone (OR 1.33, 95% CI 1.04 to 1.70) compared with placebo, while for the other medications no significant differences emerged.

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a strong recommendation that adults with a psychotic disorder (including schizophrenia) should be offered oral antipsychotic medicines (namely aripiprazole, chlorpromazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone), carefully balancing effectiveness, side-effects and individual preference (moderate certainty of evidence) (*25*).

Costs/cost–effectiveness

Second-generation antipsychotics are generally more expensive than first-generation antipsychotics. In resource-constrained countries, the use of first-generation agents is prevalent and second-generation agents are usually reserved in case of serious adverse effects or inefficacy (*26,27*). There is debate about whether routine use of second-generation antipsychotics in these countries could be favourable in terms of medical-economic resources as compared with first-generation antipsychotics, despite their higher procurement cost. Current evidence on the matter is scant and controversial. Among second-generation antipsychotics, olanzapine and risperidone often appear to have the most favourable cost–effectiveness profile.

In a multicentre randomized controlled trial in the United Kingdom, the relative costs and efficacy of first-generation versus second-generation antipsychotics were compared in more than 200 patients diagnosed with of chronic psychosis (schizophrenia, schizoaffective disorder and delusional disorder) for whom a medication change was needed. The results suggested that switching to first-generation agents was generally associated with lower costs and higher quality-adjusted life years (QALYs) compared with second-generation agents (*28*).

A pharmacoeconomic analysis modelling clinical and economic outcomes of various antipsychotics in both oral (amisulpride, aripiprazole, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone) and long-acting formulation (haloperidol and risperidone) over a 1-year horizon found that the most cost-effective treatments were haloperidol, haloperidol decanoate and olanzapine. Of the second-generation agents, olanzapine and risperidone were the most favourable treatments for outpatients with chronic schizophrenia (*29*).

In a study in Singapore modelling the cost–effectiveness of 11 oral antipsychotics (amisulpride, aripiprazole, chlorpromazine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, sulpiride, trifluoperazine and ziprasidone) for prevention of psychotic relapse over a life time, olanzapine was the most favourable treatment with the highest QALYs gained and the lowest lifetime costs, while ziprasidone, aripiprazole and paliperidone were the least favourable (*30*).

A cohort study in Germany using data from a statutory sickness fund, including more than 3000 patients diagnosed with schizophrenia, found no differences between atypical versus typical antipsychotics for rehospitalization rates (*31*).

A large-scale study including more than 3000 patients recruited from 1999 to 2004 and treated for first-episode psychosis indicated that haloperidol was more expensive than olanzapine, zotepine or quetiapine based on total hospitalization expenses and overall treatment costs (*32*).

In another cost–effectiveness analysis based on the Ugandan health care system, risperidone was potentially cost-saving compared with haloperidol and quetiapine (*33*).

In a 2005 systematic review of the cost and effectiveness of risperidone and olanzapine for schizophrenia found that the evidence was insufficient to distinguish the relative total cost of care associated with risperidone versus olanzapine, although available evidence suggested that the difference was small (*34*).

A 2019 cost–utility analysis in the United Kingdom from the National Health Service perspective between 2016 and 2017 evaluated paliperidone and amisulpride for treatment of schizophrenia. The results indicated that paliperidone was associated with an incremental cost–effectiveness ratio of £10 941 per additional QALY gained, which was lower than the suggested National Health Service threshold of £20 000–30 000. The study concluded that paliperidone should be preferred to amisulpride (*35*).

Newer antipsychotics on the market, such as asenapine, ziprasidone and lurasidone have also been the subject of pharmacoeconomic studies using Markov models. They have shown promising results for cost–effectiveness, mostly attributable to the lower incidence of cardiometabolic side-effects (*36–38*).

Different medicine formulations might also have an effect on cost–effectiveness. Studies have shown that olanzapine orodispersible treatment (ODT) is generally preferred by patients to the standard oral treatment (SOT) and therefore ODT tends to be associated with better treatment adherence and lower relapse risk (*39*). In a 12-week multinational, randomized, crossover, open-label study, 175 patients with schizophrenia were randomly assigned to olanzapine ODT or SOT for 6 weeks and then switched to the other formulation. The results showed that 61% of the sample preferred the ODT formulation, whereas only 27% favoured SOT and 12% expressed no preference (*40*). In addition, olanzapine ODT has proven particularly useful when treatment needs to be administered under difficult circumstances, such as in the case of acutely ill non-compliant or agitated patients, thus reducing the burden on nursing staff (*41,42*). According to some cost–effectiveness analyses, olanzapine ODT also has a favourable pharmacoeconomic profile compared with the corresponding SOT and with other antipsychotics. A cost–effectiveness comparison of olanzapine, aripiprazole and risperidone ODT and SOT using a 1-year Monte Carlo microsimulation economic model found that, although olanzapine ODT was more expensive than olanzapine SOT and risperidone SOT, it was cost-effective (with incremental cost-effectiveness ratios of US$ 19 643 and US$ 39 966, respectively) due to lower relapse and hospitalization rates. Moreover, if compared with risperidone and aripiprazole ODT, olanzapine ODT was not only less expensive but also more effective (*43*). A similar cost–effectiveness analysis in China gave similar results with olanzapine ODT being more cost-effective

than olanzapine SOT (US$ 16 798 per QALY gained), and more cost saving than aripiprazole SOT over a 1-year horizon (*44*).

The application included a summary of costs for second-generation antipsychotics from Australia, India, Italy, South Africa, the United Kingdom and the United States, showing wide variability across markets.

Availability

Risperidone, and all the proposed alternative second-generation antipsychotics are available in innovator and generic brands worldwide.

Other considerations

The applicants identified the second-generation antipsychotics proposed as therapeutic alternatives to risperidone according to the following criteria.

- Performs better than placebo in terms of efficacy for both acute and maintenance treatment.
- Performs better or no worse than placebo in terms of acceptability (overall drop-out rate) for both acute and maintenance treatment.
- Has a moderate or high certainty of evidence according to CINeMA appraisal for most (≥ 3/4) of these outcomes.

Committee recommendations

The Expert Committee noted that evidence from several high-quality meta-analyses on acute and maintenance treatment of schizophrenia and other chronic psychoses found most oral second-generation antipsychotics were similarly effective and tolerable.

The Expert Committee accepted the criteria applied by the applicants in identifying the proposed therapeutic alternatives and recommended the addition of a square box to the listing of risperidone on the EML for treatment of schizophrenia and related chronic psychotic disorders, specifying oral aripiprazole, olanzapine, paliperidone and quetiapine as therapeutic alternatives.

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24.2 Medicines used in mood disorders
24.2.1 Medicines used in depressive disorders
Amitriptyline – removal of square box – EML

Amitriptyline	ATC code: N06AA09

Proposal

Removal of the square box with the listing of amitriptyline for depressive disorders on the EML.

Applicant

WHO Department of Mental Health and Substance Use

WHO technical department

Mental Health and Substance Use

EML/EMLc

EML

Section

24.2.1 Medicines used in depressive disorders

Dose form(s) & strengths(s)

Tablet: 25 mg, 75 mg (hydrochloride)

Core/complementary

Core

Individual/square box listing

Individual

Background

A square box listing for amitriptyline has been included on the EML for use in depressive disorders since the first list was published in 1977, as the representative medicine for the class of tricyclic antidepressants.

In 2021, following the review of square box listings on the EML and EMLc, the Expert Committee requested the therapeutic alternatives for amitriptyline on the EML be reviewed.

Public health relevance

Not applicable

Summary of evidence: benefits

Meta-analyses using standard pairwise comparisons of tricyclic antidepressants against placebo have not been able to identify the best medicines within the class (*1*).

A 2018 systematic review and network meta-analysis evaluated the comparative efficacy of 21 different antidepressant medicines for the treatment of adults with major depressive disorder (*2*). This review examined data on two tricyclic antidepressants – amitriptyline and clomipramine – and found that both medicines were more effective than placebo for the outcome of reduction in overall depressive symptoms: amitriptyline standardized mean difference (SMD) –0.48, 95% confidence interval (CI) –0.55 to –0.41, and clomipramine SMD –0.33, 95% CI: –0.45 to –0.21. However, the estimate for clomipramine was indirect, with no included studies directly comparing clomipramine with placebo. The only study comparing clomipramine with placebo, randomized only 38 participants and did not include efficacy data suitable for reanalysis.

Summary of evidence: harms

As measured by drop-out rate, clomipramine was the only medicine among the 21 included in the above-mentioned review, found to be less acceptable than placebo (odds ratio (OR) 1.30, 95% CI 1.01 to 1.68) (*2*). In comparison, for amitriptyline, the OR for acceptability was 0.95 (95% CI 0.83 to 1.08).

Additional evidence

Not applicable

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a conditional recommendation for antidepressants (specifically, amitriptyline, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine or sertraline) to be considered for adults with moderate-to-severe depression (very-low certainty evidence) (*3*).

Costs/cost–effectiveness

Not applicable

Availability

Not applicable

Other considerations

Not applicable

Committee recommendations

The Expert Committee considered that the data were insufficient to support the inclusion of other tricyclic antidepressants as therapeutic alternatives for amitriptyline on the EML for the treatment of depressive disorders. The Committee considered that amitriptyline was the tricyclic antidepressant with the greatest amount of evidence within the class and other tricyclic antidepressants had insufficient evidence or were likely to be inferior to amitriptyline in some relevant areas.

The Expert Committee therefore recommended the square box be removed from the current listing for amitriptyline for treatment of depression on the EML.

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Fluoxetine – deletion – EMLc

Fluoxetine	ATC code: N06AB03

Proposal

Deletion of fluoxetine from the complementary list of the EMLc for treatment of depressive disorders in children.

Applicant

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy

WHO technical department

Mental Health and Substance Use

EML/EMLc

EML

Section

24.2.1 Medicines used in depressive disorders

Dose form(s) & strengths(s)

Solid oral dosage form: 20 mg (as hydrochloride)

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Fluoxetine has been included on the EMLc since the first list was published in 2007 for the treatment of children aged > 8 years with depression (*1*). In 2013, the Expert Committee considered a request to revise the age restriction from > 8 years to > 12 years (i.e. effective deletion from the EMLc) made by the WHO Department of Mental Health and Substance Abuse. The Committee recognized that depression was rare in children, and that WHO's Mental Health Gap Action Programme (mhGAP) guideline made a strong recommendation to set the age limit at 12 years for the pharmacological treatment with antidepressants of children with a depressive episode/disorder in non-specialist settings. However, the Committee decided to retain the minimum age for fluoxetine at 8 years as

the evidence on alternative antidepressants in children was not reviewed. At the same time, the Committee highlighted the need for a thorough review of the section of medicines used in depressive disorders on the EMLc (*2*).

Public health relevance

For the purpose of the application, children are defined as individuals up to and including 12 years of age, in line with the population for which the EMLc is intended.

Depression in children has been increasingly treated with antidepressant medicines over the past several years (*3*). This trend occurred despite the onset of depressive disorder being rare in children of prepubertal age (*4*). Longitudinal studies of community samples of children and adolescents suggest an average age at onset between 11 and 14 years for major depressive disorder and depressive disorder (*5*). Evidence from prospective epidemiological studies reveals a large increase in the prevalence of major depressive episodes after age 11 years (*6*). Prospective data from the Oregon Adolescent Depression Project showed that the rates of new onset of depression increase from 1% to 2% at age 13 years and from 3% to 7% at age 15 years (*7*). The incidence of depression continues to increase throughout early adulthood (*8*).

Summary of evidence: benefits

The application presented the results of a comprehensive literature search for systematic reviews on the topic of antidepressant efficacy, acceptability and tolerability in children with depression. No systematic reviews were found on the efficacy of fluoxetine specifically focused on children aged 12 years or younger. Existing reviews included a mixed population of children and adolescents, largely composed of individuals between 13 and 18 years of age. Twenty-one systematic reviews were included, from which data from 22 randomized controlled trials were extracted and reanalysed using standard Cochrane methodology.

Fluoxetine

Six randomized controlled trials (795 participants) were identified on the use of fluoxetine for the treatment of children (mean age < 12 years) with depression (*9–14*). Only short-term efficacy (up to 10 weeks) was evaluated. No data were available on medium-term (13–26 weeks) or long-term (more than 26 weeks) follow-up. All trials were industry-sponsored.

Five studies (587 participants) compared fluoxetine with placebo and evaluated depressive symptomology at study endpoint using the Children's Depression Rating Scale-Revised (CDRS-R) (*9–13*). Pooled results did not show any significant difference between fluoxetine and placebo (mean difference (MD) –2.43, 95% confidence interval (CI) –5.37 to 0.50). Based on Grading of

Recommendations, Assessment, Development, and Evaluations (GRADE), the quality of evidence was judged to be very low. The only two positive studies were published in 1997 and 2002 (*9*,*10*). These two studies were the subject of a statistical review by the Center for Drug Evaluation and Research of the United States Food and Drug Administration (*15*). The review showed that the prespecified primary outcome measure in the first study (*9*) (proportion of completing patients who achieved recovery, defined as a score of ≤ 28 on the CDRS-R and a clinical global impression-improvement (CGI-I) score of 1 or 2) was changed in the published manuscript, probably because this measure did not reach statistical significance. For the second study (*10*) the authors identified a reduction from baseline of ≥ 30% on the CDRS-R as the single primary endpoint. However, as they found no difference between fluoxetine and placebo, the focus was on secondary endpoints (symptom reduction) that favoured fluoxetine. The Food and Drug Administration independent statistical review concluded that "The sponsor did not win on these two paediatric depression studies based on the protocol specified endpoint. The evidence for efficacy based on the pre-specified endpoint is not convincing" (*15*).

One study (23 participants) compared fluoxetine with placebo and evaluated response using depression rating scales (Birleson Depression Self-Rating Scale, CGI scale and Children's Global Assessment Scale) (*14*). No significant differences between treatment groups were found in any of the rating scales.

Other antidepressants

Eighteen trials were identified that compared other antidepressants with placebo, of which nine were suitable for quantitative synthesis. Only short-term efficacy (up to 12 weeks) was evaluated. No data were available on medium-term (13–26 weeks) or long-term (more than 26 weeks) follow-up.

- One randomized controlled trial (96 participants) suggested that paroxetine was less effective than placebo in ameliorating depressive symptomology (MD 2.49, 95% CI 1.45 to 3.03) (*16*).
- One randomized controlled trial (171 participants) suggested no difference in efficacy between sertraline and placebo (MD –0.17, 95% CI –0.47 to 0.13) (*17*).
- Two randomized controlled trials (255 participants) suggested no difference in efficacy between duloxetine and placebo (MD –0.16, 95% CI –0.43 to 0.11) (*11*,*12*).
- One randomized controlled trial (170 participants) suggested no difference in efficacy between venlafaxine and placebo (MD 0.10, 95% CI –0.23 to 0.44 (*18*). Another trial (40 participants), not be included in the analysis due to lack of detailed data, reported lack of efficacy of venlafaxine versus placebo (*19*).

587

- Two randomized controlled trials (194 participants) suggested no difference in efficacy between desvenlafaxine and placebo (MD –0.17, 95% CI –0.46 to 0.12) (*13,20*).
- One randomized controlled trial (38 participants) suggested no difference in efficacy between imipramine and placebo (MD 0.00, 95% CI –0.64 to 0.64) (*21*).
- One randomized controlled trial (50 participants) suggested no difference in efficacy between nortriptyline and placebo (MD 0.08, 95% CI –0.47 to 0.64) (*22*).

One randomized controlled trial (174 participants) suggested a greater reduction in depressive symptoms in participants taking citalopram compared with placebo at 8 weeks follow-up (*23*). One randomized controlled trial (104 participants) found no statistically significant improvement in any efficacy measure in the subgroup of patients aged 6–11 years for escitalopram compared with placebo (*24*). Two randomized controlled trials failed to show superiority of mirtazapine over placebo (*25*). One randomized controlled trial (nine participants) comparing amitriptyline with placebo showed no statistical differences in reduction of depressive symptoms between treatment groups at 4 weeks follow-up (*26*).

Summary of evidence: harms

The adverse effect profile of fluoxetine in the adult population is well established. However, it is not possible to ascertain whether the frequency of adverse events is the same in adults and children. In general, knowledge of unwanted effects associated with antidepressant treatments for depression in children is inadequate. Systematic reviews have only evaluated unwanted effects of treatments for depression in mixed populations of children and adolescents. Aside from effects on suicidality, the negative effects of selective serotonin reuptake inhibitors (SSRIs) are under-reported or not reported (*27*). The safety of fluoxetine for paediatric patients has not been systematically assessed for chronic treatment longer than several months. No studies have directly evaluated the longer-term effects of fluoxetine on growth, development and maturation of children and adolescents.

The safety of prescribing antidepressants to children has been the subject of increasing concern, particularly regarding the risk of suicidality, which has led to precautions and recommendations against their use in children and adolescents (*28*).

Meta-analyses of randomized controlled trials have produced inconsistent findings. For example, one meta-analysis found that the overall risk ratio for suicidal ideation and behaviour in paediatric patients with depression taking SSRIs was 1.66 (95% CI 1.02–2.68) (*29*), and another that severe adverse events

were significantly more common with SSRIs and serotonin and norepinephrine reuptake inhibitors than placebo (*30*). However, another recent meta-analysis of randomized controlled trials concluded that only venlafaxine was associated with an increased risk of suicidal behaviour or ideation in the young population (*31,32*).

A systematic review evaluated observational studies reporting completed or attempted suicide in depressed individuals who were exposed to SSRIs compared with those who were not exposed to antidepressant medicines, and measured the overall risk of completed or attempted suicide (*33*). The use of SSRIs was associated with a reduced risk of suicide in adults with depression, while in children and adolescents, the use of SSRIs was associated with an increased suicidality behaviours. The aforementioned association was the only so-called convincing evidence included in a recent umbrella review of meta-analyses of observational studies that evaluated the adverse outcomes of antidepressants (*34*). A recent and updated systematic review of observational studies confirmed that SSRI exposure might have an increased suicidal risk in children and young adults (*35*). Across 15 studies that examined the association between SSRIs and completed or attempted suicide, SSRI exposure significantly increased the risk of completed and attempted suicide compared with no or any other antidepressant use, with a pooled risk ratio for incidence of suicide or suicide attempt of 1.28 (95% CI 1.09–1.51).

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a strong recommendation that antidepressant medicines are not recommended for the treatment of children 12 years of age and below with depressive episode/disorder (low certainty evidence) (*36*).

Costs/cost–effectiveness

No cost–effectiveness data on the use of antidepressant medications in children are available. Available data in adults are not considered generalizable to children.

Availability

Fluoxetine is available globally, however specific data on availability was not considered relevant for its proposed deletion from the EMLc.

Committee recommendations

The Expert Committee noted that fluoxetine had been included on the EMLc for the treatment of children with depression aged 8 years and older since 2007, before the publication of the first WHO mhGAP guidelines in 2010. The mhGAP

guidelines were updated in 2023 and include a recommendation not to use antidepressants for the treatment of depression in children younger than 12 years.

The Committee acknowledged that depression has been reported to affect only a small proportion of children younger than 12 years – the population covered by the EMLc. Most studies report a prevalence lower than 1% in this age group and that prevalence substantially rises throughout adolescence and into adulthood.

The Committee acknowledged the comprehensive approach taken by the applicants to evaluate the available evidence on the efficacy, acceptability and tolerability of fluoxetine and other antidepressants for the treatment of children with depression. Notably, most systematic reviews identified did not focus specifically on children aged 12 years and younger, but instead included a mixed population of children and adolescents. From six randomized clinical trials that investigated the efficacy of fluoxetine versus placebo to treat depression in children younger than 12 years, there was very low-certainty evidence suggesting no statistically significant differences between fluoxetine and placebo. The point estimate favoured fluoxetine, however the difference was not considered to be clinically meaningful.

The Committee agreed that the evidence presented in the application for use of fluoxetine in children younger than 12 years was inconclusive and insufficient to support the ongoing inclusion of this medicine in the EMLc for the treatment of depression in children. However, some Committee members reported that fluoxetine was considered a relevant treatment option and is currently used in clinical practice in children aged between 8 and 12 years in some settings where access to mental health services and non-pharmacological management is limited.

Based on the evidence presented in the application, and in alignment with recommendations in the WHO mhGAP guidelines, the Expert Committee recommended the deletion of fluoxetine from the EMLc. This recommendation also applies to the listing of fluoxetine on the EMLc in Section 2.3 Medicines for other common symptoms in palliative care. Fluoxetine is still included on the EML for use in the treatment of depression in adolescents and adults.

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Phenelzine – addition – EML

Phenelzine	ATC code: N06AF03

Proposal

Addition of phenelzine to the complementary list of the EML for the treatment of adults with treatment-resistant depression.

Applicant

PsychoTropical Research Institute, Mackay, Queensland, Australia

International MAOI Expert Group

WHO technical department

The WHO department of Mental Health and Substance Use reviewed and provided comments on the application. The technical department highlighted the following points.

- Phenelzine requires careful monitoring and has a less favourable safety profile compared with other antidepressants, such as selective serotonin reuptake inhibitors and tricyclics (currently included on the EML) and newer agents.

- The evidence base for phenelzine is limited as randomized controlled trials on this antidepressant are lacking because it was introduced to the market many years ago when such trials were not commonly performed.

- In the context of treatment-resistant depression, phenelzine lacks evidence of efficacy.

- The risk of serious treatment emergent adverse events, drug–drug interactions and overdose, as well as the need for specialized facilities and health care professionals, raise concerns about its usability in low- and middle-income countries and other settings.

EML/EMLc

EML

Section

24.2.1 Medicines used in depressive disorders

Dose form(s) & strengths(s)

Solid oral dosage form: 15 mg (as sulfate)

Core/complementary

Complementary

Individual/square box listing

Individual

Background

Phenelzine is a non-selective and irreversible inhibitor of the enzyme monoamine oxidase. Monoamine oxidase plays a role in the inactivation of several neurotransmitters such as norepinephrine and serotonin. By inhibition of the enzyme, inactivation of these neurotransmitters is prevented, thereby increasing their availability.

Phenelzine has not previously been evaluated for addition to the EML.

Antidepressant medicines currently included on the EML include the tricyclic antidepressant amitriptyline, and fluoxetine as the representative selective-serotonin reuptake inhibitor, with citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives.

Public health relevance

According to the 2019 Global Burden of Disease study, depressive disorders affected approximately 280 million people worldwide, equivalent to almost 3.8% of the global population and resulted in almost 47 million disability-adjusted life years (DALYs), equivalent to 1.8% of global DALYs (*1*).

In low- and middle-income countries, two out of three individuals suffering from depression do not receive adequate treatment (*2,3*). Alongside psychosocial interventions, medicines, particularly antidepressants, play an important role in treatment according to international guidelines, including the WHO Mental Health Gap Action Programme (mhGAP) guidelines (*4*). First-line treatments for depression include both psychological and pharmacological interventions, with antidepressant medicines recommended as the primary treatment option for moderate to severe cases of depression.

Estimates suggest that about 30–50% of patients with major depressive disorder do not respond to initial treatment with antidepressants and around 60–70% of patients achieve an incomplete response (*5*). Estimates for the prevalence of treatment-resistant depression, defined as depressive episodes that fail to respond to or achieve remission with at least two pharmacological treatments (*6*), vary considerably, from up to 15% (*7*) to around 30% of treated patients (*8,9*).

Treatment-resistant depression imposes an important personal, societal and economic burden. The effect of depression on well-being has been described

as comparable to or worse than that of chronic medical illnesses, such as diabetes and congestive heart failure (*10*). Patients with treatment-resistant depression experience substantial and lasting impairments in various aspects of functioning and well-being (*10*). Their quality of life is greatly diminished, leading to reduced work productivity and activity levels (*11*). Treatment-resistant depression is also associated with a higher risk of psychiatric and somatic comorbidities, including anxiety disorders, hypertensive diseases and central nervous system disorders (*12*). The condition also increases the risk of suicide and results in greater use of health care resources than treatment-responsive depression (*13*).

Treatment options for treatment-resistant depression include: augmentation or adjunctive therapy with non-antidepressant medications such as lithium, thyroid hormone or second-generation antipsychotics; switching to other antidepressant medicine classes; psychotherapy; electroconvulsive therapy or other forms of brain stimulation; novel therapeutics such as ketamine and esketamine; and compounds targeting the delta opioid receptor. Each approach has advantages and disadvantages, but currently no consensus has been reached on the best treatment pathway for treatment-resistant depression.

Summary of evidence: benefits

A 2021 systematic review and network meta-analysis evaluated the effectiveness and acceptability of monoamine oxidase inhibitors in the treatment of depressive disorders (*14*). This study was not specific for treatment-resistant depression. The analysis included 52 double-blind, randomized controlled trials (6462 participants) conducted between 1976 and 2012 comparing 14 different antidepressants or placebo. It included nine randomized controlled trials of phenelzine versus placebo or another active comparator. The primary outcomes were efficacy (defined as response rate measured by the proportion of participants demonstrating ≥ 50% reduction on a standardized depression rating scale) and acceptability (all-cause discontinuation rate). The results indicated that, except for fluvoxamine, all antidepressants were more effective than placebo. No significant differences were found in drop-out rates between the antidepressants and placebo. Of all antidepressants evaluated, phenelzine was associated with the highest odds ratio (OR) point estimate for efficacy relative to placebo (OR 4.66, 95% credible interval (CrI) 2.64 to 8.40). Phenelzine also had the highest surface under the cumulative ranking curve (SUCRA) score (84.3%). In head to head treatment comparisons, phenelzine demonstrated superior evidence for efficacy compared with all other antidepressants investigated. Clomipramine demonstrated superior evidence for acceptability relative to placebo of all treatments investigated (OR 0.66, 95% CrI 0.34 to 1.29; SUCRA 74.4%). For acceptability relative to placebo for phenelzine the OR was 1.00 (95% CrI 0.53 to 1.88; SUCRA 35.4%). The study acknowledged a number of factors limiting the precision of the estimates

including the small number of studies that evaluated monoamine oxidase inhibitors, particularly in recent years, and changing standards in diagnosis and reporting over time resulting in heterogeneity in the included studies. Because of the older age of studies investigating monoamine oxidase inhibitors, the authors allowed inclusion of trials with a variety of diagnoses (major depressive disorder, treatment-resistant depression, dysthymic disorder, atypical depression, bipolar depression and depressive disorder not otherwise specified).

A 2006 meta-analysis investigated the treatment of major depression with atypical features, comparing monoamine oxidase inhibitors with other antidepressants or placebo (*15*). The analysis included eight double-blind, randomized controlled trials (670 participants). For each study, effect sizes were determined by calculating the phi coefficient, representing the response-rate difference. Four randomized controlled trials provided data for the comparison of phenelzine and placebo and three randomized controlled trials provided data for the comparison of phenelzine and imipramine. Six of these seven trials showed phenelzine to be superior in terms of the proportion of responders and effect sizes (average effect size versus placebo 0.45, 95% confidence interval (CI) 0.35 to 0.60 and average effect size versus imipramine 0.27, 95% CI 0.16 to 0.42). Three randomized controlled trials provided data for comparison of phenelzine or moclobemide and fluoxetine or sertraline. Phenelzine or moclobemide were not superior to the comparators for response rate or effect size (average effect size 0.02, 95% CI −0.10 to 0.14).

A 1995 meta-analysis evaluated controlled trials comparing monoamine oxidase inhibitors approved by the United States Food And Drug Administration for treatment of depression (phenelzine, isocarboxazid and tranylcypromine) with placebo and tricyclic antidepressants in inpatient and outpatient settings (*16*). For outpatients, isocarboxazid and tranylcypromine had generally comparable overall efficacy. The drug–placebo differences in the percentage of responders were 29.5% (standard deviation (SD) 11.1%; nine studies) for phenelzine, 41.3% (SD 18.0%; three studies) for isocarboxazid and 22.1% (SD 25.4%; three studies) for tranylcypromine. Phenelzine and tranylcypromine were found to be more effective than comparator tricyclics in outpatients with differences in percentage of responders of 8.8% (SD 8.3%; 11 studies) and 16.8% (SD 27.5%; four studies), respectively. For inpatients, the drug–placebo differences in the percentage of responders were 22.3% (SD 30.7%; five studies) for phenelzine and 15.3% (SD 12.6%; four studies) for isocarboxazid. No data were available for tranylcypromine. Both phenelzine and isocarboxazid were less effective than comparator tricyclics in inpatients with differences in percentage of responders of −21.0% (SD 7.7%) and −14.1% (SD 27.5%; two studies), respectively.

A 2019 non-randomized retrospective study evaluated the relative effectiveness of tricyclic antidepressant versus monoamine oxidase inhibitor as monotherapy for treatment resistant depression (*17*). Data from about 2500

treatment charts of patients with treatment-resistant depression attending a university mood disorder clinic between 1983 and 2015 were retrospectively analysed. The study included 147 treatment outcome observations from 94 unipolar, depressed patients who received either tricyclic antidepressant ($n = 47$) or monoamine oxidase inhibitor ($n = 100$) monotherapy. Monoamine oxidase therapy was generally more effective than tricyclic antidepressant therapy for patients with treatment-resistant depression. For patients who had failed to respond in at least one prior adequate antidepressant trial, those who received tricyclic therapy showed higher (i.e. worse) end-of-treatment clinical global impressions/severity scores relative to those who received monoamine oxidase therapy.

A 2012 prospective study evaluated the longer-term outcome of treatment-resistant depression, including clinical and psychosocial factors that may be associated with outcome, in 150 patients with treatment-resistant depression at a tertiary inpatient service in the United Kingdom (*18*). The use of monoamine oxidase inhibitors (moclobemide, phenelzine, tranylcypromine and isocarboxazid) among inpatients was associated with remission at time of discharge (OR 6.49, 95% CI 1.63 to 25.91) and remission at the time of final follow-up (OR 4.78, 95% CI 1.15 to 19.85). Among the limitations highlighted by the study authors were that the sample size was small, follow-up duration variable, outcomes for 13% of participants were unaccounted for, and the cohort was taken from a specialist inpatient service and likely to represent patients with more severe illness, and therefore the results may not be generalizable to treatment-resistant depression in other settings.

Summary of evidence: harms

The potential adverse effects of monoamine oxidase inhibitors are more diverse and potentially more serious than most other antidepressants. As monoamine oxidase is found throughout the body, its inhibition can lead to various pharmacological effects. While many adverse effects of monoamine oxidase inhibitors are mild to moderate and tend to subside with continued therapy, some reactions can be severe and may necessitate discontinuation of treatment, particularly events involving the cardiovascular, central nervous and hepatic systems. Serious adverse effects, such as hypertensive crisis and serotonin syndrome, have been reported with monoamine oxidase inhibitors, especially when they are taken concomitantly with tyramine-containing foods or certain medicines. These interactions can lead to potentially life-threatening reactions; hence, careful monitoring is required, with close attention paid to potential drug–drug and drug–food interactions.

Potential adverse effects of phenelzine include blurred vision, constipation, dry mouth, headache, hypoglycaemia, insomnia, liver enzyme elevation and (rarely) hepatotoxicity, myoclonus, nausea, orthostatic hypotension, paresthesia,

pyridoxine-deficiency, oedema, sedation, sexual dysfunction, urinary retention and weight gain (*19,20*).

Phenelzine can cause dose-dependent orthostatic hypotension, especially at the start of treatment and after dose increases. Significant orthostatic hypotension (a drop of ≥ 10–15 mmHg in systolic blood pressure) is a common effect of treatment with monoamine oxidase inhibitors and typically peaks 10–14 days after a dose increase (*19*). General measures to reduce the chance of orthostatic hypotension include increasing doses slowly and dividing daily doses (*21*).

An important safety concern with the use of phenelzine are drug–drug interactions that can result in serotonin syndrome and hypertensive crisis (*20*). Concomitant use of phenelzine with other medicines or supplements that have serotonergic activity is contraindicated (*19*).

Phenelzine is also associated with multiple drug–food interactions of concern, in particular, interactions with tyramine, a vasoactive amine found in various foods and beverages including aged cheese, cured meats, soy products, yeast products, fermented foods and tyramine-containing nutritional supplements (*20,22*). Reduced breakdown of tyramine as a result of monoamine oxidase inhibition may result in hypertensive crisis. Patients receiving phenelzine must follow a tyramine-restricted diet (*23*).

WHO guidelines

Phenelzine is not currently recommended in WHO Mental Health Gap Action Programme (mhGAP) guidelines for treatment of treatment-resistant depression (*4*).

Costs/cost–effectiveness

Comparative cost–effectiveness analyses for monoamine oxidase inhibitors and newer antidepressants for treatment-resistant depression are lacking.

The application described the results of a modelled economic analysis of psychological and pharmacological interventions for social anxiety disorder. In this analysis, phenelzine was determined to be the third most cost-effective intervention, after individually delivered cognitive behavioural therapy (using the Clark and Wells model) and general individually delivered cognitive behavioural therapy (*24*). Notably, the analysis did not take into account the side-effects of pharmacological treatments.

The absolute cost of antidepressant medicines in the United Kingdom was compared in 2018 using basic prices within the National Health System The reported cost for 1 year of treatment with phenelzine 60 mg/day was £327.60. In comparison, the reported costs for 1 year of treatment with the antidepressants on the EML were £28.86 for amitriptyline 75 mg/day and £7.04 for fluoxetine 20 mg/day (*25*).

The application reported current and recent internal prices for phenelzine as €45 (60 capsules) in Belgium, Can$ 144.95 (180 tablets) in Canada, £120 (100 tablets) in the United Kingdom and US$ 108.88 (60 tablets) in the United States. No price information was presented from low- and middle-income countries.

Availability

The application reported that phenelzine is available in Australia, Belgium, Canada, the United Kingdom and the United States.

Shortages of phenelzine have been reported in many of these jurisdictions.

Committee recommendations

The Expert Committee noted that depressive disorders were highly prevalent and were responsible for a large and increasing global public health burden. The Committee acknowledged that a subgroup of patients with depression did not respond adequately or at all to initial lines of treatment.

The Committee noted that the systematic reviews and meta-analyses presented in the application which evaluated the comparative efficacy of phenelzine versus placebo or other antidepressants provided some evidence for the efficacy of phenelzine but did not specifically address the indication of treatment-resistant depression. The Committee considered that there was therefore uncertainty in the applicability of the results to the specific population of patients with treatment-resistant depression. The Committee noted that comparative evidence was lacking for phenelzine versus other treatment approaches for treatment-resistant depression.

The Committee noted that phenelzine was associated with potentially serious adverse effects and had a high potential for drug–drug and drug–food interactions. Treatment with phenelzine therefore would require careful and specialized monitoring and management, which may not be available in many low- and middle-income settings. The Committee expressed concern about the feasibility of safe use of phenelzine in settings where specialist monitoring of patients was not available.

The Committee noted that phenelzine had limited global availability and was currently more highly priced than other antidepressants in common clinical use.

Additionally, the Committee noted that phenelzine was not included in current WHO mhGAP guidelines for treatment of depression.

The Expert Committee did not therefore recommend the inclusion of phenelzine on the complementary list of the EML for use in treatment-resistant depression because of uncertain evidence of benefit in the proposed patient population and increased risk of harms.

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24.2.2 Medicines used in bipolar disorders

Quetiapine – addition – EML

Quetiapine	ATC code: N05AH04

Proposal

Addition of quetiapine to the core list of the EML for the treatment of adults with bipolar disorders. Listing is requested with a square box specifying aripiprazole, olanzapine and paliperidone as therapeutic alternatives.

Applicant

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy

WHO technical department

Mental Health and Substance Use

EML/EMLc

EML

Section

24.2.2 Medicines used in bipolar disorders

Dose form(s) & strengths(s)

Tablet (immediate-release): 25 mg, 100 mg, 150 mg, 200 mg, 300 mg

Tablet (modified-release): 50 mg, 150 mg, 200 mg, 300 mg, 400 mg

Core/complementary

Core

Individual/square box listing

Square box, with aripiprazole, olanzapine and paliperidone as the specified therapeutic alternatives.

Background

Neither quetiapine nor the proposed therapeutic alternatives has previously been evaluated for inclusion on the EML for the treatment of bipolar disorders.

Medicines for the treatment of bipolar disorders currently included on the EML are lithium carbonate (since 1977), carbamazepine (since 1997) and valproic acid (since 1997).

Public health relevance

Bipolar disorders affect about 40 million people globally, accounting for about 4% of all mental disorders in 2019. These disorders affect about 1 in 150 adults worldwide and their prevalence is relatively consistent across different regions and in males and females (*1,2*). Bipolar disorder type I has a lifetime prevalence of around 1.0%, while bipolar disorder type II has a lifetime prevalence of about 1.6% (*3*). The disease burden of bipolar disorders has been increasing over the years, with about 9.29 million disability-adjusted life years (DALYs) reported globally in 2017, a 54.4% increase from 1990 (*4*).

People with bipolar disorders have a lower life expectancy than the general population. A recent meta-analysis of 11 observational studies, including 96 601 individuals, found that the pooled life expectancy of those with bipolar disorders was 67 years (95% confidence interval (CI) 64 to 69 years). Women with bipolar disorders tended to have a slightly higher life expectancy than men. The weighted average of years of potential life lost (YPLLs) was 12.9 years (95% CI 12.7 to 13.1 years), with the highest YPLLs reported in Africa (*5*). Suicide is the most common cause of unnatural deaths in people with bipolar disorders; they have a 20- to 30-fold greater risk compared with the general population (*6*). However, excess mortality from natural causes can also be attributed to various factors, such as unhealthy lifestyle choices (including sedentary habits, smoking and substance use), metabolic side-effects of antipsychotic medications and inequitable medical care. Moreover, bipolar disorders are associated with a high prevalence of comorbid mental health conditions that develop over their course. These comorbidities add to the overall burden and challenges faced by individuals with bipolar disorders (*7*).

Bipolar disorders are associated with significant costs for individuals, health care systems and society due to factors such as reduced work productivity and unemployment. A meta-analysis of 56 United States studies estimated an annual national economic burden of more than US$ 195 billion, with 25% attributed to direct medical costs (*8*).

Prompt pharmacological treatment is crucial for managing acute manic/hypomanic and depressive episodes in bipolar disorders, along with continuous maintenance treatment from the early stages of the disease. This approach helps prevent chronic functional deterioration, reduce subthreshold symptoms and lower the risk of suicide (*9,10*). However, treatment non-adherence is an important challenge, affecting up to 40% of individuals with bipolar disorders (*11*).

In recent years, scientific evidence has increased substantially on the comparative efficacy and tolerability of pharmacological treatments for bipolar disorders, which include lithium, antiseizure medicines and antipsychotics. Not all treatments are equally effective or well tolerated, and the choice of treatment should be personalized through a shared-decision making process based on

individual needs. It is important to note that treatment effectiveness may vary across different phases of the disease, such as acute manic/hypomanic/depressive episodes or long-term prevention of recurrences. Additionally, the certainty of evidence supporting various treatments may differ (*12–16*).

As well as pharmacological interventions, psychosocial approaches such as psychoeducation, cognitive behavioural therapy and family therapy have been effective in treating bipolar disorders. A comprehensive approach that combines pharmacological and psychosocial interventions is essential for effectively managing the condition (*17*).

In low- and middle-income countries, treatment coverage for mental disorders, including bipolar disorders, is inadequate. Up to 50% of individuals with bipolar disorders do not receive sufficient treatment (*18*). Additionally, only a few countries can be considered fully aligned with the principle of providing complete access to essential psychotropic medications such as antipsychotics and mood stabilizers. Low availability and high costs of these medicines are significant barriers to access in these regions (*19*).

Summary of evidence: benefits

A 2022 systematic review and network meta-analysis of 56 randomized controlled trials (14 503 participants) evaluated pharmacological treatments (oral antipsychotics and mood stabilizers) as monotherapy for acute treatment of bipolar mania (*16*). Overall, all the included antipsychotics (risperidone, haloperidol, olanzapine, cariprazine, quetiapine, aripiprazole, paliperidone, ziprasidone and asenapine) showed better response to treatment compared to placebo: risk ratio (RR) 1.69 (95% CI 1.41 to 2.02) for risperidone, RR 1.55 (95% CI 1.32 to 1.83) for quetiapine and RR 1.28 (95% CI 1.05 to 1.56) for asenapine. In head-to-head comparisons, few differences were seen between treatments. Olanzapine outperformed haloperidol (RR 1.37, 95% CI 1.11 to 1.69), cariprazine (RR 1.56, 95% CI 1.13 to 2.13), brexpiprazole (RR 1.73, 95% CI 1.14 to 2.63), asenapine (RR 1.54, 95% CI 1.18 to 2.01) and aripiprazole (RR 1.30, 95% CI 1.05 to 1.61). When comparing oral second-generation antipsychotics with mood stabilizers included in the EML, there were relatively few and small differences. Carbamazepine showed no statistically significant differences when compared to any second-generation antipsychotic. However, olanzapine (RR 1.59, 95% CI 1.28 to 1.98) and quetiapine (RR 1.36, 95% CI 1.02 to 1.81) outperformed lithium, and olanzapine outperformed valproic acid (RR 0.76, 95% CI 0.63 to 0.93). The certainty of evidence was generally low or very low for most comparisons, except for quetiapine, for which the certainty of evidence against placebo was moderate.

A 2021 network meta-analysis of 18 randomized controlled trials (7969 participants) evaluated the efficacy and tolerability of atypical antipsychotics in the treatment of acute bipolar depression (*14*). As measured by the mean change in Montgomery Åsberg Depression Rating Scale (MADRS) score from baseline

to the end of the study, cariprazine, olanzapine, quetiapine, and lurasidone were more effective than placebo, with mean differences (MD) ranging from −4.80 (95% CI −5.93 to −3.72) for quetiapine to −2.29 (95% CI −3.47 to −1.09) for cariprazine. Aripiprazole and ziprasidone did not show significant differences compared with placebo. In head-to-head comparisons, olanzapine outperformed aripiprazole (MD −3.49, 95% CI −6.07 to −0.92), cariprazine (MD −2.29, 95% CI −4.09 to −0.46) and ziprasidone (MD −3.23, 95% CI −5.66 to −0.83). Quetiapine outperformed aripiprazole (MD −4.80, 95% CI −5.93 to −3.72), cariprazine (MD −2.52, 95% CI −4.11 to −0.92) and ziprasidone (MD −3.46, 95% CI −5.76 to −1.24). Lurasidone outperformed aripiprazole (MD −3.63, 95% CI −6.78 to −0.50) and ziprasidone (MD −3.36, 95% CI −6.38 to −0.39). The certainty of evidence based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach for network meta-analyses was high for cariprazine, lurasidone, olanzapine and quetiapine compared with placebo. It was moderate for: aripiprazole and ziprasidone compared with lurasidone; and cariprazine and aripiprazole compared with quetiapine and olanzapine. It was low for: aripiprazole and ziprasidone compared with placebo; cariprazine, olanzapine, and quetiapine compared with lurasidone; ziprasidone, and olanzapine compared with quetiapine; and cariprazine compared with aripiprazole. It was very low for all other comparisons.

A 2021 systematic review and network meta-analysis of 41 randomized controlled trials (9821 participants) evaluated antipsychotics and mood stabilizers, alone or in combination, for long-term prevention of any mood episode in clinically stable adults with bipolar disorders (*15*). Most oral antipsychotics (aripiprazole, asenapine, olanzapine, quetiapine and paliperidone) and the combination aripiprazole + lamotrigine were more effective than placebo in decreasing recurrence/relapse rate of manic/hypomanic/mixed episodes: with RRs ranging from 0.21 (95% CI 0.08 to 0.53) for asenapine to 0.55 (95% CI 0.43 to 0.71) for quetiapine. In head-to-head comparisons of oral antipsychotic monotherapies, asenapine outperformed paliperidone (RR 0.35, 95% CI 0.13 to 0.96) and quetiapine (RR 0.37, 95% CI 0.14 to 0.98), and olanzapine outperformed paliperidone (RR 0.59, 95% CI 0.37 to 0.94) and quetiapine (RR 0.62, 95% CI 0.44 to 0.89). Compared with mood stabilizers currently included in the EML: lithium was outperformed by olanzapine (RR 1.56, 95% CI 1.17 to 2.06) and asenapine (RR 0.39, 95% CI 0.15 to 0.99); carbamazepine was outperformed by asenapine (RR 0.10, 95% CI 0.01 to 0.99); and valproic acid was outperformed by olanzapine (RR 0.54, 95% CI 0.38 to 0.78) and asenapine (RR 0.33, 95% CI 0.12 to 0.86). Considering only monotherapies, the certainty of evidence was: moderate for aripiprazole, asenapine, olanzapine and paliperidone versus placebo; low for olanzapine versus placebo, and aripiprazole versus asenapine, carbamazepine, olanzapine, paliperidone, quetiapine and valproic acid; and very low for the remaining comparisons.

For the recurrence/relapse rate of depressive episodes in individuals with bipolar disorders, meta-analysis of 25 randomized controlled trials (6438 participants) was performed (*15*). The results showed that aripiprazole + valproic acid, quetiapine and olanzapine were more effective than placebo, with RRs ranging from 0.27 (95% CI 0.08 to 0.99) for aripiprazole + valproic acid to 0.74 (95% CI 0.56 to 0.98) for olanzapine. Estimates for asenapine, aripiprazole, paliperidone and cariprazine were not significant. In head-to-head comparisons of oral antipsychotic monotherapies, asenapine outperformed paliperidone (RR 0.29, 95% CI 0.09 to 0.91) and quetiapine outperformed olanzapine (RR 1.55, 95% CI 1.05 to 2.28) and paliperidone (RR 2.73, 95% CI 1.55 to 4.8). Compared with mood stabilizers already included in the EML, carbamazepine was outperformed by asenapine (RR 0.14, 95% CI 0.02 to 0.84) and quetiapine (RR 5.69, 95% CI 1.29 to 25.01), valproic acid was outperformed by quetiapine (RR 0.57, 95% CI 0.37 to 0.87), and lithium was outperformed by quetiapine (RR 1.65, 95% CI 1.21 to 2.25). The remaining head-to-head comparisons were not significant. The certainty of evidence for antipsychotic monotherapies compared with placebo and mood stabilizers was generally low, except for the comparison of paliperidone with quetiapine, which had moderate certainty according to the confidence in network meta-analysis (CINeMA) approach (*15*).

Summary of evidence: harms

In the 2022 network meta-analysis on the acute treatment of adults with bipolar mania (*16*), all-cause discontinuation (acceptability) was used as a pragmatic measure of the balance between desirable and undesirable effects of medications. The acceptability analysis included 70 randomized controlled trials with 16 324 participants. Olanzapine, quetiapine, risperidone and aripiprazole were significantly more acceptable than placebo. Paliperidone, ziprasidone, haloperidol, asenapine, cariprazine, brexpiprazole and chlorpromazine did not show significant differences from placebo in terms of acceptability. Head-to-head comparisons between second-generation antipsychotics showed that olanzapine was more acceptable than aripiprazole (RR 1.30, 95% CI 1.05 to 1.61), asenapine (RR 1.54, 95% CI 1.18 to 2.01), brexpiprazole (RR 1.73, 95% CI 1.14 to 2.63), cariprazine (RR 1.56, 95% CI 1.13 to 2.13), haloperidol (RR 1.37, 95% CI 1.11 to 1.69) and ziprasidone (RR 0.75, 95% 0.56 to 0.99). When comparing second-generation antipsychotics to mood stabilizers already included on the EML, both olanzapine (RR 1.59, 95% CI 1.28 to 1.98) and quetiapine (RR 1.36, 95% CI 1.02 to 1.81) outperformed lithium, and olanzapine outperformed valproic acid (RR 0.76, 95% CI 0.63 to 0.93). No significant differences were seen between second-generation antipsychotics and carbamazepine. The certainty of evidence based on the CINeMA approach was generally low or very low for most of the comparisons, indicating limited confidence in the results (*16*).

In the 2021 network meta-analysis on the acute treatment of adults with bipolar depression (*14*), the analysis for all-cause discontinuation included 18 randomized controlled trials with 7969 participants. Aripiprazole had a significantly higher risk of all-cause discontinuation compared with placebo (odds ratio (OR) 1.68, 95% CI 1.09 to 2.48). For cariprazine, lurasidone, olanzapine, ziprasidone and quetiapine, no significant differences in all-cause discontinuation rates were observed. In head-to-head comparisons, aripiprazole was more effective than olanzapine (OR 0.44, 95% CI 0.24 to 0.73) and quetiapine (OR 0.62, 95% CI 0.37 to 0.96), while ziprasidone outperformed olanzapine (OR 2.03, 95% CI 1.15 to 3.30). The certainty of evidence based on the CINeMA approach was rated as very low for ziprasidone, moderate for aripiprazole, cariprazine, olanzapine and quetiapine, and high for lurasidone (*14*).

In the 2021 network meta-analysis on long-term prevention of any mood episode in clinical stable adults with bipolar disorder (*15*), the analysis for all-cause discontinuation included 29 randomized controlled trials with 6899 participants. Most antipsychotics did not show significant differences in all-cause discontinuation rates compared with placebo. However, quetiapine, (RR 0.66, 95% CI 0.52 to 0.83), asenapine (RR 0.45, 95% CI 0.27 to 0.75) and olanzapine (RR 0.68, 95% CI 0.56 to 0.84) had lower discontinuation rates than placebo. In head-to-head comparisons, asenapine outperformed aripiprazole (RR 2.15, 95% CI 1.17 to 3.95) and paliperidone (RR 0.50, 95% CI 0.27 to 0.93). No other statistically significant differences were observed between antipsychotics. When mood stabilizers already included in the EML were considered, carbamazepine was outperformed by asenapine (RR 0.46, 95% CI 0.25 to 0.84) and quetiapine (RR 1.49, 95% CI 1.02 to 2.19). Asenapine outperformed valproic acid (RR 0.56, 95% CI 0.32 to 0.99) and lithium (RR 0.54, 95% CI 0.32 to 0.91). When considering monotherapies only, the certainty of evidence, based on the CINeMA approach, was very low for quetiapine versus placebo, carbamazepine and lithium, moderate for asenapine versus placebo, aripiprazole and carbamazepine, and low for all the remaining comparisons (*15*).

A 2018 systematic review and meta-analysis of 352 randomized controlled trials (84 988 participants) compared mortality risk between second-generation antipsychotics and placebo for various diagnoses. No significant differences were seen between antipsychotic medicines and placebo for death from any cause (OR 1.19, 95% CI 0.93 to 1.53), death from natural causes (OR 1.29, 95% CI 0.85 to 1.94), suicide (OR 1.15, 95% CI 0.47 to 2.81) or other non-natural causes (OR 1.55, 95% CI 0.66 to 3.63). Furthermore, significant differences in mortality risk between antipsychotics and placebo were not observed in the subgroup analysis that specifically focused on people with bipolar disorders (OR 1.09, 95% CI 0.53 to 2.25) (*20*).

A 2019 systematic review and meta-analysis of 314 randomized controlled trials (67 642 participants) compared the risk of somatic serious adverse events

between second-generation antipsychotics and placebo for various diagnoses. In the subgroup analyses for each antipsychotic, haloperidol (OR 1.61, 95% CI 1.07 to 2.43), olanzapine (OR 1.35, 95% CI 1.04 to 1.74) and risperidone (OR 1.33, 95% CI 1.04 to 1.70) showed a significantly higher risk of serious adverse events compared with placebo. No significant differences in the risk of serious adverse events compared with placebo were observed for the other antipsychotic medications studied (*21*).

The most common side-effects of quetiapine include drowsiness, dizziness, weight gain and dry mouth. As with other second-generation antipsychotics, quetiapine can also cause metabolic changes, such as increased cholesterol and blood sugar levels in some people. More serious adverse effects such as tardive dyskinesia and neuroleptic malignant syndrome are rare. Quetiapine should be used with caution during pregnancy and breastfeeding, as the medication may pose risks to the developing fetus or infant.

WHO guidelines

The proposed inclusion of quetiapine and the specified therapeutic alternatives on the EML for treatment of bipolar disorder is aligned with recommendations in the 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use (*22*).

Costs/cost–effectiveness

A pharmacoeconomic study in the Kingdom of the Netherlands compared the cost–effectiveness of mood stabilizers alone (lithium or valproic acid) with combination therapy of lithium plus a second-generation antipsychotic (quetiapine, olanzapine or risperidone) for the treatment of acute mania (*23*). The study assessed direct treatment costs, including hospitalizations, outpatient visits and medications for adverse effects, over a 100-day period. Monotherapies with lithium or valproic acid were more expensive than combination therapies. Among the combination therapies, lithium plus quetiapine was significantly more expensive (€2555) compared with lithium plus risperidone (€2365) or olanzapine (€2429) due to higher acquisition costs. However, the lithium plus quetiapine combination was associated with fewer side-effects. Additionally, other pharmacoeconomic analyses provided evidence supporting the cost–effectiveness of the quetiapine plus lithium combination therapy over lithium alone for the maintenance treatment of bipolar disorders (*24–26*).

Two retrospective studies analysed the direct costs and health care outcomes associated with different atypical antipsychotics for the treatment of bipolar disorders. The first study, using data from a Medicaid programme, compared the direct health care costs of quetiapine, olanzapine and risperidone monotherapies in the year after the start of treatment. No significant difference

in total health care costs was seen between the three antipsychotics (quetiapine US$ 14 417, olanzapine US$ 13 804 and risperidone US$ 16 214) or in costs related to bipolar disorder (quetiapine US$ 4372, olanzapine US$ 4596 and risperidone US$ 4435) (*27*). The second study used datasets of insurance claims to compare time to hospitalization and health care costs (pharmacy costs, mental health costs and overall health care costs) of different atypical antipsychotics over a year. Aripiprazole had a significantly lower time to hospitalization compared with ziprasidone, olanzapine and quetiapine (hazard ratio (HR) 1.96, 1.55 and 1.56, respectively; *P* < 0.05), but no significant difference was found between aripiprazole and risperidone (HR 1.37, *P* = 0.10). Monthly mental health care costs were significantly lower for aripiprazole compared with ziprasidone (US$ 487 versus US$ 631) and quetiapine (US$ 430 versus US$ 519), but not significantly different when compared with olanzapine (US$ 447 versus US$ 484) or risperidone (US$ 449 versus US$ 442). Total monthly health care costs were significantly lower for aripiprazole compared with quetiapine (US$ 875 versus US$ $1060), with no significant differences with the other comparators (*28*).

A Canadian cost–utility analysis compared the economic impact of asenapine versus olanzapine in treating bipolar disorder over a 5-year horizon. The study focused on weight gain and long-term metabolic complications, including diabetes, hypertension, coronary heart diseases and stroke. The use of asenapine was cost-effective, resulting in a gain of 84.8 quality-adjusted life years (QALYs) per 1000 patients and lower costs from both the Ministry of Health and societal perspectives by about Can$ 3.8 million less in each case (*29*). In a Swedish study, the cost–effectiveness of aripiprazole versus olanzapine was investigated over a lifetime horizon using a Markov health-state transition model. Assuming equivalent efficacy, the study used the annual incidence rate of metabolic syndrome to estimate the long-term cardiovascular consequences. The lower incidence of type II diabetes and coronary artery disease in patients treated with aripiprazole led to a gain of 0.09 QALYs and cost savings of US$ 3720 compared with olanzapine (*30*).

Availability

A recent analysis of 112 national essential medicine lists found that second-generation antipsychotics are not commonly included in these lists. First-generation antipsychotics such as haloperidol and chlorpromazine are more frequently listed. Inclusion of second-generation antipsychotics appears to be associated with the socioeconomic status of the country; these antipsychotics are more often included in the essential medicine lists of high-income countries but are only found in a minority of lower middle-income countries (*19*).

Quetiapine and the proposed therapeutic alternatives are variably available worldwide, in innovator and generic brands.

Other considerations

The applicants identified the second-generation antipsychotics proposed for EML listing by applying the following criteria:

- being superior to placebo in terms of efficacy for both acute treatment and long-term prevention of mania/hypomania and/or depression;

- having moderate-to-high certainty of evidence according to GRADE/CINeMA assessment for efficacy for at least one of the subpopulations considered, that is, acute mania, acute depression and clinically stable bipolar disorders;

- being superior/non-inferior to placebo in terms acceptability (all-cause discontinuation) for most of the subpopulations considered, that is, at least two among acute mania, acute depression and clinically stable bipolar disorders.

Committee recommendations

The Expert Committee noted the increasing prevalence of bipolar disorders worldwide, the significant disability associated with it, and recognized the importance of its treatment to reduce the associated morbidity and mortality. The Committee noted that the EML currently includes only carbamazepine, lithium carbonate and valproic acid for use in bipolar disorders. The Committee agreed that second-generation antipsychotics have an important role in treatment of bipolar disorders in patients who do not adequately respond to or experience adverse events from mood stabilizers. Moreover, the Committee noted that the two classes of medicines may be used in combination in selected patients in clinical practice.

The Committee noted that the detailed analysis of oral antipsychotics included in the application was aligned with the work carried out for the update of the WHO mhGAP guidelines for psychosis. The Committee also noted that the proposed inclusion of quetiapine and the specified therapeutic alternatives on the EML for treatment of bipolar disorders was aligned with recommendations in the forthcoming update of the guidelines.

According to the most recent and high-quality meta-analytical evidence on the acute and maintenance treatment of bipolar disorders, second-generation antipsychotics have been found to be either superior or non-inferior to placebo, and at least as effective as the classic mood stabilizers currently included on the EML for both treatment of acute affective episodes (mania, hypomania and depression) and maintenance treatment in clinically stable patients. Among the medicines proposed for inclusion, head-to-head comparisons generally

showed no significant differences in efficacy or acceptability between them, with moderate-to-high certainty of evidence.

The Committee noted that second-generation antipsychotics can help to manage the symptoms of bipolar disorder and improve the overall quality of life of patients by reducing the frequency and severity of manic and depressive episodes and preventing hospitalizations. They therefore reduce the burden of the disease for both individuals and healthcare systems.

The Committee noted that quetiapine, and the proposed therapeutic alternative antipsychotics, were available as generics in most countries, at varying prices and affordability.

The Expert Committee accepted the criteria applied by the applicants in identifying the second-generation antipsychotics proposed and recommended the inclusion of quetiapine, with a square box indicating aripiprazole, olanzapine and paliperidone as specified therapeutic alternatives, on the core list of the EML for treatment of bipolar disorders.

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24.3 Medicines for anxiety disorders
Diazepam – change to listing – EML

| Diazepam | ATC code: N05BA01 |

Proposal

Revision of the indications and therapeutic alternatives for diazepam in the core list of the EML for treatment of adults with anxiety disorders. The application proposed:

- the addition of a note to the listing of diazepam to indicate that use is for the short-term emergency management of acute and severe anxiety symptoms only, and
- therapeutic alternatives under the square box listing for diazepam be limited to lorazepam.

Applicant

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy

WHO technical department

Mental Health and Substance Use

EML/EMLc

EML

Section

24.3 Medicines for anxiety disorders

Dose form(s) & strengths(s)

Tablet (scored): 2 mg, 5 mg

Core/complementary

Core

Individual/square box listing

Square box

Background

Diazepam, with an unrestricted square box, has been included on the EML since the first list was published in 1977.

At its meeting in 2021, the Expert Committee considered a review of square box listings on the EML and EMLc and recommended that all square box listings be qualified to explicitly indicate the recommended therapeutic alternatives. The Committee requested that the therapeutic alternatives for diazepam for use in the treatment of anxiety disorders be reviewed and updated in 2023 (*1*).

Public health relevance

Anxiety disorders are prevalent and disabling conditions that cause excessive fear, worry and avoidance of threats in the environment. They have a high incidence, early age at onset and a tendency to relapse for a long time (*2–4*). Guidelines recommend selective serotonin reuptake inhibitors (SSRIs) as the first-choice pharmacological treatment, but benzodiazepines are still commonly used due to their rapid onset of action, perceived effectiveness and favourable side-effects profile in the short term (*5–8*).

Benzodiazepines are classified, under the United Nations Convention of Psychotropic Substances, as schedule IV substances and have a high potential for abuse with addictive potential (*9*). In 2020 in the United States, 4.8 million individuals misused or abused prescription benzodiazepines (*10*). In Finland, a population-based cohort study of almost 130 000 new benzodiazepine users found that 39.4% (51 099) of the continuous benzodiazepine users became long-term users (*11*). Long-term use of benzodiazepines can lead to adverse effects, especially in older individuals, such as cognitive and psychomotor impairments, and increased risk of falls, fractures and even death in many age ranges (*12–18*). Factors associated with long-term benzodiazepine use include sex, comorbid conditions, older age, lower income, psychiatric comorbidities, substance abuse and poorer health status (*11,19–21*).

Concerns about tolerance and the development of physical dependence have been associated with benzodiazepines for more than 50 years (*22,23*). Physical dependence can occur with regular use for several days or weeks, leading to withdrawal symptoms when the medication is tapered or reduced (*5*). Discontinuation of long-term benzodiazepine use is challenging, with only a small percentage of users (13%) able to successfully discontinue within a year (*24–26*). Benzodiazepine use is associated with a high risk of re-initiation after discontinuation, and abrupt withdrawal or rapid dose reduction can result in life-threatening withdrawal reactions including seizures (*23,27*).

Concomitant use of benzodiazepines and opioids is a major risk factor for drug-related deaths (*28*), and benzodiazepines, along with cannabis, are among the most prevalent psychoactive substances used by vehicle drivers and their use can impair driving ability including judgement and reaction time, thus increasing the risk of road traffic crashes especially when combined with alcohol (*28–30*).

In September 2020, the United States Food and Drug Administration updated the safety warnings and labelling for all benzodiazepines, highlighting the risks of abuse, misuse, addiction, physical dependence and withdrawal reactions (*31*).

Summary of evidence: benefits

There is consensus among studies that benzodiazepines are generally more effective than placebo in treatment of panic disorders, with no significant differences in efficacy observed between different benzodiazepines (*32*). Two meta-analyses-compared the effectiveness of psychological and pharmacological treatments (*33*), and the effect of antidepressants and benzodiazepines versus placebo (*34*) in the treatment of panic disorders. Both studies showed superiority of benzodiazepines over a placebo in adults. These findings are supported by the results of a 2019 Cochrane systematic review, which found that benzodiazepines had a higher response rate (risk ratio (RR) 1.65, 95% confidence interval (CI) 1.39 to 1.96) and lower drop-out rate (RR 0.50, 95% CI 0.39 to 0.64) compared with placebo (*35*). Similar results were also found for generalized anxiety disorder (*36*), social anxiety disorder (*37,38*) and specific phobias (*39,40*). Notably, these studies primarily focused on short-term efficacy and did not assess long-term efficacy or the risks of dependency and withdrawal symptoms.

A 2022 network meta-analysis of 154 randomized controlled trials (40 089 participants) estimated the comparative effectiveness of pharmacological treatments for acute and long-term treatment of adults with insomnia disorder (*41*). The study included an analysis of the comparative efficacy of benzodiazepines, grouping them according to half-life (short-, intermediate- and long-acting). No significant differences were found in efficacy for acute treatment of insomnia among the three groups of benzodiazepines. This finding indirectly supports the notion that, when administered at equivalent dosages, all benzodiazepines have a similar beneficial effect on symptoms, noting that the outcome assessed in this study was the resolution of insomnia rather than anxiety symptoms.

Summary of evidence: harms

The harms associated with benzodiazepines are well known and well established. Benzodiazepines have similar toxicity profiles and, with some exceptions, abuse, misuse and dependency potential. Common short-time adverse effects include drowsiness, confusion, dizziness, somnolence, fatigue, weakness, memory impairment, impaired coordination and psychomotor retardation. A paradoxical increase in anxiety or disinhibition and delirium may particularly affect elderly patients. Long-term adverse effects include cognitive impairment, increased risk of falls, increased risk of vehicle crashes, depression and emotional blunting. Symptoms of overdose include extreme sedation or drowsiness, reduced respiration rate, confusion and difficulty thinking, slurred speech, loss of muscle control, and coma. Overdose may be fatal if used in combination with alcohol or opioids.

Benzodiazepine dependence tends to be more prevalent in populations that already have a history of substance abuse. Studies have shown that about 11% to 15% of adults have used benzodiazepines at least once in the past year. However, only around 1% to 2% have taken benzodiazepines daily for a period of 12 months or more (*42*). In specific settings, such as psychiatric treatment facilities and among populations struggling with substance abuse, the rates of benzodiazepine use, abuse and dependence are significantly higher than the general population (*43,44*).

The development of physical dependence on benzodiazepines can be predicted to some extent and is related to the total exposure, determined by the dose and duration of treatment. As a result of physical dependence, withdrawal symptoms emerge with rapid dose reduction or abrupt discontinuation of the drug. Withdrawal symptoms are possible after only 1 month of daily use (*45*).

The incidence of benzodiazepine overdose is influenced by the availability of the medicines (*46,47*), with the most commonly available benzodiazepines most prone to abuse. In terms of addictive potential, diazepam and lorazepam are not more dangerous than other benzodiazepines. Benzodiazepines with greater addictive potential include flunitrazepam, temazepam and alprazolam. Flunitrazepam is illegal in the United States (*48*), temazepam is banned in Sweden (*5*) and alprazolam and flunitrazepam are scheduled as controlled drugs in Australia (*49*).

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders include a strong recommendation that benzodiazepines not be used for the treatment of adults with generalized anxiety and/or panic disorder. However, for the emergency management of acute and severe anxiety symptoms, benzodiazepines may be considered only as a short-term measure (3–7 days maximum) measure (low certainty of evidence) (*50*).

Costs/cost–effectiveness

The availability and cost of benzodiazepines vary substantially among countries and across public and private sectors.

There are no comparative cost–effectiveness studies of single benzodiazepines.

Evidence suggests that the use of benzodiazepines may be associated with unnecessary medicine, dispensing and consultation costs resulting from misuse and unnecessary prescribing. A study in the United Kingdom estimated that 67–72% of the total costs associated with benzodiazepines were unnecessary. Over a 3-year period (April 2015–March 2018), the estimated unnecessary

costs ranged from about £115.6 million to £129.9 million, with an annual mean unnecessary cost of about £38.5 million to £43.3 million (*51*).

In adults with generalized anxiety disorder, long-term use of benzodiazepines has been shown to significantly increase health care costs. A retrospective cohort study in the United States involving 866 adults found that mean total health care costs increased by US$ 2334 after the start of a long-term (> 90 days) course of benzodiazepine. The costs associated with benzodiazepine use primarily stemmed from accident-related encounters (e.g. treatment of fractures) and care received for other reasons possibly related to benzodiazepine use, such as sedation and dizziness (*52*).

A cost–utility analysis assessed the economic impact of potentially inappropriate prescribing and related adverse events in adults aged 65 years and older. Inappropriate prescribing of benzodiazepines had the largest reduction in quality-adjusted life years (QALYs) and incurred greater incremental costs compared with other medications subject to potentially inappropriate prescribing, such as non-steroidal anti-inflammatory drugs and proton-pump inhibitors. The reduction in QALYs was estimated to be –0.07 QALY, while reduction in the incremental cost was €3470 (*53*).

These findings demonstrate the financial consequences associated with unnecessary use and inappropriate prescribing of benzodiazepines, underscoring the importance of judicious and evidence-based practices in their use.

Availability

Both diazepam and lorazepam are available globally in originator and generic brands.

Other considerations

The application proposed including lorazepam as an alternative to diazepam because it complements diazepam pharmacokinetically as well as for their therapeutic indications. Diazepam has a long half-life (20–80 hours), while lorazepam has a short half-life (10–20 hours). Diazepam is a medium-potency agent, indicated for milder forms of anxiety, while lorazepam is a high-potency agent, indicated for anxiety surges during panic attacks (*54*).

Although concerns exist about the potential for abuse, misuse and dependence with all benzodiazepines, specific benzodiazepines such as alprazolam, flunitrazepam and temazepam have the higher risks. Thus, these agents were not proposed as therapeutic alternatives to diazepam.

Committee recommendations

The Expert Committee noted that the long-term use of benzodiazepines in the treatment of anxiety disorders was known to be associated with considerable

harms in terms of dependence and addiction potential. With short-term use, these risks were greatly reduced.

The Committee noted that the updated WHO mhGAP guidelines will include a recommendation limiting the use of benzodiazepines to short-term use (3–7 days) for the emergency management of acute and severe anxiety symptoms only.

The Expert Committee therefore recommended the addition of a note to the listing of diazepam for use in anxiety disorders stating that it is only for short-term emergency management of acute and severe anxiety symptoms, as the balance of benefits and risks of diazepam use under these circumstances is favourable.

The Expert Committee also accepted the rationale applied by the applicants in selecting lorazepam as the only therapeutic alternative to diazepam for short-term treatment of acute and severe anxiety and recommended that lorazepam be specified as the only therapeutic alternative under the square box listing for diazepam for this indication.

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Fluoxetine – new indication – EML

Fluoxetine	ATC code: N06AB03

Proposal

Inclusion of fluoxetine on the core list of the EML for the new indications of treatment of generalized anxiety disorder, panic disorder and social anxiety disorder in adults. Listing is requested with a square box specifying citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives.

Applicant

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Mental Health and Substance Use

EML/EMLc

EML

Section

24.3 Medicines for anxiety disorders

Dose form(s) & strengths(s)

Solid oral dosage form: 20 mg (as hydrochloride)

Core/complementary

Core

Individual/square box listing

Square box listing for fluoxetine as the representative selective serotonin reuptake inhibitor (SSRI), with citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as the therapeutic alternatives.

Background

Fluoxetine has not been previously considered for inclusion on the EML for use in the treatment of anxiety disorders. The EML currently includes only diazepam for this indication.

Fluoxetine has been included on the EML for treatment of depressive disorders since 2007. A square box was added in 2019 to indicate citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives.

Public health relevance

Anxiety disorders are prevalent and disabling, creating a large global burden of disease. People affected by these disorders suffer from excessive fear and nervousness, avoidance of perceived threats and autonomic dysfunction (e.g. palpitations, dizziness and insomnia) (*1–3*). Early onset and persistent relapses further add to the severity (*4*). Anxiety disorders are responsible for more than 28.6 million years lived with disability (YLD), accounting for 3.34% of the total global YLD, and 26.7 million disability-adjusted life years (DALYs) per year, or 1.13% of total DALYs due to any disease (*5*). Overall, anxiety disorders have been among the top 10 causes of YLDs for the past 20 years (*6*). The COVID-19 pandemic has had a serious effect on global mental health, including a 26% rise in anxiety disorders cases (*7*). Women and younger people are more affected, with the highest increases in countries with high COVID-19 infection rates and severe restrictions on movement (lockdowns and school closures).

Anxiety affects overall health as it is associated with a heightened risk of coronary artery disease, unstable angina and heart attacks, and increased mortality rates. Furthermore, anxiety can lead to insulin resistance and may contribute to noncommunicable illnesses such as diabetes, heart disease and cancer (*8–10*). Anxiety disorders also have large financial costs. Globally, an estimated 12 billion work days are lost every year to depression and anxiety at an annual cost of US$ 1 trillion in lost productivity (*11*).

Summary of evidence: benefits

A 2022 systematic review and network meta-analysis of 87 randomized controlled trials (12 800 participants) evaluated medicines for treatment of adults with panic disorder (with or without agoraphobia) (*12*). A total of 21 comparisons were considered for analysis. Most studies compared benzodiazepines or SSRIs with placebo. Other comparisons included tricyclic antidepressants versus placebo and comparisons between different drug classes. The most common duration of treatment was 8 weeks (35%), followed by 12 weeks (19%). Compared with placebo, the risk ratios (RR) for symptom remission significantly favoured serotonin-noradrenaline reuptake inhibitors (RR 1.27, 95% confidence interval (CI) 1.12 to 1.42), SSRIs (RR 1.38, 95% CI 1.26 to 1.5), monoamine oxidase inhibitors (RR 1.30, 95% CI 1.00 to 1.69), benzodiazepines (RR 1.47, 95% CI 1.36 to 1.6) and tricyclic antidepressants (RR 1.39, 95% CI 1.26 to 1.54). SSRIs were found to be the most effective (66.4%) with the fewest adverse events (58.5%) for treating panic disorder, according to the surface under cumulative ranking curves (SUCRA) clustered ranking plot. Certainty of evidence against placebo was rated as moderate.

A 2019 systematic review and meta-analysis of 89 randomized controlled trials (25 441 participants) evaluated pharmacotherapy for the treatment of adults with generalized anxiety disorder (*13*). Most studies used the Diagnostic and

Statistical Manual of Mental Disorders (DSM) criteria for diagnosis. Duration of follow-up ranged from 4 to 26 weeks, and measured change in the Hamilton Anxiety Scale (HAM-A) score as the efficacy outcome. Most medicines (16/22, 73%) performed better than placebo. SSRIs were superior to placebo in reducing symptoms of anxiety. Standardized mean differences of treatment efficacy were: –2.22 (95% CI –4.28 to –0.19) for citalopram; –2.45 (95% CI –3.27 to –1.63) for escitalopram; –2.43 (95% CI –3.74 to –1.16) for fluoxetine; –2.29 (95% CI –3.11 to –1.47) for paroxetine; and –2.88 (95% CI –4.17 to –1.59) for sertraline. The certainty of evidence was rated as moderate for sertraline, low for citalopram, escitalopram and fluoxetine, and very low for paroxetine.

A 2020 systematic review and network meta-analysis of 67 randomized controlled trials (12 122 participants) evaluated pharmacotherapy for the treatment of adults with social anxiety disorder (*14*). The primary efficacy outcome was change in symptom severity measured using the Leibowitz Social Anxiety Scale. Paroxetine was significantly more effective than placebo in reducing symptom severity (mean difference (MD) –15.89, 95% CI –29.94 to –1.84), based on low to very low-certainty evidence. Other SSRIs investigated were also superior to placebo, however the differences were not statistically significant: MD –17.45, 95% CI –43.76 to 8.86 for sertraline; MD –8.05, 95% CI –41.81 to 25.71 for escitalopram; and MD –2.132, 95% CI –21.88 to 17.64 for fluvoxamine.

Summary of evidence: harms

The 2022 systematic review and network meta-analysis of medicines for treatment of adults with panic disorder (with or without agoraphobia) provided data on the acceptability of treatments (i.e. all-cause treatment discontinuation) and tolerability (i.e. adverse events) (*12*). SSRIs were more acceptable than tricyclic antidepressants (RR 0.78, 95% CI 0.61 to 0.99) and benzodiazepines (RR 0.51, 95% CI 0.38 to 0.67), and equally acceptable as placebo (RR 0.92, 95% CI 0.77 to 1.1). In terms of tolerability, SSRIs had a higher risk of adverse events than placebo (RR 1.19, 95% CI –1.01 to 1.41). However, benzodiazepines (RR 1.47, 95% CI 1.18 to 1.84) and tricyclic antidepressants (RR 1.50, 95% CI 1.20 to 1.88) had a higher risk of adverse events than SSRIs.

The 2019 systematic review and meta-analysis of pharmacotherapy for the treatment of adults with generalized anxiety disorder provided data on acceptability (i.e. all cause discontinuation) (*13*). The risk of discontinuation for SSRIs did not differ significantly from placebo, except for paroxetine (odds ratio (OR) 1.24, 95% CI 1.03 to 1.50), which had a higher discontinuation rate.

The 2020 systematic review and network meta-analysis of pharmacotherapy for the treatment of adults with social anxiety disorder also provided data on acceptability (i.e. all cause discontinuation) (*14*). Discontinuation rates for SSRIs were not significantly different from placebo, with the exception of fluvoxamine (OR 1.51, 95% CI 1.06 to 2.14).

Risk of suicidality

A meta-analysis of individual-level data from almost 100 000 patients from published and unpublished clinical trials was undertaken using data collected by the United States Food and Drug Administration in 2005–2006 (*15*). Industry sponsors of 12 antidepressant medicines, including SSRIs, were requested to submit datasets from double-blind randomized placebo-controlled trials on the use of antidepressants in adults for any indication to evaluate the risk of suicidality in clinical trials of antidepressants. The risk of suicidality associated with antidepressant use was found to be age dependent. Compared with placebo, an increased risk of suicidality and suicidal behaviour was seen in depressed children and adolescents. The net effect was: neutral for suicidal behaviour; possibly protective for suicidal ideation in adults aged 25–64 years; reduced for both suicidality and suicidal behaviour in patients aged 65 years and older. No information was specifically reported for anxiety disorders.

Risk of QT-prolongation

SSRIs can cause delayed repolarization of cardiac myocytes, leading to a prolonged QT interval and risk of life-threatening arrhythmias. A 2014 meta-analysis found that different SSRIs have varying effects on QTc prolongation. Fluoxetine (MD 4.50, 95% CI –4.32 to 13.32) and paroxetine (MD –1.04, 95% CI –5.76 to 3.68) had no significant association with QTc prolongation. Fluvoxamine was associated with shortened QTc (MD –5.00, 95% CI –6.05 to –3.95). Citalopram (MD 10.58, 95% CI 3.93 to 17.23), escitalopram (MD 7.27, 95% CI 3.78 to 10.83) and sertraline (MD 3.00, 95% CI 2.95 to 3.05) were significantly associated with QTc prolongation (*16*).

Risk of sexual side-effects

SSRIs are known to cause sexual dysfunction. A 2014 network meta-analysis compared the risk of sexual side-effects of 13 second-generation antidepressants including SSRIs. Most comparisons did not show significant differences in the risk of sexual side-effects between the SSRIs. Escitalopram (OR 0.37, 95% CI 0.13 to 0.85) and paroxetine (OR 3.86, 95% CI 1.44 to 8.40) had a statistically significant higher risk of sexual dysfunction than fluoxetine (*17*).

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders include a conditional recommendation that SSRIs be considered for adults with panic disorder and adults with generalized anxiety disorder (low certainty of evidence) (*18*).

Many other current clinical guidelines include recommendations for the use of SSRIs as first-choice pharmacological treatment for generalized anxiety disorder,

panic disorder and social anxiety disorder (*19–24*). Clinical guidelines do not provide indications on which individual medicine to choose, generally agreeing on the importance of tailoring the choice to individual characteristics of the patient and actively involving individuals and caregivers in a shared decision-making process.

Costs/cost–effectiveness

The availability and affordability of SSRIs vary across countries and settings. At the same time, the cost of anxiety disorders is high for individuals, health care systems and society due to productivity loss.

Comparative cost–effectiveness studies suggest that cognitive behavioural therapy with or without SSRIs is the most cost-effective intervention for anxiety disorders (*25,26*). However, implementing widespread access to cognitive behavioural therapy poses equity and feasibility challenges due to the need for policy changes and resources.

Evidence on the cost–effectiveness of SSRIs specifically for anxiety disorders is lacking, but indirect evidence of the cost–effectiveness of these medicines for depression is available.

A 2015 network meta-analysis in Singapore estimated the cost–effectiveness of different antidepressants and found that agomelatine was the most cost-effective antidepressant, followed by venlafaxine and mirtazapine (*27*). Escitalopram was the most cost-effective SSRI for depression, followed by fluvoxamine. The effectiveness-based model used in the study had limitations, effectiveness was based on efficacy (rather than recorded costs) and the estimated costs were specific to Singapore's health system, limiting generalizability.

Another meta-analysis compared the efficacy of 10 antidepressants for treating moderate to severe depression in primary care (*28*). Escitalopram was the most effective in achieving remission at the 8- to 12-week follow-up. Despite its higher acquisition cost, escitalopram was both more effective and had lower total costs than other antidepressants from a societal perspective. From a health care perspective, the cost per quality-adjusted life year of escitalopram was €3732 compared with venlafaxine.

Availability

The proposed SSRIs are available globally, off-patent and with multiple branded and generic versions.

Committee recommendations

The Expert Committee acknowledged the public health relevance of effective treatments for anxiety disorders, from patient, societal and health system perspectives. In particular, the Committee noted the substantial disability and lost-productivity costs associated with anxiety disorders.

The Committee noted from the evidence presented in the application that SSRIs were more effective in reducing anxiety symptoms than placebo and had a well known and acceptable safety profile. While some differences in efficacy and safety may exist between SSRIs, in general the evidence does not indicate that any medicine significantly outperforms the others; therefore, the choice of medicine within the class should be based on patients' clinical characteristics and preferences.

The Committee noted that SSRI therapy was recommended for use in the treatment of anxiety disorders in many clinical guidelines and would also be included in the updated the WHO mhGAP guidelines.

The Committee noted that the medicines proposed for inclusion were already in the EML for use in the treatment of depression, and were widely available and generally affordable, with generic brands available.

The Expert Committee therefore recommended extending the listing of fluoxetine on the EML to include the new indications of generalized anxiety disorder, panic disorder and social anxiety disorder. Listing is recommended with a square box specifying citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives.

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24.4 Medicines used for obsessive–compulsive disorders

Fluoxetine – new indication – EML

Fluoxetine	ATC code: N06AB03

Proposal

Inclusion of fluoxetine on the core list of the EML for the new indication of treatment of obsessive–compulsive disorders in adults. Listing is requested with a square box specifying citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives.

Applicant

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WHO technical department

Mental Health and Substance Use

EML/EMLc

EML

Section

24.4 Medicines for obsessive–compulsive disorders

Dose form(s) & strengths(s)

Solid oral dosage form: 20 mg (as hydrochloride)

Core/complementary

Core

Individual/square box listing

Square box listing for fluoxetine as the representative selective serotonin reuptake inhibitor (SSRI), with citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives.

Background

Fluoxetine has not been previously considered for inclusion on the EML for use in the treatment of obsessive–compulsive disorders. The EML currently includes only clomipramine for this indication.

Fluoxetine has been included on the EML for treatment of depressive disorders since 2007. A square box was added in 2019 to indicate citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives.

Public health relevance

Obsessive–compulsive disorder is a common mental disorder and is responsible for substantial disability worldwide (*1,2*). Estimates of the prevalence of obsessive–compulsive disorder in the literature vary, but generally suggest that between 1% and 4% of the population are affected in their lifetime (*3–5*). In two thirds of cases, the age at onset is younger than 25 years, while in 15% of cases, onset occurs after the age of 35 years. In about one third of cases, age at onset is in childhood or early adolescence. Males tend to have an earlier onset and worse prognosis (*6*). The COVID-19 pandemic has had a significant impact on obsessive–compulsive disorder, leading to an increase in its prevalence (*7,8*). A systematic review found that individuals, both with and without a prior diagnosis of obsessive–compulsive disorder, experienced a worsening of symptoms during the pandemic (*9*).

People with obsessive–compulsive disorder experience recurrent and intrusive thoughts (obsessions) that cause anxiety or distress. They often engage in repetitive behaviours or mental acts (compulsions) to cope with these obsessions (*10*). Obsessive–compulsive disorder greatly affects the quality of life for patients, caregivers and relatives, and is associated with increased mortality (*11,12*). The condition tends to be chronic, with intermittent episodes (*13*). Individuals with obsessive–compulsive disorder often have other psychiatric disorders as well, leading to impaired health and functioning (*14–16*). Obsessive–compulsive disorder is associated with significant impairment in overall functioning and quality of life. Compared with healthy controls or community cohorts, individuals with obsessive–compulsive disorder report significantly worse quality of life in many areas, including overall sense of well-being, social and family relationships, ability to enjoy leisure activities, and general ability to function in daily and working life (*17,18*).

Summary of evidence: benefits

The applicants conducted a systematic review and network meta-analysis of 48 randomized controlled trials (5840 participants) comparing the efficacy (reduction of obsessive–compulsive symptoms) and acceptability (all-cause discontinuation) of different antidepressants.

For the outcome of efficacy, clomipramine (standardized mean difference (SMD) –0.67, 95% confidence interval (CI) –0.89 to –0.45; very low-certainty evidence), sertraline (SMD –0.64, 95% CI –0.92 to –0.36; low-certainty evidence), fluvoxamine (SMD –0.57, 95% CI –0.82 to –0.32; very low-certainty evidence), paroxetine (SMD –0.44, 95% CI –0.70 to –0.17; low-certainty evidence), citalopram (SMD –0.47; 95% CI –1.02 to 0.07; low-certainty evidence), escitalopram (SMD –0.45, 95% CI -0.92 to 0.02; low-certainty evidence) and fluoxetine (SMD –0.39, 95% CI –0.78 to 0.00; low-certainty evidence) were

significantly more effective than placebo. In head-to-head comparisons with clomipramine, the only medicine currently included on the EML for obsessive–compulsive disorder, each SSRI demonstrated similar efficacy. Head-to-head comparisons also showed no significant differences between individual SSRIs.

For the outcome of acceptability, escitalopram (odds ratio (OR) 0.68, 95% CI 0.46 to 1.02; moderate-certainty evidence), sertraline (OR 0.79, 95% CI 0.58 to 1.08; low-certainty evidence), fluvoxamine (OR 0.83, 95% CI 0.59 to 1.15; moderate-certainty evidence), paroxetine (OR 0.87, 95% CI 0.65 to 1.16; moderate-certainty evidence), citalopram (OR 0.89, 95% CI 0.49 to 1.64; moderate-certainty evidence) and fluoxetine (OR 0.92, 95% CI 0.57 to 1.48; very low-certainty evidence) were comparable to placebo. In contrast, clomipramine was significantly less acceptable than placebo (OR 1.41, 95% CI 10.7 to 1.85; moderate-certainty evidence). Head-to-head comparisons showed escitalopram, sertraline, fluvoxamine and paroxetine were more acceptable than clomipramine.

The results from the network meta-analysis conducted by the applicants complement the findings of a 2016 network meta-analysis of 54 trials (6652 participants), which compared the efficacy of pharmacological and psychotherapeutic interventions for the management of obsessive–compulsive disorder in adults (*19*). The primary outcome was symptom severity as measured by the Yale-Brown Obsessive Compulsive Scale. The SSRIs included were citalopram, escitalopram fluoxetine, fluvoxamine, paroxetine and sertraline. In this analysis SSRIs as a class were more effective than placebo (mean difference (MD) −3.49, 95% credible interval (CrI) −5.12 to −1.81) and equally efficacious in head-to-head comparisons with each other. No significant difference was found between clomipramine and SSRIs as a class (MD −1.23, 95% CrI −3.41 to 0.94).

Summary of evidence: harms

The systematic review and network meta-analysis conducted by the applicants evaluated tolerability (drop-outs due to adverse events) using data from 43 randomized controlled trials. Among SSRIs, escitalopram (OR 1.26, 95% CI 0.69 to 2.32), fluoxetine (OR 1.28, 95% CI 0.56 to 2.96), sertraline (OR 1.77, 95% CI 1.05 to 2.98), paroxetine (OR 1.82, 95% CI 1.19 to 2.78) and citalopram (OR 2.42, 95% CI 0.54 to 10.85) did not show a statistically significant difference in tolerability compared with placebo. Fluvoxamine (OR 2.98, 95% CI 1.80 to 4.92) and clomipramine (OR 4.82, 95% CI 3.0 to 7.73) were less tolerable than placebo. In head-to-head comparisons, escitalopram (OR 0.21, 95% CI 0.13 to 0.33), fluoxetine (OR 0.27, 95% CI 0.11 to 0.63), sertraline (OR 0.37, 95% CI 0.21 to 0.63) and paroxetine (OR 0.38, 95% CI 0.22 to 0.64) were better tolerated than clomipramine. Citalopram (OR 0.5, 95% CI 0.10 to 2.42) and fluvoxamine (OR 0.62, 95% CI 0.37 to 1.02) did not show a significant difference in tolerability compared with clomipramine. Data on specific side-effects and tolerability issues were limited, primarily due to reporting bias in the original studies.

Risk of suicidality

A meta-analysis was done of individual level data of almost 100 000 patients from published and unpublished clinical trials submitted to the United States Food and Drug Administration in 2005–2006 (*20*). Industry sponsors of 12 antidepressant medicines, including SSRIs, were requested to submit datasets from double-blind randomized placebo-controlled trials of antidepressants in adults for any indication, to evaluate the risk of suicidality in clinical trials of antidepressants. The analysis found that the risk of suicidality associated with antidepressant use was age dependent. Compared with placebo, an increased risk of suicidality and suicidal behaviour was observed in depressed children and adolescents. The net effect was neutral on suicidal behaviour, possibly protective for suicidal ideation in adults aged 25–64 years and reduced the risk of both suicidality and suicidal behaviour in patients aged 65 years and older. No information was specifically reported for anxiety disorders.

Risk of QT-prolongation

SSRIs can cause delayed repolarization of cardiac myocytes, leading to a prolonged QT interval and risk of life-threatening arrhythmias. A 2014 meta-analysis found that different SSRIs had varying effects on QTc prolongation. Fluoxetine (MD 4.50, 95% CI –4.32 to 13.32) and paroxetine (MD –1.04, 95% CI –5.76 to 3.68) had no significant association with QTc prolongation. Fluvoxamine was associated with shortened QTc (MD –5.00, 95% CI –6.05 to –3.95). Citalopram (MD 10.58, 95% CI 3.93 to 17.23), escitalopram (MD 7.27, 95% CI 3.78 to 10.83) and sertraline (MD 3.00, 95% CI 2.95 to 3.05) were significantly associated with QTc prolongation (*21*).

Risk of sexual side-effects

SSRIs are known to cause sexual dysfunction. A 2014 network meta-analysis compared the risk of sexual side-effects of 13 second-generation antidepressants including SSRIs. Most comparisons did not demonstrate significant differences between the SSRIs. Escitalopram (OR 0.37, 95% CI 0.13 to 0.85) and paroxetine (OR 3.86, 95% CI 1.44 to 8.40) had a statistically significant higher risk of sexual dysfunction than fluoxetine (*22*).

WHO guidelines

WHO guidelines for treatment of obsessive–compulsive disorders are not currently available.

Many other current clinical guidelines include recommendations for the use of SSRIs as the first-choice pharmacological treatment for obsessive–compulsive disorder (*23–26*). Clinical guidelines do not provide indications on which individual medicine to choose, generally agreeing on the importance

of tailoring the choice to individual characteristics of the patient and actively involving individuals and caregivers in a shared decision-making process.

Costs/cost–effectiveness

The availability and affordability of SSRIs vary across countries and settings. At the same time, the cost of anxiety disorders is high for individuals, health care systems and society due to productivity loss.

Evidence on the cost–effectiveness of SSRIs compared with clomipramine and other pharmacological classes for obsessive–compulsive disorder is lacking.

Studies focusing on cost–effectiveness compare SSRIs with cognitive behavioural therapy and indicate that monotherapy with SSRIs or a combination of cognitive behavioural therapy and an SSRIs is the most cost-effective approach.

A 2016 systematic review of 86 randomized controlled trials evaluated the clinical and cost–effectiveness of pharmacological and psychological interventions for the management of obsessive–compulsive disorder in children, adolescents and adults in the United Kingdom (*27*). The review reported the net monetary benefit to estimate cost–effectiveness if the National Health Service was willing to pay £20 000 for each quality-adjusted life year gained. Fluvoxamine in combination with cognitive behavioural therapy had the lowest net monetary benefit of £57 174 (i.e. least cost-effective), while strategies involving cognitive or behavioural therapies had the highest net monetary benefit of £59 668 and £59 695, respectively (i.e. most cost-effective). Pharmacological monotherapies had net monetary benefit of £58 373 for SSRIs, £58 549 for clomipramine and £58 664 for venlafaxine.

A 2018 randomized feasibility study evaluated the cost–effectiveness of combining cognitive behavioural therapy with sertraline versus either treatment given as monotherapy over 52 weeks in 49 adults with obsessive–compulsive disorder in the United Kingdom (*28*). Resource use and quality of life data were available (at baseline, 16 and 52 weeks) for 23/49 (46.9%) participants. Compared with sertraline monotherapy, mean costs were higher for both cognitive behavioural therapy as monotherapy and combination treatment (£1329 and £2176, respectively. Mean quality-adjusted life year scores for sertraline monotherapy were 0.18 greater than that of cognitive behavioural therapy monotherapy, and 0.11 greater than that of combination treatment. Sertraline monotherapy was considered dominant and cost-effective, as it was estimated to be both less costly and more effective than both other options.

Availability

The proposed SSRIs are available globally, off-patent and with multiple branded and generic versions.

Committee recommendations

The Expert Committee acknowledged the public health relevance of effective treatments for obsessive–compulsive disorder, from patient, societal and health system perspectives. In particular, the Committee noted the substantial disability associated with the condition, especially in the context of the COVID-19 pandemic.

The Committee noted from the evidence presented in the application that SSRIs were superior to placebo and had similar efficacy and a more favourable safety profile than clomipramine in the treatment of obsessive–compulsive disorder. While some differences in efficacy and safety may exist between SSRIs, in general the evidence does not indicate that any medicine significantly outperforms the others; therefore, the choice of medicine within the class should be based on patients' clinical characteristics and preferences.

The Committee noted that SSRI therapy was recommended for use in the treatment of obsessive–compulsive disorder in many clinical guidelines, although WHO guidelines for treatment of obsessive–compulsive disorder are not currently available.

The Committee noted that the medicines proposed for inclusion were already included on the EML for use in the treatment of depression, and were widely available and generally affordable, with generic brands available.

The Expert Committee therefore recommended extending the listing of fluoxetine on the EML to include the new indication of obsessive–compulsive disorder. Listing is recommended with a square box specifying citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline as therapeutic alternatives.

References

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24.5 Medicines for disorders due to psychoactive substance use
24.5.1 Medicines for alcohol use disorders
Acamprosate – addition – EML

Acamprosate calcium	ATC code: N07BB03

Proposal

Addition of acamprosate calcium to the core list of the EML for maintenance treatment of alcohol use disorder in adults.

Applicant

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WHO technical department

The WHO Department of Mental Health and Substance Use reviewed and provided comments on the application. The technical unit stated that the application to include acamprosate on the EML was timely and in line with guidance provided by WHO global policy frameworks and action plans.

EML/EMLc

EML

Section

24.5.1 Medicines for alcohol use disorders

Dose form(s) & strengths(s)

Tablet: 333 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Medicines for treatment of alcohol use disorders have not previously been evaluated for inclusion in the EML.

Public health relevance

Globally in 2016, alcohol use was the seventh leading risk factor for premature death and disability and was the leading risk factor in people aged 15 to 49 years. Worldwide, 2.8 million deaths were attributable to alcohol use. Alcohol consumption was shown to have a strong association with a higher risk of cancer, injuries and communicable disease (*1*).

The 2018 WHO *Global status report on alcohol and health* recognized that the harmful use of alcohol directly affects numerous targets of the Sustainable Development Goals including those for maternal and child health, infectious diseases, noncommunicable diseases, mental health, injuries and poisonings (*2*). Globally in 2016, estimates suggest that the harmful use of alcohol was responsible for 3 million deaths and caused 132.6 million disability-adjusted life years (DALYs) or 5.1% of total DALYs that year. The age-standardized burden of disease and injury associated with alcohol use varied geographically across WHO regions and was highest in the African region, where it was responsible for 70.6 deaths and 3044 DALYs per 100 000 people (*2*).

During the COVID-19 pandemic, a cross-sectional survey in the United States found that respondents reported consuming more drinks per day, more binge drinking and more alcohol consumption beyond recommended drinking limits than before the introduction of stay-at-home orders (*3*).

Summary of evidence: benefits

A 2004 systematic review and meta-analysis evaluated the efficacy and safety of acamprosate and naltrexone in the treatment of alcohol dependence. The study included 13 randomized-controlled trials (4000 participants) of acamprosate in people who met the *Diagnostic and statistical manual of mental disorders*, third edition (DSM-III) criteria for alcohol dependence and who had undergone a detoxification process (*4*). A meta-analysis of 12 of the 13 studies showed that acamprosate was associated with an increased rate of continuous abstinence compared with placebo (Peto odds ratio (OR 1.88, 95% confidence interval (CI) 1.57 to 2.25; number needed to treat (NNT) = 10). Acamprosate was also associated with a doubling of the days of cumulative abstinence based on seven studies that measured this outcome.

Another 2004 systematic review and meta-analysis of 17 randomized controlled trials (4087 participants) evaluated the efficacy of acamprosate for maintenance of abstinence in alcohol-dependent individuals (*5*). Participants

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treated with acamprosate compared with placebo had significantly higher continuous abstinence rates at 6 months (36.1% versus 23.4%, relative benefit (RB) 1.47, 95% CI 1.29 to 1.69). The pooled difference in success rates for continuous abstinence at 12 months between acamprosate and placebo was 13.3% (95% CI 7.8% to 18.7%; NNT = 8).

A 2008 meta-analysis compared the efficacy profiles of acamprosate and naltrexone. The analysis included 21 randomized controlled trials (5280 participants) that evaluated the efficacy and safety of acamprosate compared with placebo (*6*). Treatment with acamprosate reduced the risk of having a first drink by 84% compared with placebo (risk ratio (RR) 0.84, 95% CI 0.78 to 0.91; NNT to prevent one additional incidence of drinking = 8). Acamprosate was also associated with a reduced the risk of returning to heavy drinking compared with placebo (RR 0.82, 95% CI 0.73 to 0.92; NNT = 9). However, acamprosate did not significantly reduce the risk of heavy drinking among the subgroup of non-abstinent participants (RR 0.98, 95% CI 0.94 to 1.02).

A 2010 Cochrane systematic review of 24 randomized controlled trials (6915 participants) evaluated the effectiveness and tolerability of acamprosate in comparison with placebo and other pharmacological agents (*7*). Acamprosate significantly reduced the risk for the primary outcome of return to any drinking (RR 0.86, 95% CI 0.81 to 0.91; NNT for an additional beneficial outcome = 10) compared with placebo. Sensitivity analyses to assess the effect of the funding source/sponsorship of the trials found that partially industry-supported trials had the highest magnitude of effect (RR 0.84, 95% CI 0.78 to 0.89), while fully industry-supported trials had the lowest magnitude of benefit (RR 0.88, 95% CI 0.80 to 0.97). For the outcome of cumulative abstinence duration, a statistically significant difference was found between acamprosate and placebo groups favouring acamprosate (mean difference (MD) 10.9, 95% CI 5.08 to 16.8).

A 2013 meta-analysis of 64 randomized, placebo-controlled trials conducted between 1970 and 2009 that evaluated the efficacy of naltrexone and acamprosate included 16 randomized controlled trials (4349 participants) comparing acamprosate with placebo and three randomized controlled trials (1210 participants) comparing naltrexone, acamprosate and placebo (*8*). Outcome measures included aggregate measures of abstinence and heavy drinking. For abstinence outcomes, acamprosate showed a significantly larger effect size than naltrexone (Hedges g 0.36, 95% CI 0.25 to 0.47 for acamprosate versus Hedges g 0.12, 95% CI 0.05 to 0.18 for naltrexone). The NNT for one additional case of abstinence was 8. For heavy drinking outcomes, naltrexone (Hedges g 0.19, 95% CI 0.12 to 0.25) showed a larger effect than acamprosate (Hedges g 0.07, 95% CI –0.08 to 0.22), however the difference was not statistically significant. The NNT to prevent one additional case of return to heavy drinking was 9.

A 2014 meta-analysis of 123 studies (22 803 participants) evaluated the benefits and harms of pharmacotherapy for alcohol use disorders and included 27 randomized controlled trials (7519 participants) comparing acamprosate and placebo (*9*). As in previous studies, acamprosate was associated with improvements in consumption outcomes compared with placebo. The risk difference (RD) for acamprosate for return to any drinking was –0.09 (95% CI –0.14 to –0.04; NNT = 12). Acamprosate did not reduce the risk of return to heavy drinking (RD –0.01, 95% CI –0.04 to 0.03).

A 2015 meta-analysis of 22 randomized controlled trials (5236 participants) evaluated the efficacy of acamprosate in the treatment of alcohol dependence and examined the variance in outcomes in Europe versus other countries (*10*). A significantly reduced risk of individuals returning to any drinking at 6 months follow-up was observed in the acamprosate group compared with placebo (RR 0.83, 95% CI 0.78 to 0.89). No difference in risk reduction was observed between European studies and studies outside of Europe.

A 2020 network meta-analysis of 64 randomized controlled trials compared interventions used in primary care for patients with alcohol dependency who recently underwent detoxification (*11*). Acamprosate was associated with increased probability of abstinence up to 12 months following detoxification compared with placebo (OR 1.86, 95% CI 1.49 to 2.33, corresponding to an absolute probability of 38%).

A 2022 systematic review and network meta-analysis of pharmacotherapies for alcohol use disorders included 35 randomized controlled trials comparing acamprosate with placebo (*12*). Acamprosate significantly improved both total abstinence (rate ratio 1.33, 95% CI 1.15 to 1.54) and reduce heavy drinking (rate ratio 0.78, 95% CI 0.70 to 0.86).

The combined pharmacotherapies and behavioural interventions study (COMBINE) was a multicentre, randomized controlled trial that compared the effectiveness of acamprosate with placebo and naltrexone (1383 participants). Patients received 16 weeks of treatment and were followed for 1 year after treatment completion (*13*). Participants were randomly assigned after 4 to 21 days of abstinence to receive either acamprosate, naltrexone, acamprosate in combination with naltrexone, or placebo, with or without a combined behavioural intervention. All treatment groups experienced an increase in percentage of days abstinent, from 25% pre-study to 73% during treatment. All groups receiving medicines or placebo showed improvements in abstinent days compared with the group who only received combined behavioural intervention. The strong placebo effect in this trial may have made it difficult to detect any additional effect of acamprosate. Additionally, this study began treatment after 4 days of abstinence whereas most positive studies of acamprosate had a longer pretreatment abstinence period.

Summary of evidence: harms

The application did not present a summary of evidence on the harms of acamprosate.

The most common adverse effect of acamprosate is diarrhoea, which is usually mild and self-limiting, but in some patients can be severe and persistent. Other less common adverse effects are suicidal ideation (infrequent but requires discontinuation), other gastrointestinal symptoms (intestinal cramps, flatulence and nausea), headache, dizziness, increased or decreased libido, insomnia, anxiety, muscle weakness and itchiness (*14*).

From the 2010 Cochrane systematic review, diarrhoea was the only adverse effect that occurred more frequently with acamprosate than placebo (risk difference 0.11, 95% CI 0.10 to 0.13; NNT for an additional case of diarrhoea = 10). The risk of drop-outs due to adverse events was significantly greater for acamprosate than placebo (RR 1.35, 95% CI 1.01 to 180), but the risk of drop-outs due to any cause was significantly lower with acamprosate (RR 0.91, 95% CI 0.83 to 0.99) (*7*).

Acamprosate is not metabolized in the liver and is excreted unchanged in the urine. The pharmacokinetics of acamprosate are not altered in patients with mild-to-moderate hepatic insufficiency, indicating that no dosage adjustments are necessary. However, there is risk of accumulation of acamprosate with prolonged administration of therapeutic doses in patients with renal impairment and the use of acamprosate is contraindicated in patients with severe renal impairment. Dosage adjustment is recommended for patients with moderate renal impairment (*15*).

Acamprosate is more effective if started after detoxification is completed, but its pharmacokinetics are not altered by co-administration with alcohol or benzodiazepines and can therefore be safely used before alcohol cessation and during relapse (*14–16*).

Acamprosate should be avoided in pregnant women unless benefits are considered to outweigh potential risks (*14*).

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a strong recommendation that combined psychosocial and pharmacological interventions should be offered for adults with alcohol dependence (moderate certainty of evidence). Pharmacological treatments considered included acamprosate, disulfiram and naltrexone (*17*).

Costs/cost–effectiveness

A health technology assessment performed by the National Institute for Clinical Excellence (NICE) in the United Kingdom found that the the incremental cost–effectiveness ratio of acamprosate and naltrexone compared with standard care were both within the cost–effectiveness threshold of £20 000 to £30 000 per quality-adjusted life year (QALY) (*18*). The finding was robust for various scenarios evaluated in the one-way sensitivity analysis.

Several modelling studies have evaluated the cost–effectiveness of acamprosate. A model from the perspective of the German health care system using data from a randomized controlled trial of acamprosate versus placebo which retrospectively applied costing demonstrated net savings with acamprosate (*19*). Another German study examined the lifetime cost–effectiveness of acamprosate and found that adjunctive acamprosate with standard counselling compared with counselling alone resulted in more life years gained (15.9 versus 14.6) and lower costs (*20*). Another model-based study from the Belgian health payers' perspective also showed cost savings with acamprosate (*21*). A modelling study using a hypothetical cohort and Scottish health service estimates found that acamprosate resulted in net savings compared with standard care (*22*).

A prospective study of costs from the perspective of German health insurance found that adjunctive acamprosate (with psychosocial rehabilitation support) resulted in higher abstinence and lower costs than psychosocial rehabilitation support alone (*23*).

A 2007 prospective cost and cost–effectiveness study of the COMBINE study interventions found three of the nine interventions to be cost-effective from the treatment provider perspective: medical management plus placebo; medical management plus naltrexone; and medical management plus naltrexone and acamprosate. Estimated treatment costs per patient were US$ 409, US$ 671 and US$ 1003, respectively, using 2007 costs (*24*).

An additional cost study using data from COMBINE examined the effect of treatment arms on social costs of alcohol dependence and outcomes at 3 years (in terms of health care use, arrests and motor vehicle incidents in the United States) (*25*). Median social cost savings comparing medical management and placebo were: US$ 2547 for medical management plus acamprosate; US$ 2991 for medical management plus naltrexone; US$ 3871 for medical management plus acamprosate and naltrexone; and US$ 3277 for medical management plus acamprosate plus cognitive behavioural interventions. A substantial effect on cost differences was related to the outcomes of arrests and motor vehicle incidents (*25*).

Availability

Acamprosate has regulatory approval globally for use in alcohol use disorder and is available in most countries in innovator and generic brands.

Committee recommendations

The Expert Committee noted the public health importance of treatment of alcohol dependence and harmful use of alcohol from a medical, social and economic perspective. Currently, only one in six people globally with alcohol use disorder receives treatment and rates are even lower in low- and lower middle-income countries.

The Committee recognized the need to identify and address the various factors that increase alcohol consumption and influence its effects, as well as the need to develop and implement appropriate policies to decrease the harmful use of alcohol. The Committee considered that the availability of pharmacotherapies for the treatment of alcohol use disorder should be seen as part of this complex strategy of interventions.

The Committee noted that evidence from several randomized clinical trials (6 to 12 months follow-up) was available, indicating acamprosate efficacy on abstinence rates compared with placebo. The magnitude of treatment effects appeared to be moderate, but the Committee considered the impact at the population level would be significant. Post-treatment follow-up studies have shown that the effects of acamprosate are maintained for up to 1 year after the last dose. Psychosocial interventions, such motivation enhancement and cognitive behavioural treatment improve the likelihood that people treated with acamprosate meet their goals for recovery. The Committee noted that acamprosate was generally well tolerated and its use did not require specialized supervision meaning acamprosate can be effectively and safely used in primary care and other community settings.

The Committee noted that in head-to-head trials that compared acamprosate with naltrexone, no statistically significant difference was found between the two medications for some outcomes (e.g. return to any drinking).

The Committee noted that acamprosate was one of the medicines recommended in the WHO mhGAP guidelines for treatment of alcohol use disorder and was also recommended in other international guidelines. The Committee considered that the availability of different medicines for alcohol use disorder would provide valuable options and choice for patients and clinicians. It could also facilitate increased market competition, reduce costs and improve affordable access for national health systems.

The Committee therefore recommended the inclusion of acamprosate on the core list of the EML for the treatment of alcohol use disorder in adults.

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Naltrexone – addition – EML

Naltrexone	ATC code: N07BB04

Proposal

Addition of naltrexone oral formulation and extended-release injection to the core list of the EML for maintenance treatment of alcohol use disorder in adults.

Applicant

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WHO technical department

The WHO Department of Mental Health and Substance Use reviewed and provided comments on the application. The technical unit stated that the application to include naltrexone on the EML was timely and in line with guidance provided by WHO global policy frameworks and action plans.

EML/EMLc

EML

Section

24.5.1 Medicines for alcohol use disorders

Dose form(s) & strengths(s)

Injection suspension (extended-release): 380 mg in vial

Tablet: 50 mg

Core/complementary

Core

Individual/square box listing

Individual

Background

Medicines for treatment of alcohol use disorders have not previously been evaluated for inclusion in the EML.

Public health relevance

Globally in 2016, alcohol use was the seventh leading risk factor for premature death and disability and was the leading risk factor in people aged 15 to 49 years. Worldwide, 2.8 million deaths were attributable to alcohol use. Alcohol consumption was shown to have a strong association with a higher risk of cancer, injuries and communicable disease (*1*).

The 2018 WHO *Global status report on alcohol and health* recognized that the harmful use of alcohol directly affects numerous targets of the Sustainable Development Goals including those for maternal and child health, infectious diseases, noncommunicable diseases, mental health, injuries and poisonings (*2*). Globally in 2016, estimates suggest that the harmful use of alcohol was responsible for 3 million deaths and caused 132.6 million disability-adjusted life years (DALYs) or 5.1% of total DALYs that year. The age-standardized burden of disease and injury associated with alcohol use varied geographically across WHO regions and was highest in the African region, where it was responsible for 70.6 deaths and 3044 DALYs per 100 000 people (*2*).

During the COVID-19 pandemic, a cross-sectional survey in the United States found that respondents reported consuming more drinks per day, more binge drinking and more alcohol consumption beyond recommended drinking limits than before the introduction of stay-at-home orders (*3*).

Summary of evidence: benefits

Systematic reviews and meta-analyses

A 2014 meta-analysis of 123 studies (22 803 participants) evaluated the benefits and harms of pharmacotherapy for alcohol use disorders and included 53 randomized-controlled trials (9140 participants) comparing naltrexone and placebo (*4*). Naltrexone was associated with improvement in alcohol consumption outcomes compared with placebo. Oral naltrexone 50 mg daily was associated with a reduced risk of return to any drinking (risk difference (RD) –0.05 (95% confidence interval (CI) –0.10 to –0.00; number needed to treat (NNT) to prevent return to any drinking = 20) and return to heavy drinking (RD –0.09, 95% CI –0.13 to –0.04; NNT to prevent return to heavy drinking = 12). A significant association was also found between oral naltrexone 50 mg daily and reduction in percentage of drinking days (weighted mean difference (WMD) –5.4, 95% CI –7.5 to –3.2) and percentage of heavy drinking days (WMD –4.1, 95% CI –7.6 to –0.6). Naltrexone extended-release injection was associated with a significant reduction in percentage of heavy drinking days (WMD –4.6, 95% CI –8.5 to –0.6), but no significant association was observed for return to any or heavy drinking.

Individual randomized trials

A double-blind, placebo-controlled randomized trial evaluated oral naltrexone 50 mg per day for 12 weeks as adjunct to standard rehabilitation treatment in 70 men who had undergone initial alcohol detoxification (*5*). Compared with placebo, naltrexone was associated with a significantly lower mean alcohol craving score (1.41 versus 3.42), non-significantly lower mean liver enzyme levels (aspartate aminotransferase: 23.6 U/L versus 50.4 U/L; gamma-glutamyl transferase 51.4 U/L versus 127.3 U/L) and significantly fewer drinking days (1.6% versus 8.3% of study days). Naltrexone treatment did not prevent study participants from sampling alcohol, however, it was associated with decreased subsequent drinking once drinking occurred (3.6% versus 14.0% of study days). Significantly fewer patients treated with naltrexone relapsed (23% versus 54%). Within the subgroup of patients who reported any drinking during the study period, significantly fewer patients treated with naltrexone relapsed (50% versus 95%).

A double-blind, placebo-controlled randomized trial of 12 weeks duration compared the additive effects of pharmacotherapy (oral naltrexone 50 mg daily versus placebo) and psychotherapy (coping skills training versus standard supportive therapy) in 97 patients with alcohol dependency (*6*). Rates of continuous abstinence over the study period were 61% for patients receiving naltrexone and supportive therapy, 28% for patients receiving naltrexone and coping skills training, 21% for patients receiving placebo and coping skills training and 19% for patients receiving placebo and supportive therapy. The rate of relapse, defined as drinking five or more (for men) or four or more (for women) drinks on an occasion, was 34% and 43% in the naltrexone and supportive therapy group and naltrexone and coping skills training group, respectively. Compared with patients treated with placebo, those receiving naltrexone drank on fewer study days (4.3% versus 9.9%) and consumed fewer standard drinks on average during the trial (13.7 versus 38.0).

The combined pharmacotherapies and behavioural interventions study (COMBINE) was a multicentre, randomized controlled trial that compared effectiveness of oral naltrexone with placebo and acamprosate (1383 participants). Patients received 16 weeks of treatment and were followed for 1 year after treatment completion (*7*). Participants were randomly assigned after 4 to 21 days of abstinence to receive either naltrexone, acamprosate, acamprosate and naltrexone in combination, or placebo, with or without a combined behavioural intervention. All treatment groups experienced an increase in percentage of days abstinent, from 25% pre-study to 73% during treatment. All groups receiving medicines or placebo showed improvements in abstinent days compared with the group who only received combined behavioural intervention. Naltrexone also reduced the risk of return to heavy drinking compared with placebo (hazard ratio (HR) 0.72, 97.5% CI, 0.53 to –0.98).

The PREDICT study was a double-blind, placebo-controlled randomized study in Germany that attempted to replicate the findings of the COMBINE study (*8*). As in COMBINE, participants (*n* = 426) received oral treatment with acamprosate, naltrexone or placebo. The primary outcome measure was time until the first occurrence of heavy drinking. No significant difference in time to first heavy drinking day was found between treatment groups. A subgroup analysis examined whether so-called reward drinking (drinking driven by positive reinforcement) versus so-called relief drinking (drinking driven by negative reinforcement) moderated treatment response (*9*). Participants who were predominantly reward drinkers who received naltrexone had an 83% lower likelihood of any heaving drinking during treatment compared with placebo. Greater effects of naltrexone in reward drinkers have subsequently been reported in other randomized trials (*10–12*).

A multicentre, randomized, double-blind, placebo-controlled trial evaluated the efficacy and tolerability of naltrexone extended release intramuscular injection in 627 adults with alcohol dependency (*13*). Participants were randomized to receive 190 mg or 380 mg long-acting naltrexone or a matching volume of placebo for 24 weeks and all received standardized supportive therapy. Rates of heavy drinking decreased in both active treatment groups. Those treated with naltrexone 380 mg had about a 25% greater reduction in the rate of heavy drinking relative to participants treated with placebo (HR 0.75, 95% CI 0.60 to 0.94). Subgroup analyses showed that treatment effects were greater in men and participants with lead-in abstinence receiving naltrexone.

A randomized, double-blinded, placebo-controlled trial evaluated the efficacy of combining extended-release naltrexone and behavioural harm reduction treatment for alcohol use disorder in 308 homeless adults with alcohol use disorders (*14*). Participants were randomized to receive: harm reduction treatment plus extended-release naltrexone 380 mg injection; harm reduction treatment plus placebo injection; harm reduction treatment alone; or usual supportive services (control group). Primary outcome measures were self-reported alcohol use (quantity and frequency), alcohol-related harm to oneself, and physical and mental health-related quality of life. Compared with the control group, participants receiving combined harm reduction treatment and naltrexone had significant improvements from baseline to 12 weeks post-treatment in peak alcohol quantity (Cohen's d –0.68), alcohol frequency (Cohen's d –0.16), alcohol-related harm (Cohen's d –0.56) and physical health-related quality of life (Cohen's d 0.43).

A systematic review and meta-analysis (seven randomized controlled trials, 1500 participants) evaluated the effect of extended-release naltrexone injection versus placebo on alcohol consumption in patients with alcohol use disorder, and determined the effects of lead-in abstinence and treatment duration on efficacy (*15*). For drinking days per month, the pooled WMD was –2.0

(95% CI –3.4 to –0.6) in favour of naltrexone. For heavy drinking days per month, the pooled WMD was –1.2 (95% CI –0.2 to –2.1) in favour of naltrexone. Trials in which lead-in abstinence was not an inclusion criteria and trials of duration of at least 3 months reported larger reductions in heavy drinking days per month with naltrexone: WMD –2.0 (95% CI –3.52 to –0.48) and –1.9 (95% CI –3.2 to –0.5), respectively.

Observational cohort studies

Cohort studies have been used to evaluate the effectiveness of treatment of alcohol use disorder on relevant health care outcomes (16,17). In a Swedish nationwide cohort study covering 10 years and 125 556 individuals with alcohol use disorder, 10 872 participants received treatment with naltrexone (16). Naltrexone in combination with acamprosate (HR 0.74, 95% CI 0.61 to 0.89) or disulfiram (HR 0.76, 95% CI 0.60 to 0.96) and as monotherapy (HR 0.89, 95% CI 0.81 to 0.97) was associated with a significantly lower risk of hospitalization due to alcohol use disorder compared with those time periods when the same individual did not use any treatment. Longer duration of naltrexone use was associated with lower risk of hospitalization due to alcohol use disorder. Naltrexone was also associated with a significantly decreased risk of hospitalization due to any cause when used in combination with acamprosate or disulfiram (HR 0.80, 95% CI 0.69 to 0.94 and HR 0.77, 95% CI 0.64 to 0.94, respectively) or used alone (HR 0.89, 95% CI 0.83 to 0.96).

Similarly, a cohort study of 127 480 patients in Boston, United States identified 9635 individuals with alcohol use disorder of whom 1135 had alcohol-related liver disease (17). Patients treated with naltrexone had significantly decreased odds of developing liver disease during follow-up compared with those who had no pharmacological treatment for alcohol use disorder (adjusted odds ratio (OR) 0.67, 95% CI 0.46 to 0.95) (17). For patients with a diagnosis of liver cirrhosis, those treated with naltrexone had significantly decreased odds of having hepatic decompensation compared with those who were untreated (adjusted OR 0.27, 95% CI 0.10 to 0.64).

Summary of evidence: harms

The application did not present a summary of evidence for the harms of naltrexone.

The most common adverse effects of naltrexone include nausea, vomiting, headache, dizziness, fatigue, nervousness, anxiety and somnolence. Injection site reactions have been reported with the extended-release injection formulation. Naltrexone should not be used if a patient is currently using opioids to avoid precipitating withdrawal. Naltrexone should be discontinued if there are anticipated opioid requirements within 7 days (18).

The United States Food and Drug Administration's approval label for naltrexone includes a black box warning about hepatotoxicity, which usually occurs at higher doses than those used in clinical practice. Due to hepatotoxicity and potential increases in levels of liver enzymes, liver function tests are recommended to be performed before starting treatment and at intervals of 1, 3 and 6 months, and then annually thereafter (or more frequently if baseline liver function tests are high). Naltrexone is contraindicated in patients with acute hepatitis or liver failure (*18*).

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a strong recommendation that combined psychosocial and pharmacological interventions should be offered for adults with alcohol dependence (moderate certainty of evidence). Pharmacological treatments considered included acamprosate, disulfiram and naltrexone (*19*).

Costs/cost–effectiveness

A 2007 prospective cost and cost–effectiveness study of the COMBINE study interventions found three of the nine interventions to be cost-effective from a treatment provider perspective: medical management plus placebo; medical management plus naltrexone; and medical management plus naltrexone and acamprosate. Estimated treatment costs per patient were US$ 409, US$ 671 and US$ 1003, respectively, using 2007 costs (*20*).

An additional cost study using data from COMBINE examined the effect of treatment arms on social costs of alcohol dependence and outcomes at 3 years (in terms of health care use, arrests, and motor vehicle incidents in the United States) (*21*). Median social cost savings comparing medical management and placebo were: US$ 2547 for medical management plus acamprosate, US$ 2991 for medical management plus naltrexone, US$ 3871 for medical management plus acamprosate and naltrexone, and US$ 3277 for medical management plus acamprosate plus cognitive behavioural interventions. A substantial effect on cost differences was related to the outcomes of arrests and motor vehicle incidents (*21*).

A health technology assessment by the National Institute for Clinical Excellence (NICE) in the United Kingdom found that the the incremental cost-effectiveness ratio of acamprosate and naltrexone compared with standard care were both within the cost–effectiveness threshold of £20 000 to £30 000 per quality-adjusted life year (QALY) (*22*). The finding was robust under various scenarios evaluated in the one-way sensitivity analysis.

The use of extended-release naltrexone injection was reported to cost significantly more than oral naltrexone. Studies report that individuals treated

with extended-release naltrexone had fewer alcohol-related inpatient days and more outpatient visits for treatment of alcohol use disorder than other medication regimens (*23*). Extended-release naltrexone was more likely to be refilled, was associated with fewer hospitalizations and – despite the higher cost for extended-release naltrexone itself – total health care cost was not different from that of oral naltrexone (*24*). Patients treated with extended-release naltrexone were also more likely to persist with pharmacotherapy compared with those treated with oral naltrexone, acamprosate or disulfiram thus resulting in lower non-pharmacy health care costs and use of inpatient and emergency services (*25*). In contrast to these findings, one retrospective study by a Veterans Affairs facility found that patients on extended-release naltrexone had higher health care utilization than those on oral naltrexone (*26*). A meta-analysis of health care utilization studies showed that extended-release naltrexone (1565 patients) had longer medication refill persistence and lower or as low health care utilization and costs compared with other pharmacotherapies for alcohol use disorder, including oral naltrexone (*27*). Randomized controlled data comparing extended-release naltrexone with oral naltrexone are lacking, although the results of one trial are pending which will analyse cost–effectiveness (*28*).

Availability

Oral naltrexone has regulatory approval globally for use in alcohol use disorder and is available in most countries in innovator and generic brands.

Naltrexone extended-release injection has regulatory approval for alcohol dependence in patients who can abstain from alcohol in an outpatient setting prior to initiation of treatment. It remains under patent protection in several jurisdictions.

Committee recommendations

The Expert Committee noted the public health importance of treatment of alcohol dependence and harmful use of alcohol from a medical, social and economic perspective. Currently, only one in six people globally with alcohol use disorder receives treatment and rates are even lower in low- and lower middle-income countries.

The Committee recognized the need to identify and address the various factors that increase alcohol consumption and influence its effects, as well as the need to develop and implement appropriate policies to decrease the harmful use of alcohol. The Committee considered that the availability of pharmacotherapies for the treatment of alcohol use disorder should be seen as part of this complex strategy of interventions.

The Committee noted that a large body of evidence confirmed that naltrexone improved alcohol consumption outcomes in patients with alcohol use

disorders compared with placebo. The magnitude of treatment effects appeared moderate, but the Committee considered the impact at the population level would be significant. The Committee noted that the benefits of naltrexone may be greater in people whose drinking is driven by positive reinforcement.

The Committee noted that naltrexone was generally well tolerated but has been associated hepatotoxic effects when used at higher doses for extended periods of time. The Committee noted that liver function tests should be performed before starting treatment and at regular intervals during treatment.

The Committee noted that injectable extended-release formulations of naltrexone were more costly than the oral formulation. However, the Committee considered that the possibility of monthly administration may increase treatment persistence in some patient subgroups.

The Committee noted that in head-to-head trials that compared naltrexone with acamprosate, no statistically significant difference was found between the two medications for some outcomes (e.g. return to any drinking).

The Committee noted that naltrexone was one of the medicines recommended in the WHO mhGAP guidelines for treatment of alcohol use disorder and was also recommended in other international guidelines. The Committee considered that the availability of different medicines for alcohol use disorder would provide valuable options and choice for patients and clinicians. It could also facilitate increased market competition, reduce costs and improve affordable access for national health systems.

The Committee therefore recommended the inclusion of naltrexone oral tablets and extended-release injection on the core list of the EML for use in the treatment of alcohol use disorder in adults.

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24.5.2 Medicines for nicotine use disorders

Nicotine replacement therapy – new formulation – EML

Nicotine replacement therapy	ATC code: N07BA01

Proposal

Addition of new formulations of nicotine replacement therapy (NRT) as lozenges and mouth spray on the core list of the EML for tobacco cessation in adults.

Applicant

Johnson & Johnson Consumer Inc., Skillman, NJ, United States of America

WHO technical department

The WHO Department of Health Promotion reviewed and provided comments on the application. The technical department supported the inclusion of nicotine lozenges and mouth spray on the EML and considered that their inclusion could help tobacco users to quit by providing a wider choice of NRT options. The technical department highlighted that the proposal was supported by great need among populations and the evidence of efficacy and comparative cost-effectiveness.

EML/EMLc

EML

Section

24.5.2 Medicines for nicotine use disorders (new subsection)

Dose form(s) & strengths(s)

Lozenge: 2 mg, 4 mg

Oromucosal spray: 1 mg per actuation

Core/complementary

Core

Individual/square box listing

Individual

Background

NRT as chewing gum and transdermal patch has been included on the EML since 2009. The Expert Committee recommended listing on the basis of public

health need, high-quality evidence of effectiveness, and acceptable safety and cost–effectiveness. Other formulations were not recommended for inclusion at the time because less evidence was available on comparative safety, effectiveness and cost in different populations (*1*).

Public health relevance

The public health relevance of smoking cessation interventions is well established and accepted. The tobacco epidemic is a major public health threat, killing more than 8 million people a year. In 2020, 22.3% of the world population used tobacco. More than 80% of global tobacco users live in low- and middle-income countries (*2*).

Summary of evidence: benefits

NRT – all forms

A 2018 Cochrane systematic review of 133 randomized controlled trials (64 640 participants) evaluated the effectiveness and safety of different NRT preparations compared with placebo or no NRT interventions for achieving long-term smoking cessation (*3*). The review included eight randomized controlled trials (4439 participants) on nicotine oral tablets/lozenges and one randomized controlled trial (542 participants) on nicotine mouth spray. The outcome measure evaluated was abstinence from smoking after at least 6 months of follow-up. The risk ratio (RR) of abstinence for any form of NRT compared with control was 1.55 (95% confidence interval (CI) 1.49 to 1.61). From a pooled analysis of the trials for oral tablets/lozenges, the RR for abstinence was 1.52 (95% CI 1.32 to 1.74). The RR for abstinence for mouth spray was 2.48 (95% CI 1.24 to 4.94). In comparison, the RRs for abstinence for the NRT forms currently included on the EML were 1.49 (95% CI 1.40 to 1.60) for nicotine gum (56 randomized controlled trials, 22 581 participants) and 1.64 (95% CI 1.53 to 1.75) for nicotine transdermal patch (51 randomized controlled trials, 25 754 participants). The authors concluded that there was high-quality evidence that NRT increased quit rates at 6 months or longer in adult smokers who were motivated to quit. Furthermore, the delivery form of NRT was unrelated to effectiveness, therefore preference, availability and cost might determine the form chosen. The quality of evidence was rated as high, based on Grading of Recommendations, Assessment, Development, and Evaluations (GRADE).

NRT mouth spray

A randomized controlled trial in the United States compared nicotine mouth spray with placebo in 1198 smokers motivated to quit (*4*). For the primary study endpoint of self-reported, objectively verified continuous abstinence from smoking from week 2 until week 6, 5.0% of participants in the intervention group

had quit smoking compared with 2.5% in the placebo group (RR 2.0, 95% CI 1.1 to 3.7). For the secondary study endpoint of self-reported, objectively verified continuous abstinence from smoking from week 2 until and including week 26, 3.4% of participants in the intervention group had quit smoking compared with 1.2% in the placebo group (RR 2.87, 95% CI 1.23 to 6.71).

A multicentre, randomized, double-blind efficacy and safety study compared nicotine mouth spray with placebo and evaluated self-reported, carbon monoxide-verified continuous abstinence from smoking in 479 smokers at clinics in Denmark and Germany (5). Study participants also received low-intensity counselling. Treatment with nicotine mouth spray was associated with significantly higher continuous abstinence rates than placebo at all time points: week 6 (26.1% versus 16.1%; RR 1.62, 95% CI 1.09 to 2.41), week 24 (15.7% versus 6.8%; RR 2.30, 95% CI 1.23 to 4.30) and week 52 (13.8% versus 5.6%; RR 2.48, 95% CI 1.24 to 4.94).

A 2010 randomized, within-subject, crossover trial compared the effects on craving, user satisfaction and consumption patterns of nicotine mouth spray 1 mg/dose, lozenge 2.5 mg, gum 4 mg, and placebo used for 8 hours after overnight tobacco abstinence (6). The study included 47 dependent adult smokers, and rated craving, irritability, concentration and restlessness before and during the first 60 minutes of product use on a 100-point visual analogue scale. Mean reductions in craving scores from baseline to 60 minutes were 28.6, 25.8, 24.7 and 8.9 points for mouth spray, gum, lozenge and placebo, respectively. Compared with placebo, nicotine mouth spray was associated with a significant reduction in craving scores within 5 minutes. Compared with nicotine gum, nicotine mouth spray was associated with a significant reduction in craving scores at time points up to 15 minutes. No significant differences were seen between active products. The authors concluded that the mouth spray may be particularly useful for acute craving relief.

A 2007 randomized study evaluated patient preference, safety and efficacy of nicotine mouth spray 1 mg/dose, nicotine gum 2 mg and nicotine inhaler 10 mg for 12 weeks in 100 adult smokers motivated to quit (7). The results of the efficacy analysis for continuous abstinence at 12 weeks were 16% for the mouth spray, 20% for the gum and 8% for the inhaler. At 12 months, continuous abstinence rates were 12%, 8% and 4% for the mouth spray, gum and inhaler, respectively. Point-prevalence abstinence rates at 12 months were 16%, 8% and 4% for the mouth spray, gum and inhaler, respectively. Results for patient preference showed that 54% of participants preferred the mouth spray, 28% preferred the inhaler and 18% preferred gum. Direct comparisons significantly favoured mouth spray over gum and mouth spray over inhaler.

Summary of evidence: harms

A number of adverse effects are commonly associated with NRT use, however serious adverse effects are rare. The adverse effects associated with NRT are due

to the pharmacological action of nicotine as well as the mode and site of the NRT application.

A 2010 systematic review and meta-analysis of 92 randomized clinical trials of NRT versus inert controls (32 185 participants) and 28 observational studies (145 205 participants) evaluated the magnitude of reported adverse effects with NRT (*8*). Pooled evidence from the randomized controlled trials of various formulations of NRT found that NRT was associated with a significantly increased risk of heart palpitations and chest pain (odds ratio (OR) 2.06, 95% CI 1.51 to 2.82), nausea and vomiting (OR 1.67, 95% CI 1.37 to 2.04), gastrointestinal complaints (OR 1.54, 95% CI 1.25 to 1.89) and insomnia (OR 1.42, 95% CI 1.21 to 1.66). Orally administered NRT formulations were associated with significantly increased risk of hiccups (OR 7.68, 95% CI 4.59 to 12.85), cough (OR 2.89, 95% CI 1.92 to 4.33), mouth and throat soreness (OR 1.87, 95% CI 1.36 to 2.57), and mouth ulcers (OR 1.49, 95% CI 1.05 to 2.20). NRT transdermal patches were associated with a significant increase in skin irritations (OR 2.80, 95% CI 2.28 to 3.24). No significantly increased risk in anxiety or depressive symptoms was observed for NRT use.

The 2018 Cochrane review supported these earlier safety findings, stating that adverse events from using NRT were related to the type of product and included skin irritation from patches and irritation to the inside of the mouth from gum and tablets (*3*). Attempts to quantitatively synthesize the incidence of various adverse effects were hindered because of the wide variation in reporting the nature, timing and duration of symptoms. The OR of chest pains or palpitations for any form of NRT relative to control was 1.88 (95% CI 1.37 to 2.57; 15 trials, 11 074 participants). However, chest pains and palpitations were rare in both groups and serious adverse events were extremely rare.

The 2018 Cochrane review described the most common adverse events associated with nicotine gum to be hiccups, gastrointestinal disturbances, jaw pain and orodental problems. For nicotine patches, skin sensitivity and local irritation was common, affecting up to 54% of users, but it was usually mild and rarely led to treatment discontinuation. The main adverse events associated with nicotine inhaler and oral or nasal sprays were local irritation at the site of administration (e.g. throat irritation, coughing, burning in the mouth and hiccups).

These findings are supported by data synthesized by the applicants from randomized clinical trials of oromucosal nicotine formulations (gum and lozenges) for smoking cessation.

WHO guidelines

WHO guidelines for tobacco cessation in adults to guide proper use of tobacco cessation medications including NRT are currently in development and are expected to be published in late 2023.

Costs/cost–effectiveness

Evidence for the comparative cost–effectiveness of nicotine lozenges and mouth spray was not presented in the application.

From pricing data purchased and reported by the applicants, available globally representative pricing data show that NRT lozenge is sold at an average cost of US$ 0.42 per piece (22% less than gum) and a weighted average daily cost of US$ 3.41 a day (9% less than gum), while NRT mouth spray is sold at an average cost of US$ 0.37 per spray and an estimated daily cost of US$ 6.06 (based on 30 sprays a day, which is consistent with dosage for a moderate cigarette smoker).

Availability

The Johnson & Johnson brand of nicotine lozenge has regulatory approval in 26 (predominantly high-income) countries. Generic brands of nicotine lozenge are available in some countries.

The Johnson & Johnson brand of nicotine mouth spray has regulatory approval in 54 (predominantly high- and upper middle-income) countries. Generic brands of nicotine mouth spray are available in some countries.

Other considerations

In August 2023, WHO issued the first invitation to manufacturers of medicinal products for treatment of disorders caused by the use of tobacco to submit an expression of interest for WHO prequalification. Medicinal products in the invitation included NRT such as chewing gum 2 mg and 4 mg, and transdermal patches 5 mg to 25 mg/16 hours and 7 mg to 21 mg/24 hours (*9*).

Committee recommendations

The Expert Committee acknowledged the substantial public health burden posed by smoking and the need for effective smoking cessation treatments. Smoking is the most important modifiable risk factor of morbidity and mortality and is associated with negative outcomes in a range of diseases. The Committee considered that adding additional smoking cessation options to the EML could be an important step in increasing access to smoking cessation treatment.

The Committee considered that the evidence presented in the application supported the effectiveness of all forms of NRT in increasing abstinence and cessation rates. The Committee also noted that there did not appear to be significant differences in efficacy between different NRT formulations. With regard to safety, the Committee noted that the adverse effects associated with NRT were well known and generally acceptable. The Committee considered that the benefits of treatment in helping users to achieve abstinence and cessation were sufficient to outweigh the risks, and that the balance of benefits and harms was favourable.

The Committee recognized that smoking cessation interventions were among the most cost-effective public health interventions. The Committee recalled that NRT was considered to be cost-effective by the 2009 Expert Committee when NRT as gum and transdermal patches were recommended for addition to the EML. The Committee considered that the availability of different forms of NRT would provide options and choice for patients and clinicians, and could facilitate increased market competition, reduce costs and improve affordable access for health systems.

The Committee also welcomed the information from the WHO Department of Health Promotion that WHO guidelines for tobacco cessation were in development.

Based on these considerations, the Expert Committee recommended the inclusion of nicotine lozenges and mouth spray on the core list of the EML as additional forms of NRT for tobacco and smoking cessation.

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Section 29: Medicines for diseases of joints
29.3 Juvenile joint diseases

Anakinra – addition – EML and EMLc

Anakinra	ATC code: L04AC03

Proposal

Addition of anakinra to the complementary list of the EML and the EMLc for the treatment of systemic-onset juvenile idiopathic arthritis (JIA) with macrophage activation syndrome.

Applicant

Paediatric Global Task Force for Musculoskeletal Health

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

29.3 Juvenile joint diseases

Dose form(s) & strengths(s)

Injection: 100 mg/0.67 mL in a prefilled syringe

Core/complementary

Complementary

Individual/square box listing

Individual

Background

An application for the inclusion of anakinra, an interleukin-1 receptor antagonist, for the treatment of children with systemic onset JIA with macrophage activation syndrome was evaluated by the Expert Committee in 2021. Listing was not recommended at the time because of uncertainties about the estimates of clinical benefit and concerns about affordability and access to specialist medical services in lower-resource settings.

The Committee noted that macrophage activation syndrome is a rare but serious condition involving excessive immune activation that can occur in children

with systemic-onset JIA, and that it is associated with high short-term mortality, especially if untreated. The Committee noted that the application reported data only from uncontrolled cohort studies or case series, most of which enrolled only a small number of patients. The Committee considered that extrapolating clinical benefits and potential harms of anakinra and comparing anakinra with other potentially relevant therapeutic alternatives based on this type of evidence was difficult. The Committee also noted that anakinra was often highly priced, with potentially important limitations in accessibility and affordability at the country level. The Committee further acknowledged the limited availability of specialist paediatric rheumatologists in many settings (*1*).

Public health relevance

JIA is the most common chronic rheumatic disease in children, with a prevalence of about 1 in 1000 children (*2*). In 2017, more than 2 million children younger than 16 years worldwide were estimated to have JIA, with the highest prevalence in south Asia and Africa (*3*). The disease is characterized by joint inflammation lasting more than 6 weeks, onset before the age of 16 years and no other identifiable cause (*4–6*).

Untreated disease can have severe consequences, including pain, fatigue, joint damage, functional disability and impaired quality of life. JIA can also lead to anaemia, poor growth, delayed puberty and complications such as uveitis, which can cause blindness if not detected and treated (*5–7*). The impact of untreated JIA extends to difficulties in walking, performing daily activities and educational participation, which can result in psychosocial challenges, mental health problems and higher unemployment rates compared with healthy peers (*8–10*).

Access to proper care for children with JIA is a major challenge, particularly in resource-constrained settings (*11*). The shortage of paediatricians, especially in Asia and Africa, contributes to limited access to specialist care and treatment for many children with JIA, resulting in worse clinical outcomes in these regions (*7,12*).

Systemic-onset JIA is the rarest subtype of the disease. It is characterized by arthritis, fever, rash and systemic inflammation, and is considered an autoinflammatory syndrome (*13,14*). The age at onset is typically 1–5 years (*15*) and it imposes a significant disease burden as patients usually require treatment for months to years after the onset of symptoms, as well as close monitoring for complications or flare-ups of the disease. Systemic-onset JIA is reported to account for 4–9% of cases of JIA in European countries – a population-based study in five Nordic countries reported an incidence of 0.6 per 100 000 children per year (*16*). Systemic-onset JIA is more common in other geographical settings, representing up to 25% and 50% of JIA cases in India and Japan, respectively (*14*). Uncontrolled inflammation in systemic-onset JIA carries a significant risk of high morbidity

and potential mortality from macrophage activation syndrome, an uncontrolled cytokine storm (*14,17,18*). A study in the United Kingdom found higher mortality rates in people with systemic-onset JIA compared with people with other forms of JIA (*19*). Macrophage activation syndrome has been reported to affect about 33% of patients with systemic-onset JIA (*20*) and has a fatality rate of up to 23% (*21*).

Summary of evidence: benefits

The application presented a review of the available evidence on the use of anakinra for systemic-onset JIA and macrophage activation syndrome in systemic-onset JIA. It asserted that the most important way to treat macrophage activation syndrome in systemic-onset JIA was to control the underlying inflammation caused by the disease.

Anakinra in systemic-onset JIA

Randomized trials

A multicentre, randomized, double-blind trial compared the efficacy of 1-month treatment with anakinra (2 mg/kg daily, up to a maximum of 100 mg) versus placebo in 24 patients with systemic-onset JIA (*22*). Response was defined as a 30% improvement in the paediatric American College of Rheumatology criteria for JIA (ACRpedi 30), absence of disease-related fever and a decrease of at least 50% of both C-reactive protein and erythrocyte sedimentation rate compared with baseline. After 1 month, a response was observed in 67% (8/12) of patients in the anakinra arm and 8% (1/12) of patients in the placebo arm ($P = 0.003$). An open-label treatment period followed the first part of the trial, in which all patients received anakinra for up to 12 months. Two patients from the placebo group stopped treatment during the first month of treatment due to injection pain and withdrew from the trial. Nine of the remaining 10 patients who switched to anakinra had responded at month 2. Seventeen patients continued in the trial until month 6, of whom six responded. Sixteen patients continued in the trial for 12 months, of whom seven responded. The authors concluded that anakinra treatment was effective in the treatment of systemic-onset JIA, at least in the short term.

Non-randomized trials

A 5-year follow-up, single-centre, prospective study in the Netherlands (Kingdom of the) evaluated anakinra as first-line monotherapy in 42 patients (age range 3.9–11.8 years) with active systemic-onset JIA (*23*). The median time to achieve clinically inactive disease was 33 days. For children who had inactive disease at 3 months, anakinra was tapered and ultimately stopped. At 1 year, 76% of all the children had inactive disease, and 52% of the children who had stopped receiving medication earlier continued to have inactive disease. Factors positively associated with inactive disease at 1 year included high neutrophil count at baseline and complete response after 1 month of anakinra treatment. After 5 years of follow-up,

96% of all the patients had inactive disease, and 75% continued to have inactive disease while not receiving medication. Articular or extra-articular damage was reported in < 5% of patients and only 33% received glucocorticoids. Treatment with anakinra was equally effective in systemic-onset JIA patients without arthritis at disease onset. The authors concluded that "treatment to target" (where disease activity is accurately monitored and clinical remission is actively pursued by regular adjustment of therapy, starting with first-line, short-course monotherapy with anakinra) is a highly effective strategy to induce and sustain inactive disease and to prevent damage from the disease and glucocorticoids.

A single-centre retrospective study in Italy evaluated 25 patients with systemic-onset JIA treated with anakinra for at least 6 months (*24*). The median age at disease onset was 5.8 years and the median age at start of treatment was 7.3 years. Of note, 14 patients were receiving concomitant glucocorticoids, nine patients were receiving concomitant disease-modifying antirheumatic drugs (methotrexate or ciclosporin) and six patients had previously received biological agents (etanercept, abatacept and infliximab). After 6 months of anakinra treatment, 14 (56%) patients had clinically inactive disease (defined as the absence or rash, fever and active arthritis), which was reached at a median of 2.1 months after the start of treatment. Clinically inactive disease was maintained in all 14 patients at median follow-up of 2.8 years. Nine patients were able to withdraw from anakinra and five continued with anakinra monotherapy. No cases of macrophage activation syndrome were observed during anakinra treatment. Demographic characteristics and clinical and laboratory features at baseline were also compared in responders and non-responders: no differences were observed in the number of active joints before starting anakinra or concomitant glucocorticoid treatment. The only variable significantly associated with response was the time from disease onset to receiving anakinra, with earlier treatment being associated with a better outcome.

An international multicentre series assessed the use of anakinra as first-line disease-modifying therapy in 46 children with systemic-onset JIA (*25*). Among the 46 children studied, 10 received anakinra monotherapy, 21 received anakinra plus corticosteroids, five received anakinra plus disease-modifying antirheumatic drugs and 10 received anakinra plus corticosteroids and disease-modifying antirheumatic drugs. Outcomes were evaluated after a median follow-up of 14.5 months. Fever and rash resolved within 1 month in more than 95% of patients, while C-reactive protein and ferritin normalized within this time in more than 80% of patients. Active arthritis persisted in 39% of patients at 1 month, in 27% of patients at 3 months and in 11% of patients at more than 6 months of follow-up. Almost 60% of patients, including eight of 10 receiving anakinra monotherapy, attained a complete response without escalation of therapy. Disease characteristics and treatment were similar in partial and complete responders, except that partial responders were markedly younger at

onset of the disease (median age 5.2 years versus 10.2 years, $P = 0.004$). Eleven episodes of macrophage activation syndrome (in nine patients) were observed, six episodes at presentation and five episodes after starting anakinra during the study. Anakinra effectively managed five out of the six cases of macrophage activation syndrome at presentation; increasing doses of anakinra and additional agents such as steroids and ciclosporin A were used to control these episodes.

A retrospective case series in the United States evaluated the effect of anakinra on disease activity and corticosteroid dose in 33 patients with systemic-onset JIA (*26*). The median duration of systemic-onset JIA before treatment was 29 months and most patients had used more than one other medication before starting anakinra: prednisone (94%), methotrexate (76%), tumour necrosis factor inhibitors (61%), ciclosporin (36%) and cyclophosphamide (6%). Anakinra treatment was associated with a reduction in corticosteroid dosage and erythrocyte sedimentation rate and increases in haemoglobin and albumin, all indicators of response to therapy. Large joint arthritis counts decreased after 3–4 months but not small joint counts. More significant decreases in erythrocyte sedimentation rates from pre- to post-treatment (1–2 months) were seen in patients on high doses of anakinra than those on low doses, implying a dose–response effect. Fever and rash, present in seven cases before treatment, resolved in all cases. Eight patients had periods of arthritis, one developed macrophage activation syndrome and another Epstein–Barr virus infection.

A single-centre series in Germany reported on four patients who received anakinra as first-line therapy for systemic-onset JIA (*27*). The median age of the patients was 4.6 years (range 2.75–9.25 years). The mean follow-up time was 13.5 months (range 2–50 months). Anakinra was started at doses from 1.5 to 4 mg/kg for a median duration of 3 (range 3–18) months. Two patients responded to anakinra monotherapy and two cases required corticosteroids. Normalized body temperature and the absence of evanescent rashes were achieved after a median of 4 (range 2–10) days.

Macrophage activation syndrome in systemic-onset JIA

A single-centre study in Türkiye evaluated the use of anakinra to treat macrophage activation syndrome in 15 hospitalized paediatric patients, 13 with systemic-onset JIA and two with other autoinflammatory diseases (*28*). Nineteen episodes of macrophage activation syndrome were observed in the 15 patients. Anakinra (2 mg/kg a day) was started within a median of 1 day of admission. Clinical symptoms resolved within a median (range) of 2 (1–4) days of the introduction of anakinra and laboratory findings normalized within a median of 6 (4–9) days. Corticosteroid treatment was stopped within a median of 10 (4–13) weeks of starting anakinra. Patients were followed for a median of 13 (6–24) months. Two patients developed recurrent macrophage activation syndrome episodes when the anakinra dose was reduced, while the other patients achieved remission.

A retrospective case series in Canada reported on the use of anakinra in 12 children with macrophage activation syndrome related to paediatric rheumatic disease (eight due to systemic onset JIA) in whom treatment with corticosteroids and other immunosuppressants had provided only limited benefit (*29*). Five patients required intensive care. Anakinra 2 mg/kg/day was added to pre-existing therapy. All patients achieved remission of macrophage activation syndrome within a median of 13 (range 2–19) days. Corticosteroids were discontinued within 6 weeks for seven patients. Over a median follow-up of 22 (range 2–40) months, all patients remained in remission from macrophage activation syndrome at the final follow-up and had effective control of their underlying rheumatic disease.

Summary of evidence: harms

Adverse effects associated with anakinra include gastrointestinal disturbances (nausea, vomiting and diarrhoea), headache, abdominal pain, upper respiratory and urinary tract infections, and neutropenia (*30*).

In the multicentre, randomized trial of anakinra, 14 adverse events were reported in patients receiving anakinra in the double-blind phase, with injection pain being the most common adverse event, followed by post-injection erythema and infections. No serious adverse events were reported. During the open-label phase, 89 adverse events were reported, of which five were considered serious. The most common adverse events were infections, followed by injection pain and post-injection erythema. Six patients discontinued treatment: two due to adverse events; two due to lack of efficacy; and two due to a disease flare (*22*).

In the international multicentre series of anakinra as first-line treatment of systemic-onset JIA in 46 children, adverse events included injection site reactions (20 cases), serious infections (three cases), elevated liver enzymes (two cases), hepatitis (one case) and mild asymptomatic neutropenia (one case) (*25*).

In the single-centre case series in Germany that assessed the efficacy and safety of first-line anakinra treatment no reported treatment-related adverse reactions were observed other than local injection-site inflammation (*27*). Similarly, the Canadian case series on the effect of anakinra in 12 children with macrophage activation syndrome, no adverse effects were reported from anakinra administration (*29*).

A prospective, open-label, single-centre, clinical cohort study from the United States investigated the long-term safety of anakinra treatment for up to 5 years in 43 patients with cryopyrin-associated periodic syndromes (*31*). Safety was evaluated using adverse event reports, laboratory assessments, vital signs and diary reports. In total, 1233 adverse events were reported during the study, with a yearly rate of 7.7 adverse events per patient. The event rate decreased over time and dose escalation during the study did not affect the frequency of adverse events. Anakinra had similar safety profiles in adults and children. The most frequently reported adverse events were typical symptoms of cryopyrin-associated periodic

syndrome such as headache and arthralgia. Injection site reactions occurred mainly during the first month of treatment. A total of 24 serious adverse events were reported in 14 patients, which all resolved during the study period. The most commonly reported serious adverse events were infections (pneumonia and gastroenteritis). Other serious adverse events included post-lumbar puncture headaches and one episode of macrophage activation syndrome triggered by infection (which was alleviated with temporary corticosteroid therapy). No permanent treatment discontinuation occurred due to adverse events.

WHO guidelines

WHO guidelines for the treatment of systemic-onset JIA and macrophage activation syndrome in systemic-onset JIA are not currently available.

Costs/cost–effectiveness

No comparative cost–effectiveness studies of anakinra for the treatment of macrophage activation syndrome in systemic-onset JIA were identified in the application.

The application described the unit cost of anakinra 100 mg subcutaneous injection as Aus\$ 53.00 in Australia, Can\$ 41.10 in Canada, £26.23 in the United Kingdom and US\$ 142.50 in the United States. Corresponding annual drug treatment costs for a 50 kg child would be Aus\$ 19 345–38 690, Can\$ 15 001–60 006, £9574–38 296 and US\$ 52 013–208 050.

Availability

Anakinra has regulatory approval as a treatment for systemic-onset JIA in Australia, Austria, Belgium, Bulgaria, Canada, Cyprus, Czechia, Denmark, Estonia, Finland, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands (Kingdom of the), Norway, Poland, Portugal, Romania, Slovenia, Slovakia, Spain, Sweden, United Kingdom and the United States of America.

Anakinra does not yet have regulatory approval as a treatment for macrophage activation syndrome.

Anakinra is not widely available globally and there are reports of recent supply issues stemming from its use in clinical trials for the treatment of complications related to COVID-19 that are similar to macrophage activation syndrome (cytokine storm).

Other considerations

Diagnosis, monitoring and use

The diagnosis of macrophage activation syndrome in systemic-onset JIA is based on defined criteria (*18*) validated in clinical practice (*32,33*). Macrophage activation

syndrome is a life-threatening cytokine storm (*34*), often triggered by infection, which is of particular concern in resource-constrained settings, where access to specialist paediatric rheumatologists, multidisciplinary teams and treatments are challenges. Such inequity further contributes to the burden of disease and long-term disability (*35*). The diagnosis of macrophage activation syndrome, evaluation of its severity and monitoring of response to treatment are assessed using blood markers of inflammation (C-reactive protein and full blood counts) as well as specific markers of macrophage activation syndrome (ferritin, triglycerides, liver function tests and clotting profiles) (*32,33*). Monitoring of anakinra treatment follows the routine monitoring of systemic-onset JIA in acute disease flare-up, concomitant infection or where macrophage activation syndrome is suspected (*32,33*).

Use of anakinra in acute macrophage activation syndrome in systemic-onset JIA is limited to highly specialized care in tertiary facilities. Its use in systemic-onset JIA outside of the hospital setting requires specialized training of caregivers and adequate storage conditions. The medication must be stored in cold temperatures (2–8 °C), and parents and caregivers need training in administration and to have suitable cold storage facilities available.

Tuberculosis risk

Awareness of the risk of tuberculosis in patients with JIA receiving treatment with anakinra or other biological disease-modifying antirheumatic drugs is of particular importance in resource-constrained settings with high rates of tuberculosis (*35*). Patients starting immunosuppressive treatments should undergo tuberculosis testing, although this might not be feasible during acute presentations of macrophage activation syndrome. The American College of Rheumatology suggests that low-risk children with negative initial tuberculosis screening should be retested if their tuberculosis risk changes (*36*). It is also recommended that patients with JIA with a positive tuberculosis test receive appropriate prophylaxis for tuberculosis (as per current national and/or international guidelines): at the start of biological therapy; during biological therapy; when a previously negative purified protein derivative test converts to positive at the mandatory annual tuberculosis screening; and if the patient has a new exposure to tuberculosis (*35*).

Committee recommendations

The Expert Committee acknowledged that macrophage activation syndrome was a rare and potentially life-threatening uncontrolled cytokine storm that occurred in up to one third of patients with systemic-onset JIA, and that it was associated with a fatality rate of over 20%. The Committee noted that early detection and treatment of systemic-onset JIA was essential to improve clinical outcomes and reduce the risk of macrophage activation syndrome.

The Committee noted that, as was the case in 2021, the clinical evidence for the benefit of anakinra in both systemic-onset JIA and macrophage activation syndrome in systemic-onset JIA was limited and derived primarily from small uncontrolled studies and case series, with only one small short-term randomized trial identified in the narrative review provided with the application. The Committee also noted that anakinra did not have regulatory approval for the requested indication from national regulatory authorities and had only a weak recommendation suggesting its use in the 2013 JIA guidelines of the American College of Rheumatology.

The Committee also noted that safety data for anakinra were still limited and concerns remained about the safe use of the medicine, particularly in settings with high rates of infection, especially for tuberculosis. The Committee acknowledged that anakinra for the treatment of macrophage activation syndrome should be only used in specialized tertiary care facilities by appropriately trained clinical personnel, and noted the limited availability of specialist paediatric rheumatologists in resource-limited settings. The high price and limited availability of anakinra in low- and middle-income countries was also a concern.

Therefore, the Expert Committee did not recommend the inclusion of anakinra for treatment of systemic-onset JIA with macrophage activation syndrome. As was the case when anakinra was considered for this indication in 2021, the Expert Committee considered that the clinical benefits and safety of this medicine (including risk of infection) remained uncertain based on the limited available evidence. The Committee also considered that the feasibility of use of anakinra, particularly in resource-constrained settings, was unlikely unfeasible given the current high price, limited availability, and requirements for specialized care, monitoring and management of adverse events.

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Tocilizumab – addition – EML and EMLc

Tocilizumab	ATC code: L04AC07

Proposal

Addition of tocilizumab to the complementary list of the EML and EMLc for the treatment of systemic-onset juvenile idiopathic arthritis (JIA).

Applicant

Paediatric Global Musculoskeletal Task Force

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

29.3 Juvenile joint diseases

Dose form(s) & strengths(s)

Injection (subcutaneous): 162 mg/0.9 mL in prefilled syringe

Injection (intravenous): 80 mg/4 mL in 4 mL vial, 200 mg/10 mL in 10 mL vial, 400 mg/20 mL in 20 mL vial

Core/complementary

Complementary

Individual/square box listing

Individual

Background

An application requesting the inclusion of tocilizumab, a monoclonal antibody against the interleukin-6 receptor, for the treatment of children with systemic-onset JIA was evaluated by the Expert Committee in 2021. Listing was not recommended at that time because of uncertainties about the estimated clinical benefits, as well as concerns about accessibility and affordability in different settings, given the high costs of the medicine.

The Committee acknowledged that management of systemic-onset JIA with disease-modifying therapy had the potential to minimize the severe side-effects of corticosteroids and noted that antitumour necrosis factor medicines

were included on the Model Lists for JIA in 2019. The Committee noted that while antitumour necrosis factor medicines have proven efficacy in many subtypes of JIA, they may be less effective for patients with systemic-onset disease, and that anti-interleukin-6 receptor monoclonal antibodies such as tocilizumab are preferred as the first-line option in some guidance documents. However, the Committee considered that the comparative benefit of tocilizumab virus antitumour necrosis factor agents was uncertain because of the low quality of the evidence presented in the application. The Committee also noted that the evidence from the randomized trials presented in the application supported tocilizumab as an effective treatment for systemic-onset JIA, but that all this evidence came from trials and studies conducted in well resourced settings, and that the generalizability of the findings to resource-constrained settings was uncertain.

The Committee acknowledged the multiple disease-modifying therapies being used in clinical practice for systemic-onset JIA and requested that a comprehensive evaluation of all medicines used to treat this disease be undertaken for future consideration (*1*).

Public health relevance

JIA is the most common chronic rheumatic disease in children, with a prevalence of about 1 in 1000 children (*2*). In 2017, more than 2 million children younger than 16 years worldwide were estimated to have JIA, with the highest prevalence in south Asia and Africa (*3*). The disease is characterized by joint inflammation lasting more than 6 weeks, onset before the age of 16 years and no other identifiable cause (*4–6*).

Untreated disease can have severe consequences, including pain, fatigue, joint damage, functional disability and impaired quality of life. JIA can also lead to anaemia, poor growth, delayed puberty and complications such as uveitis, which can cause blindness if not detected and treated (*5–7*). The impact of untreated JIA extends to difficulties in walking, performing daily activities and educational participation, which can result in psychosocial challenges, mental health problems and higher unemployment rates compared with healthy peers (*8–10*).

Access to proper care for children with JIA is a major challenge, particularly in resource-constrained settings (*11*). The shortage of paediatricians, especially in Asia and Africa, contributes to limited access to specialist care and treatment for many children with JIA, resulting in worse clinical outcomes in these regions (*7,12*)

Systemic-onset JIAs is the rarest subtype of the disease. It is characterized by arthritis, fever, rash and systemic inflammation, and is considered an autoinflammatory syndrome (*13,14*). The age at onset is typically 1–5 years (*15*) and it imposes a significant disease burden as patients usually require treatment for months to years after the onset of symptoms, as well as close monitoring for complications or flare-ups of disease. Systemic-onset JIA is reported to account

for 4–9% of JIA cases in European countries – a population-based study in five Nordic countries reported an incidence of 0.6 per 100 000 children per year (*16*). Systemic-onset JIA is more common in other geographical settings, representing up to 25% and 50% of JIA cases in India and Japan, respectively (*14*). Uncontrolled inflammation in systemic-onset JIA carries a significant risk of high morbidity and potential mortality from macrophage activation syndrome, an uncontrolled cytokine storm (*14,17,18*). A study in the United Kingdom found higher mortality rates in people with systemic-onset JIA compared with people with other forms of JIA (*19*).

Summary of evidence: benefits

The following data were also reported in the 2021 application for tocilizumab for systemic-onset JIA.

Systematic reviews and meta-analyses

A 2016 systematic review and meta-analysis of five placebo-controlled randomized trials (one each for anakinra, canakinumab and tocilizumab, two for rilonacept; 458 participants) aimed to define the optimal biological agent for systemic-onset JIA based on safety and efficacy data (*20*). The primary efficacy outcome was a 30% improvement from baseline according to the modified American College of Rheumatology Paediatric 30 response criteria (ACR Pedi 30). Outcomes were analysed by pairwise and network meta-analyses. While all treatments were more effective than placebo, there was low-quality evidence from the network meta-analysis that patients treated with rilonacept were less likely to respond than those treated with canakinumab (odds ratio (OR) 0.10, 95% confidence interval (CI) 0.02 to 0.38) or tocilizumab (OR 0.12, 95% CI 0.03 to 0.44).

A 2020 meta-analysis of 19 randomized controlled trials (11 parallel trials (754 participants) and eight withdrawal trials (704 participants)) assessed the net benefit of biological agents used in JIA (abatacept, adalimumab, anakinra, canakinumab, etanercept, infliximab, rilonacept and tocilizumab) (*21*). The efficacy outcome was ACR Pedi 30 and the safety outcome was serious adverse events. Net benefit was determined by subtracting the risk difference of safety from the risk difference of efficacy. In systemic-onset JIA, the net benefit was 22.8% for rilonacept, 54.5% for tocilizumab and 70.3% for canakinumab in parallel trials, and 32.3% for canakinumab and 58.2% for tocilizumab in withdrawal trials.

A 2017 systematic review of 25 randomized and non-randomized studies (more than 4000 participants) evaluated the efficacy of different biological therapies in JIA subtypes, including in people with systemic-onset JIA (*n* = 1185) (*22*). Over 12 weeks, systemic-onset JIA was less responsive to etanercept (ACR30 58% to 78%) compared with tocilizumab (ACR30 85%). Longer-term responses over 12 months were similar for the two treatments (ACR30 83% to 100% for etanercept versus 87% to 98% for tocilizumab).

Individual randomized trials comparing tocilizumab to placebo

A randomized, double-blind, placebo-controlled, withdrawal phase III trial evaluated the efficacy and safety of tocilizumab in 56 children aged 2–19 years with systemic-onset JIA not responding to disease-modifying antirheumatic drugs and biological agents (*23*). After an initial open-label lead-in phase where all participants were given tocilizumab (three intravenously administered doses of 8 mg/kg every 2 weeks), ACR Pedi 30, 50 and 70 responses were achieved by 51 (91%), 48 (86%) and 38 (68%) of patients, respectively. Thereafter, 43 participants who had achieved both an ACR Pedi 30 response and C-reactive protein concentrations of less than 5 mg/L were randomized to receive tocilizumab or placebo in a double-blind phase for 12 weeks (administration of placebo or tocilizumab 8 mg/kg every 2 weeks). Patients who remained on tocilizumab in the double-blind phase had sustained improvement in clinical measures of effectiveness and well-being. In contrast, most of the patients in the placebo group (18/23 patients) required rescue treatment. After the lead-in and double-blind phases, corticosteroid doses were reduced by at least 50% in most patients. Patients responding to tocilizumab and needing further treatment were then enrolled in an open-label extension phase for at least 48 weeks. By week 48 of the open-label extension phase, ACR Pedi 30, 50 and 70 responses were achieved by 47 (98%), 45 (94%) and 43 (90%) of 48 patients, respectively (*24*).

A multicentre, randomized phase III trial evaluated the efficacy of tocilizumab compared with placebo in 112 children aged 2–17 years with persistent systemic-onset JIA of at least 6 months and inadequate response to non-steroidal anti-inflammatory drugs and glucocorticoids (*25*). Patients were randomized in a 2:1 ratio to either tocilizumab (12 mg/kg if weighing < 30 kg or 8 mg/kg if weighing ≥ 30 kg) or placebo intravenously every 2 weeks for 12 weeks. After 12 weeks, the primary endpoint of ACR Pedi 30 response and absence of fever was met by 85% (64/75) in the tocilizumab group and 24% (9/37) in the placebo group (*P* < 0.001). In this study, 84% of the patients in the treatment group had previously received a biological agent, including 55% who had received interleukin-1 inhibitors and 73% who had received antitumour necrosis factor agents. At week 52, ACR Pedi 70 response was achieved by 80% of the patients who received tocilizumab, including 59% who achieved ACR Pedi 90. After 52 weeks, 48% of patients treated with tocilizumab had no joints with active arthritis and 52% had discontinued oral glucocorticoids.

Registry and retrospective studies

A German study evaluated the efficacy and safety of treatment with etanercept, tocilizumab, and the interleukin-1 inhibitors anakinra and canakinumab in systemic-onset JIA patients using data from the German biologics register (*26*). Over a 5-year period, 245 patients with systemic-onset JIA exposed to biological

agents were identified: 143, 71 and 60 patients received treatment with etanercept, tocilizumab and interleukin-1 inhibitors, respectively. At baseline, patients in the etanercept group had fewer systemic disease manifestations but more active joints. JIA-ACR 30, 50, 70 and 90 responses over 24 months were reached more often in the groups receiving tocilizumab and interleukin-1 inhibitor than the etanercept group. A Juvenile Disease Activity Score ≤ 1 (JADAS-remission) was achieved in 20% (etanercept), 37% (tocilizumab) and 52% (interleukin-1 inhibitors) of patients. Minimal disease activity (JADAS ≤ 3.8) was reported in 35% (etanercept), 61% (tocilizumab) and 68% (interleukin-1 inhibitors) of patients, and inactive disease in 24% (etanercept), 33% (tocilizumab) and 56% (interleukin-1 inhibitors).

Another German study evaluated the clinical response rate, disease course and adverse effects of tocilizumab for systemic-onset JIA in a real-life clinical setting using data from the German-AID-registry (*27*). Over a 5-year period, 46 of 200 patients with systemic-onset JIA were treated with tocilizumab. A clinical response rate (defined as no symptoms and typical inflammatory markers) of 35% was reported in the first 12 weeks of treatment, and inactive disease/remission on medication (as defined in the Wallace criteria (*28*)) was reported in 75% of patients after 1 year.

A French retrospective study using data from the Centre des Maladies Rares register: analysed the effectiveness of biological agents in achieving inactive disease or clinical remission in patients with systemic-onset JIA; described the effects of switching or discontinuing a biological agent; and assessed the proportion of patients able to maintain response without corticosteroids after withdrawing biological therapy (*29*). Seventy-seven patients were included with a cumulative follow-up of 245.5 patient-years. As first-line biological therapy, inactive disease was achieved in 37 patients (48%), including 33/61 (54%) patients receiving interleukin-1 inhibitors, 2/2 (100%) patients receiving tocilizumab, 1/1 (100%) patient receiving abatacept and 1/13 (8%) patients receiving antitumour necrosis factors. Switching to a second (*n* = 34), third (*n* = 18) or fourth (*n* = 4) line of biological treatment resulted in a further 13 patients achieving inactive disease, six with canakinumab and seven with tocilizumab. At the final follow-up, 40/77 (52%) patients were in clinical remission either on (29 patients) or off (11 patients) biological treatment.

Summary of evidence: harms

In the 2016 meta-analysis of biological medicines versus placebo in systemic-onset JIA (*20*), adverse events were infrequent and likely due to the short duration of follow-up in the analysed studies. While no significant difference in serious adverse effects was found between the medications, the overall quality of evidence was considered very low. Adverse events were more common with

tocilizumab than placebo or canakinumab. However, a posthoc analysis of adverse events (measured as the total number of events per total patient-days) indicated that tocilizumab did not differ significantly from placebo. Both tocilizumab and canakinumab were associated with a statistically significant increased risk of infections compared with placebo, although this significance was not maintained when evaluating events per total patient days.

In the 2020 meta-analysis which assessed the net benefit of biological agents used in JIA (*21*), significantly more serious adverse events occurred with biological medicines compared with control groups in the parallel trials (pooled OR 2.00, 95% CI 0.94 to 4.26), including for tocilizumab (OR 4.62, 95% CI 0.56 to 38.36). In the withdrawal trials, both pooled results (OR 1.01, 95% CI 0.45 to 2.24) and results for tocilizumab (OR 1.03, 95% CI 0.25 to 4.19) did not show a significant difference.

A postmarketing surveillance study in Japan evaluated the safety of tocilizumab in 417 patients with systemic-onset JIA treated in a real-world setting for 52 weeks (*24*). The rates of total adverse events and serious adverse events were 224.3/100 patient-years and 54.5/100 patient-years, respectively, which were higher than previously reported in clinical trials. Adverse events leading to the discontinuation of tocilizumab occurred in 4% (17/417) of patients. The most frequent adverse events were infections and infestations (69.8/100 patient-years and 18.2/100 patient-years, respectively). Notably, 74 serious infections occurred in 55 patients (18.2/100 patient-years) and 26 cases of macrophage activation syndrome occurred in 24 patients (6.4/100 patient-years). Two deaths were recorded during the 52-week period: one due to vasculitis with cardiac failure, and the other to Pseudomonas infection, interstitial lung disease and sepsis. Of the seven episodes of macrophage activation syndrome, infections were contributing factors, and in two cases, a reduced dose of corticosteroids was deemed contributory to the events.

In the double-blind phase of the phase III trial in children with persistent systemic-onset JIA following inadequate response to non-steroidal anti-inflammatory drugs and glucocorticoids (*25*), the most common adverse events were infections, occurring in 80% (60/75; two classified as severe) of patients in the tocilizumab group compared with 41% (15/37; none severe) of patients in the placebo group. In the double-blind and extension periods combined, including patients initially assigned to placebo who made the transition to open-label tocilizumab, 39 serious adverse events occurred (equivalent to 25 per 100 patient-years), including 18 serious infections (11 per 100 patient-years). Adverse events led to discontinuation of tocilizumab in six patients (for two because of elevated aminotransferase levels). Three episodes of macrophage activation syndrome occurred, all of which resolved. Three deaths occurred during treatment, including one from probable streptococcal sepsis. Neutropenia

was reported in 17% (19/112) of patients, of whom 17 had grade 3 and two had grade 4 neutropenia.

From the German study that evaluated the efficacy and safety of treatment with etanercept, tocilizumab, anakinra and canakinumab in systemic-onset JIA patients using data from the German biologics register (*26*), rates of adverse events were significantly higher in the tocilizumab group than the etanercept group (risk ratio (RR) 5.3, *P* < 0.0001). Rates of serious adverse events were observed more frequently with tocilizumab (RR 2.5, *P* < 0.5) and interleukin-1 inhibitors (RR 2.9, *P* < 0.01) compared with etanercept.

Long-term safety of biological medicines for systemic-onset JIA was reported in another study using data from the German biologics register (*30*). The average follow-up duration was about 4.3 years, with a total exposure time to biological medicines of 856 exposure years and 244 exposure years for tocilizumab specifically. Safety assessments were based on adverse event reports after the first dose up to 90 days after the last dose. Rates of adverse events, serious adverse events and 25 predefined adverse events of special interest were analysed. Incidence rates were compared for each biological medicine against all other biological medicine combined using a mixed-effect Poisson model. Serious adverse events were reported with higher frequency in patients receiving canakinumab (20/100 patient-years) and tocilizumab (21/100 patient-years). Cytopenia and hepatic events occurred with higher frequency with tocilizumab and canakinumab. Medically important infections were seen more often in patients using interleukin-6 or interleukin-1 inhibitors. Macrophage activation syndrome occurred in all cohorts with a higher frequency in patients using canakinumab (3.2/100 patient-years) and tocilizumab (2.5/100 patient-years) compared with anakinra (0.83/100 patient-years) and etanercept (0.5/100 patient-years). Among the patients, 96 had received more than one biological agent. After adjustment for a number of factors (e.g. concomitant use of methotrexate and steroids, presence of systemic signs and disease duration), only an elevated risk for infections in patients treated with anakinra remained significant. Three definite malignancies were reported in patients exposed to biological agents. Two deaths occurred in patients treated with etanercept. The authors observed changes in preferred biological agents, with a shift toward tocilizumab, anakinra and canakinumab after 2013. Patients treated with tocilizumab and systemic corticosteroids had significantly higher rates of adverse events and serious adverse events compared with those treated with tocilizumab alone (127.5/100 exposure years versus 79.4/100 exposure years for adverse events, *P* = 0.002; and 28.4/100 exposure years versus 15.6/100 exposure years for serious adverse events, *P* = 0.019). Adverse events included 93 infectious events in 37 patients treated with tocilizumab (38/100 exposure years; RR 1.4, 95% CI 0.97 to 2.00). Cytopenia was reported in 22 cases, with higher rates in patients given tocilizumab (6.2/100 exposure years;

RR 5.37, 95% CI 2.19 to 13.17). However, the difference in cytopenia rates did not remain significant after adjusting for a number of factors (e.g. concomitant use of methotrexate and steroids, presence of systemic signs and disease duration).

In the German study that evaluated tocilizumab for systemic-onset JIA in a real-life clinical setting using data from the German-AID-registry (*27*), adverse events were reported in 24% (11/46) of patients, with severe adverse events in 4% (2/46) of patients (a case of Hodgkin lymphoma and one of gut perforation). No cases of macrophage activation syndrome or death were reported. Discontinuation of treatment due to adverse events was reported in 11% (5/46) of patients (three with neutropenia and two with serious adverse event).

A pilot observational study compared consensus treatment plans provided by the Childhood Arthritis and Rheumatology Research Alliance in 30 newly diagnosed patients with systemic-onset JIA (*31*). Ten participants received tocilizumab. One grade 4 infusion reaction and one case of macrophage activation syndrome occurred with tocilizumab treatment. Grade 2 adverse events reported in tocilizumab treated patients included fever, rash, arthritis flare-up, headache, neutropenia, viral illness and infusion reaction.

The application stated that children treated with tocilizumab (or any biological disease-modifying antirheumatic drug) must have access to a paediatric rheumatologist for ongoing monitoring during treatment and for urgent review should they develop complications such as infection. This is of particular importance in resource-constrained countries where up to 50% of deaths in children 5–15 years is due to infection. The trials and studies listed above all were conducted in well resourced countries. Local factors (e.g. availability of specialist services such as doctors, nurses, urgent review and access to intravenous antibiotics), as well as patient factors (e.g. health literacy rates, distance and transport to hospital, comorbid conditions, poverty and malnutrition) may significantly affect the mitigation of adverse events in resource-constrained settings.

WHO guidelines

WHO guidelines for the treatment of systemic-onset JIA are not currently available.

Costs/cost–effectiveness

The application reported that in the United Kingdom, intravenous tocilizumab costs £102.40, £256.00 and £512.00 per vial for 80 mg, 200 mg and 400 mg vials, respectively, and subcutaneous tocilizumab costs £228.28 per 162 mg/0.9 mL prefilled pen/syringe. The manufacturer offers a confidential patient access scheme within the National Health Service that provides a discount. In Australia, the dispensed price under the Pharmaceutical Benefit Scheme for intravenous tocilizumab was reported as 82 Australian dollars (Aus$), Aus$ 203 and Aus$ 405 per vial for 80 mg, 200 mg and 400 mg, respectively.

A Canadian cost–utility analysis evaluated the cost–effectiveness of tocilizumab with or without methotrexate compared with placebo plus methotrexate in the treatment of systemic-onset JIA (*32*). The base-case analysis focused on direct medical costs (in 2011 Canadian dollars (Can$)) from the perspective of the Canadian Ministry of Health. The incremental cost–utility ratio for tocilizumab with or without methotrexate was Can$ 69 787 per additional quality-adjusted life year (QALY) gained compared with placebo plus methotrexate. Tocilizumab treatment was the dominant treatment strategy from a societal perspective.

A Finnish study compared cost–effectiveness of tocilizumab with methotrexate and anakinra (*33*). The incremental cost per additional QALY gained for treatment with tocilizumab was €15 181 compared with methotrexate and €14 496 compared with anakinra. Based on a willingness-to-pay threshold of €20 000 per QALY gained, tocilizumab had a 93% probability of being cost-effective compared with methotrexate and 88% compared with anakinra. This probability increased to 100% with a willingness-to-pay threshold of €27 000 per QALY.

A cost–utility analysis in Thailand assessed the effect of the addition of tocilizumab to standard treatment in patients with refractory systemic-onset JIA (*34*). The incremental cost–effectiveness ratio of standard treatment plus tocilizumab was US$ 35 799 per QALY gained compared with standard treatment alone. The study was based on cases of refractory disease in 43 patients treated in seven tertiary hospitals in Thailand. The patients in the study had a long duration of disease and a greater overall severity.

A pharmacoeconomic study evaluated the cost-efficiency of treatment with tocilizumab versus standard treatment with methotrexate and prednisolone in Russian patients with systemic-onset JIA (*35*). The cost–effectiveness in terms of ACR 90 and 70 was 4.4 million and 3.0 million Russian roubles (Rub), respectively, in the standard treatment group, and Rub 1.2 million and Rub 615 000, respectively, in the tocilizumab group. Pharmacotherapy was responsible for more than half of the costs in the tocilizumab group, but hospitalization costs were 12 times lower than in the standard treatment group. Annual state budget losses due to the social burden of systemic-onset JIA were almost double in the standard treatment group compared with the tocilizumab group (Rub 426 000 versus Rub 227 000).

Availability

Tocilizumab has regulatory approval for the treatment of systemic-onset JIA from various global regulatory agencies. The intravenous form is indicated for children aged 2 years and older, while the subcutaneous form is approved for children aged 1 year and older, weighing at least 10 kg.

Recent reports indicate supply issues and shortages in some countries, mainly due to the use of tocilizumab as a novel treatment for COVID-19 and its use in clinical trials for the disease.

Other considerations

Tocilizumab in the treatment of systemic-onset JIA should only be used by appropriately trained and experienced clinical personnel. In addition, families need to be educated on the potential side-effects of and safety concerns about tocilizumab and know when to seek health care. These principles are based on recommendations and standards of care for JIA (*36,37*).

Intravenous tocilizumab requires specialized facilities and trained staff, including a hospital bed or clinic, cannulation equipment and expert personnel. Some patients require premedication to prevent infusion reactions, which is influenced by factors such as age, height, weight and disease activity (*38*). Travel distance to the hospital and transport availability can affect attendance for treatment for the child. Regular follow-up is required for children on tocilizumab to assess treatment response and potential adverse events.

Before starting tocilizumab treatment, all patients should be tested for tuberculosis due to a risk of tuberculosis reactivation. The American College of Rheumatology advises that children initially deemed at low tuberculosis risk, with a negative test, have repeated screenings if their tuberculosis risk becomes moderate or high according to regional infectious disease guidelines (*39*). Understanding tuberculosis risk in patients on tocilizumab and other biological disease-modifying antirheumatic medications is particularly important in resource-constrained settings with high tuberculosis rates (*40*).

Committee recommendations

The Expert Committee acknowledged that systemic-onset JIA was associated with serious morbidity in children and associated with greater morbidity than other subtypes of the disease. The Committee also noted the severe and potentially fatal complication of macrophage activation syndrome had a high mortality rate in this population.

The Committee recognized that early introduction of disease modifying antirheumatic agents such as tocilizumab was proposed as safe and effective to avoid joint destruction, control systemic-onset JIA, improve quality of life and minimize long-term corticosteroid use, aiming at better physical and psychosocial function.

However, as was the case in 2021, the Committee noted that only a small number of clinical studies provided comparative evidence of efficacy and safety for tocilizumab versus the antitumour necrosis factor medicines currently included on the Model List for JIA. Furthermore, the quality of evidence in these studies

was rated as low or very low, and none was conducted in resource-constrained settings. The Committee acknowledged that tocilizumab should only be used in specialized care facilities and by appropriately trained clinical personnel. Its safe and effective use also required careful monitoring for adverse effects, such as infections, and tuberculosis risks and this may not be available in resource-constrained settings. The limited availability of tocilizumab in low- and middle-income countries was also a matter of concern.

Therefore, the Expert Committee did not recommend the inclusion of tocilizumab for treatment of systemic-onset JIA on the Model Lists. As was the case when these medicines were considered in 2021, the Expert Committee considered that the clinical benefits and safety of these medicines (including risk of infection) remained uncertain based on the limited available evidence. The Committee also considered that the feasibility of tocilizumab, particularly in resource-constrained settings, was unlikely given the current high price and requirements for specialized care, monitoring and management of adverse events.

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Triamcinolone – addition – EML and EMLc

Triamcinolone hexacetonide	ATC code: H02AB08

Proposal

Addition of triamcinolone hexacetonide on the complementary list of the EML and EMLc for the treatment of juvenile idiopathic arthritis (JIA).

Applicant

Paediatric Global Musculoskeletal Task Force

WHO technical department

Not applicable

EML/EMLc

EML and EMLc

Section

29.3 Juvenile joint diseases

Dose form(s) & strengths(s)

Injection: 20 mg/mL in vial

Core/complementary

Complementary

Individual/square box listing

Square box listing with triamcinolone acetonide as a specified therapeutic alternative.

Background

Triamcinolone hexacetonide was previously considered for inclusion on the Model Lists for treatment of JIA in 2021.

The Expert Committee noted that the evidence presented supporting the use of intra-articular corticosteroids in JIA was limited and of suboptimal quality. Almost all studies were in high-income countries and specialized settings and the generalizability of findings to lower-income settings was uncertain. No data were included on the role and the comparative benefits and risks of triamcinolone hexacetonide compared with oral corticosteroids or disease-modifying treatments such as methotrexate. Although intra-articular steroids are considered an important tool in the treatment of JIA, the Committee noted that consensus is lacking about their efficacy and safety in different settings.

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The Committee noted that administration of intra-articular corticosteroids is an invasive procedure requiring specialized training and experience. It is also associated with risks of infection. Dose adjustment based on the targeted joint is an important aspect of practice, as overdose of corticosteroids might lead to joint atrophy. Laboratory tests are needed to determine disease activity and risk of progression, and to evaluate a patient's suitability for treatment. The Committee also expressed concerns about the limited availability of specialist paediatric rheumatology care in low- and middle-income settings.

The Expert Committee therefore did not recommend the inclusion of triamcinolone hexacetonide on the EML or the EMLc at that time, because of the uncertain clinical benefit of triamcinolone hexacetonide given the low quality of evidence and its limited generalizability, and safety concerns associated with administration procedures (*1*).

Public health relevance

JIA is the most common chronic rheumatic disease in children, with a prevalence of about 1 in 1000 children (*2*). In 2017, more than 2 million children younger than 16 years worldwide were estimated to have JIA, with the highest prevalence in south Asia and Africa (*3*). The disease is characterized by joint inflammation lasting more than 6 weeks, onset before the age of 16 years and no other identifiable cause (*4–6*).

Untreated disease can have severe consequences, including pain, fatigue, joint damage, functional disability, and impaired quality of life. JIA can also lead to anaemia, poor growth, delayed puberty and complications such as uveitis, which can cause blindness if not detected and treated (*5–7*). The impact of untreated JIA extends to difficulties in walking, performing daily activities and educational participation, which can result in psychosocial challenges, mental health problems and higher unemployment rates compared with healthy peers (*8–10*).

Access to proper care for children with JIA is a major challenge, particularly in resource-constrained settings (*11*). The shortage of paediatricians, especially in Asia and Africa, contributes to limited access to specialist care and treatment for many children with JIA, resulting in worse clinical outcomes in these regions (*7,12*).

Summary of evidence: benefits

Note: the terms pauciarticular juvenile rheumatoid arthritis or juvenile chronic arthritis are used below because they are found in some older studies cited. They are equivalent to oligoarticular juvenile idiopathic arthritis.

The effectiveness of steroid injections in pauciarticular juvenile rheumatoid arthritis and other forms of inflammatory arthritis was evaluated in a prospective study of 40 children who had failed therapy with non-steroidal anti-inflammatory drugs (*13*). Twenty-nine children had juvenile rheumatoid arthritis. Active knee

joints were injected with 20–40 mg of triamcinolone hexacetonide and the effects were evaluated at 6, 12 and 24 months. A good response was defined as complete resolution of active joint inflammation and a relapse was defined as a sustained reaccumulation of joint effusion. All injected joints had a good initial response to treatment. At 6, 12 and 24 months follow-up, a good response was maintained in 67.6% (25/37), 50.0% (15/30) and 17.4% (4/23), respectively, of the joints of children with juvenile rheumatoid arthritis. No significant differences based on disease group, sex or dose were observed. Relapse was seen in eight joints. These joints were re-injected, of which five maintained a good response for 12 months. The mean dose administered was significantly higher in the relapse group than the group with a good response in the children with juvenile rheumatoid arthritis ($P < 0.01$), but the difference was not statistically significant in other types of juvenile arthritis.

A retrospective study evaluated the efficacy and duration of benefit of triamcinolone hexacetonide injections in 194 children with various subgroups of juvenile chronic arthritis (*14*). A total of 1439 injections (including 368 reinjections) were administered and outcomes were measured after mean durations of 3, 15, 30 and 64 weeks. Significant differences in response were seen among subgroups. Efficacy lasted for 121 weeks in early-onset pauciarticular juvenile chronic arthritis type I, 47 weeks in late-onset pauciarticular juvenile chronic arthritis type II, 105 weeks in rheumatoid factor negative polyarticular juvenile chronic arthritis, 63 weeks in rheumatoid factor positive polyarticular juvenile chronic arthritis and 36 weeks in systemic juvenile chronic arthritis. The study concluded that intra-articular triamcinolone injections were effective in treating inflammatory joint disease in all subgroups of juvenile chronic arthritis.

An open-label, non-randomized, prospective study compared response rates in 85 patients with juvenile idiopathic arthritis who received triamcinolone hexacetonide and triamcinolone acetonide injections; of 130 joints, 70 received triamcinolone hexacetonide and 60 received triamcinolone acetonide (*15*). The response rate was evaluated using core outcome measures, including joint swelling, limitation of joint range of motion, pain on passive movement and warmth to the touch. A good response was defined as the absence of inflammation or a reduction in joint inflammation of more than 60% from baseline. Relapse was defined as the reappearance of arthritis after a period of good response. The response rate was significantly higher with triamcinolone hexacetonide than triamcinolone acetonide: 81.4% versus 53.3% ($P = 0.006$) at 6 months, 67.1% versus 43.3% ($P = 0.006$) at 12 months and 60.0% versus 33.3% ($P = 0.002$) at 24 months. The rate of relapse was 2.7 times higher in the triamcinolone acetate group than the triamcinolone hexacetonide group (95% confidence interval (CI) 1.6 to 4.8).

A retrospective study compared the time to relapse following treatment with triamcinolone hexacetonide and triamcinolone acetonide in 85 patients with juvenile idiopathic arthritis; of 277 joints, 114 received triamcinolone

hexacetonide and 112 received triamcinolone acetonide (*16*). The mean, standard deviation (SD), time to relapse was significantly longer in the triamcinolone hexacetonide group than the triamcinolone acetonide group (10.14, SD 0.49 months versus 7.75, SD 0.49 months, *P* < 0.0001). A Cox regression model analysis showed that after adjusting for sex, duration of illness or type of disease, a significant difference existed in relapse time favouring triamcinolone hexacetonide (hazard ratio (HR) 1.99, 95% CI 1.43 to 2.78).

A double-blind trial compared the efficacy of triamcinolone acetonide at twice the dose of triamcinolone hexacetonide in 37 children with juvenile idiopathic arthritis (*17*). Children with symmetrical joints requiring injection received triamcinolone acetonide in one joint and triamcinolone hexacetonide in the other. Clinical assessments were performed at baseline, and at 3, 6, 9, 12, 18 and 24 months after injection. The response rate was assessed based on core outcome measures, including joint swelling, limitation of joint range of motion, pain on passive movement and warmth to the touch. All joints showed improvement post-injection. However, after 2–21 months of follow-up, relapse occurred more frequently in joints treated with triamcinolone acetonide (53.8%) than those treated with triamcinolone hexacetonide treated joints (15.4%). The rate of persisting or sustained response was significantly higher with triamcinolone hexacetonide than with triamcinolone acetonide at 6 months (89.7% versus 61.5%, *P* = 0.008), 12 months (84.6% versus 48.7%, *P* = 0.001) and 24 months (76.9% versus 38.5%, *P* = 0.001).

The efficacy of intra-articular injections with triamcinolone hexacetonide and triamcinolone acetonide was compared in a retrospective single-centre chart review study of 102 patients with juvenile idiopathic arthritis (*18*). Of 292 included joints, 154 received triamcinolone hexacetonide and 138 received triamcinolone acetonide. The primary outcome measure for efficacy was defined as full recovery from arthritis 1 month after treatment. Rate of relapse at 3 months was also assessed. Similar efficacy was seen between treatments 1 month after injection. However, a significant difference was seen in the length of effect, with a significantly higher relapse rate at 3 months in the triamcinolone acetonide group (20.1% relapsed) compared with the triamcinolone hexacetonide group (8.8% relapsed). The significant difference persisted over time, up to 40 months. The odds ratio for relapse with triamcinolone acetonide was 2.24 (95% CI 1.39 to 3.58) compared with triamcinolone hexacetonide.

Summary of evidence: harms

The adverse event profiles of triamcinolone hexacetonide and triamcinolone acetonide are similar and most adverse events are rare (*5*,*17*,*19–21*). Potential adverse events include infection (septic arthritis at the injection site), subcutaneous atrophy caused by extravasation of the drug from the joint space,

steroid lipodystrophy, initial post-injection pain, calcium deposition in the joint, systemic absorption and avascular necrosis in the hip joint. Proper clinical technique and accurate needle placement can greatly reduce these effects, highlighting the importance that joint injections are performed by appropriately trained clinicians (*21,22*).

The risk of systemic absorption of glucocorticosteroids through injections can lead to adrenal suppression and/or iatrogenic Cushing syndrome, although these adverse effects are rare (*23*). Diabetic children may require a temporary increase in insulin doses following intra-articular glucocorticosteroid injections (*20*).

A prospective study evaluated the efficacy and safety of intra-articular triamcinolone hexacetonide for the treatment of coxitis in 50 patients with juvenile rheumatoid arthritis (*24*). Five cases of femoral head necrosis were reported among 20 children receiving triamcinolone hexacetonide and long-term systemic corticosteroids. No cases of femoral head necrosis were observed in 30 children who received triamcinolone hexacetonide without systemic corticosteroids.

Triamcinolone intra-articular injections are contraindicated in active, systemic mycoses and parasitoses, herpes simplex keratitis, and acute psychoses because of the potential effect of systemic absorption of steroids. Caution should be exercised in a number of circumstances, including the presence of active infection near the affected joint, cardiac insufficiency, acute coronary artery disease, hypertension, thrombophlebitis, thromboembolism, myasthenia gravis, Cushing syndrome, diabetes mellitus, hypothyroidism, osteoporosis, gastric ulcer, diverticulitis, ulcerative colitis, recent intestinal anastomosis, exanthematous diseases, renal insufficiency, acute glomerulonephritis, chronic nephritis, cirrhosis, infections that cannot be treated with antibiotics and metastatic carcinoma.

Triamcinolone hexacetonide should not be used in neonates due to the presence of benzyl alcohol as a preservative. However, a diagnosis of juvenile idiopathic arthritis in neonates is extremely rare and consultation with a paediatric rheumatologist would be necessary in such cases.

WHO guidelines

WHO guidelines for the management of JIA are not currently available.

Costs/cost–effectiveness

Studies on the cost–effectiveness of intra-articular corticosteroid injections for JIA are not available.

The application reported that the cost per vial of triamcinolone (hexacetonide or acetonide) varies by country. The cost of treatment per child depends on the number and size of joints to be injected.

The cost of untreated JIA is likely to be high for patients, their families and society (*25*).

Availability

Global shortages of triamcinolone hexacetonide have been reported.

Aristospan® brand of triamcinolone hexacetonide has been listed as being in short supply in the United States and has been discontinued on the United States market by the Food and Drug Administration, although it can be imported on an individual patient basis. Triamcinolone hexacetonide is not approved by the Australian Therapeutic Goods Administration but can be accessed through a special access scheme from international manufacturers. Canada has approved triamcinolone hexacetonide for inclusion in public drug formularies. Triamcinolone hexacetonide has marketing approval for intra-articular use in the United Kingdom and is included in the British National Formulary. Several European countries, including Austria, Czechia, Netherlands (Kingdom of the), Portugal, Slovenia and Spain granted marketing authorization for triamcinolone hexacetonide in 2013, before the supply problems arose.

Triamcinolone acetonide has regulatory approval for intra-articular administration in Australia, New Zealand and the United States. It has marketing authorization in Canada, Sweden and Switzerland. It does not appear to have supply shortages in the same way as triamcinolone hexacetonide.

Other considerations

Joint injections are uncomfortable and analgesia with local, inhaled or general anaesthesia or sedation is recommended, especially if several joints are injected. Imaging (such as ultrasound or radiographic image intensifier) can be used to optimize the accuracy of needle placement, especially for small joints or deep joints such as the hip or subtalar joints (*21,26*).

It is recommended that triamcinolone be administered only by appropriately trained clinical personnel experienced in using intra-articular steroids to treat active joint disease in JIA (*5,21,22,27–29*).

Committee recommendations

The Expert Committee noted that JIA was the most common chronic rheumatic disease of childhood and was associated with significant morbidity, functional disability and reduced quality of life if not appropriately treated.

As was the case in 2021, the Committee considered that the available evidence was still limited, and of suboptimal quality, but accepted that use of intra-articular glucocorticoid injections with triamcinolone (hexacetonide, and to a lesser extent acetonide) may be associated with improvements in joint inflammation in oligoarticular forms of JIA and had advantages over long-

term systemic corticosteroid use in terms of harms. No additional evidence was identified during the application review process and the Committee considered that it was unlikely that new evidence would be generated soon.

The Committee noted that the evidence indicated that triamcinolone hexacetonide was superior to triamcinolone acetate in terms of efficacy and duration of response but that there were shortages in supply worldwide. The Committee considered that inclusion of triamcinolone hexacetonide with triamcinolone acetonide as a therapeutic alternative was appropriate and may contribute to improving access and resolving shortage problems.

The Committee noted that the costs for triamcinolone hexacetonide varied across settings and other costs associated with administration must also be taken into consideration, such as analgesia and imaging. The Committee also reiterated the need for administration to be performed only by appropriately trained specialized clinical personnel.

Based on these considerations, the Expert Committee recommended the inclusion of triamcinolone hexacetonide on the complementary list of the EML and EMLc for use in the treatment of JIA. Listing was recommended with a square box to indicate triamcinolone acetonide as a therapeutic alternative for national selection in situations where triamcinolone hexacetonide was not available.

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Section 30: Dental medicines and preparations
Fluoride – new formulations – EML and EMLc

Fluoride	ATC code: A01AA

Proposal

Addition of fluoride gel, mouthrinse and varnish formulations on the core list of the EML and EMLc for prevention of dental caries in adults and children.

Applicant

Benoit Varenne, Dental Officer, Oral Health Programme, Noncommunicable Diseases Department, Division of UHC/Communicable and Noncommunicable Diseases, WHO Headquarters, Geneva, Switzerland

WHO technical department

Noncommunicable Diseases

EML/EMLc

EML and EMLc

Section

30 Dental medicines and preparations

Dose form(s) & strengths(s)

Gel: containing 2500 to 12 500 ppm fluoride (any type)

Mouthrinse: containing 230 to 900 ppm fluoride (any type)

Varnish: containing 22 500 ppm fluoride (any type)

Core/complementary

Core

Individual/square box listing

Individual

Background

Sodium fluoride tablets were initially added to EML in 1979 as a preventive measure against dental caries in areas without fluoridated water supplies. In 1993, the listing was modified to include other formulations. In 2005, there was a proposal to remove sodium fluoride tablets due to the established efficacy of topical fluoride in preventing dental caries. The 2005 Expert Committee

considered local circumstances, including the fluoride content of drinking water, and acknowledged the risk of fluorosis with excessive tablet use. Consequently, sodium fluoride was retained on the EML but with a revised description to specify "in any appropriate topical formulation". In 2007, sodium fluoride was also included in the first edition of the EMLc.

In 2021, in consideration of an application proposing the addition of fluoride toothpaste to the EML and EMLc, the Expert Committee noted that the current listing for sodium fluoride did not specify the form and concentration range of topical fluoride products used to prevent dental caries. The Committee considered that to provide the best guidance for selection of products for national EMLs, the Model Lists should include specific recommendations of the different formulation types and ideal concentrations of fluoride-containing preparations. The Committee recommended that the listing for sodium fluoride be transferred to a new section of the Model Lists for dental preparations, and the listing be amended to "fluoride", noting that topical fluoride-containing preparations use fluoride in a variety of forms. Fluoride toothpaste, containing between 1000 and 1500 ppm fluoride of any type was recommended for addition, and the Committee requested WHO to identify and define the alternative fluoride-containing formulations recommended for use in the prevention of dental caries so that these could be clearly indicated in the Model Lists in 2023 to provide clear guidance for countries (*1*).

Public health relevance

The WHO global oral health status report, using the latest available data of the Global Burden of Disease Study 2019, estimates that oral diseases affect close to 3.5 billion people worldwide. Dental caries is the most widespread oral disease with more than 2.5 billion untreated cases. This includes more than 2 billion estimated cases of caries in permanent teeth (global average prevalence of 29%) and 514 million estimated cases of caries in primary (deciduous) teeth (global average prevalence of 43%). Among the 194 WHO Member States, 134 have prevalence figures greater than 40% for caries in primary teeth. More than three quarters of cases of untreated caries in teeth are found in middle-income countries. Over the past 30 years, cases of untreated caries have increased and surpassed the demographic population growth during the same period (*2*).

Untreated dental caries may cause pain and infection, and may lead to systemic infections requiring hospitalization and complex treatment. The high prevalence and severity of untreated dental caries in children can contribute to low body mass index and stunting (*3–5*). Additionally, dental caries result in significant absenteeism in schools and workplaces (*6,7*). Good oral health is essential for healthy ageing (*8*).

The burden of dental caries varies significantly across populations within and between countries, with a clear socioeconomic gradient showing higher disease burden in deprived and disadvantaged communities, who also

have limited access to prevention and oral health services (*2,9*). Caries affects people throughout their lives, with varying patterns of burden across age groups – starting in early childhood, increasing notably in adolescence and continuing to rise in adulthood (*10*).

Summary of evidence: benefits

Fluoride gel

A 2015 Cochrane systematic review of 28 randomized controlled trials (9140 participants) assessed the effectiveness of fluoride gels for preventing dental caries in children and adolescents (*11*). The primary outcome measure was caries increment measured by the change from baseline at the nearest increment to 3 years in decayed, missing/extracted and filled tooth surfaces in permanent and primary teeth. From the meta-analysis of fluoride gel compared with placebo or no treatment, fluoride gel significantly reduced decayed, missing and filled tooth surfaces in permanent teeth (prevented fraction (PF) 28%, 95% confidence interval (CI) 19% to 36%; 25 randomized controlled trials, 8479 participants, moderate quality evidence) and in primary teeth (PF 20%, 95% CI 1% to 38%; three randomized controlled trials, 1254 participants, low quality evidence). The effects showed no dependency on baseline caries level, or exposure to other fluoride sources, or to application features such as the method or frequency of gel application or fluoride concentration. The relative effect was not dependent on length of follow-up, whether prophylaxis was undertaken before application of the gel, or according to drop-out rate.

Fluoride mouthrinse

A 2016 Cochrane systematic review of 37 randomized trials (15 813 participants) assessed the effectiveness of fluoride mouthrinse for preventing dental caries in children and adolescents (*12*). Most participants received a mouthrinse formulated with sodium fluoride on either a daily or weekly/fortnightly basis and at two main strengths, 230 or 900 ppm fluoride. Meta-analysis found that fluoride mouthrinse significantly reduced decayed, missing and filled tooth surfaces in permanent teeth (PF 27%, 95% CI 23% to 30%; 35 randomized controlled trials, 15 305 participants, moderate quality evidence). No significant association was found between estimates of effect and baseline caries severity, exposure to other fluorides, rinsing frequency or fluoride concentration.

A 2020 systematic review and network meta-analysis of nine controlled clinical trials (4030 participants) assessed the effect of topical fluoride preparations in preventing root caries (*13*). Daily use of 0.2% sodium fluoride mouthrinse, and daily use of fluoride toothpaste followed by 0.05% sodium fluoride mouthrinse were more effective than interventions in the control groups (different concentrations or content of fluoride, placebo and no special intervention) in preventing root caries.

Fluoride varnish

A 2013 Cochrane systematic review of 22 randomized controlled trials (12 455 participants) assessed the effectiveness of fluoride varnishes in preventing dental caries in children and adolescents (*14*). The primary outcome measures were caries increment measured by the change in decayed, missing and filled tooth surfaces in both permanent and primary teeth. Compared with placebo or no treatment, fluoride varnishes (applied two to four times a year) significantly reduced decayed, missing and filled tooth surfaces in permanent teeth (PF 43%, 95% CI 30% to 57%; 13 randomized controlled trials, moderate quality evidence) and in primary teeth (PF 37%, 95% CI 24% to 51%; 10 randomized controlled trials, moderate quality evidence). No significant associations were found between estimates of effect and baseline caries severity, background exposure to fluorides, application features (such as prior prophylaxis), concentration of fluoride, or frequency of application.

A 2020 Cochrane systematic review of 11 randomized controlled trials (3374 participants) evaluated the relative effectiveness of dental sealants compared with fluoride varnishes, or dental sealants plus fluoride varnishes compared with fluoride varnishes alone for prevention of dental caries in occlusal surfaces of permanent teeth in children and adolescents (*15*). No significant difference was seen between resin-based sealants and fluoride varnish for preventing caries in first permanent molars at 2–3 years of follow-up (odds ratio (OR) 0.67, 95% CI 0.37 to 1.19; four randomized controlled trials, 1683 participants). There was also low certainty evidence that resin-based sealant plus fluoride varnish was superior to fluoride varnish alone (OR 0.30, 95% CI 0.17 to 0.55; one randomized controlled trial, 92 participants).

Combination treatment

A 2004 Cochrane systematic review of 12 randomized controlled trials (5946 participants) compared the effectiveness of combined topical fluoride therapy versus topical fluoride monotherapy (mainly toothpaste) for the prevention of dental caries in children (*16*). From the meta-analysis of the effect of fluoride mouthrinses, gels or varnishes used in combination with fluoride toothpaste versus fluoride toothpaste alone, combined treatment significantly reduced decayed, missing and filled tooth surfaces in permanent teeth (PF 10%, 95% CI 2% to 17%; nine randomized controlled trials, 4026 participants). Separate meta-analyses of fluoride gel or mouthrinse combined with toothpaste versus toothpaste alone favoured the combined regimens, but differences were not statistically significant.

Summary of evidence: harms

Potential harms of topical fluorides are associated with over-ingestion, leading to symptoms of nausea and vomiting, and dental fluorosis (while tooth enamel is developing, up to 6 years) (*17*). Use of topical fluoride gel, mouthrinse and

varnish preparations is contraindicated in cases of ulcerative gingivitis because of the increased risk of systemic fluoride absorption.

Fluoride gel

The 2015 Cochrane systematic review of fluoride gels for preventing dental caries in children and adolescents found no reports of adverse effects (*11*). Ingestion can be prevented by seating the patient upright, not overfilling application trays, use of well-fitted or custom trays, use of a suction device and by separate insertion of upper and lower trays. Gagging may occur in young children during application (*18*). Studies suggest that professionally applied fluoride gel has a low risk of causing dental fluorosis, even in children younger than 6 years, as it is applied relatively infrequently (*19*).

Fluoride mouthrinse

The 2016 Cochrane systematic review of fluoride mouthrinses for preventing dental caries in children and adolescents reported limited information on the possible adverse effects or acceptability of the treatment regimen in the included trials (*12*). Incompletely reported data on tooth staining were available from three trials, and on mucosal irritation/allergic reaction from one trial. No trials reported on acute adverse events during treatment.

 The 1994 WHO report on fluorides and oral health raised concern about alcohol-based fluoride mouthrinse formulations. The report noted that such preparations were costly and that there was no justification, other than flavour and formulation, to use an alcohol base. Daily use and inadvertent or intentional ingestion of alcohol-based fluoride mouthrinses should be strongly discouraged. The concern related to a potentially increased risk of oral and oropharyngeal cancers, where harmful use of alcohol is a key risk factor (*20*). A 2020 systematic review found no evidence of an increased risk of oral cancer associated with use of alcohol-based mouthrinses alone; however, in the presence of other risk factors, there may be a potentially increased risk that would justify discouraging use. Moreover, no added therapeutic benefit of alcohol-based formulations was identified (*21*).

Fluoride varnish

The 2013 Cochrane systematic review of fluoride varnishes for prevention of dental caries in children and adolescents found little information on possible adverse effects or acceptability of treatment (*14*). When fluoride varnishes are applied professionally and used as recommended, fluoride is not ingested in significant amounts or over an extended period of time, making systemic adverse effects unlikely (*17*).

 A study of the pharmacokinetics of fluoride after application of 5% sodium fluoride dental varnish in six children aged between 12 and 15 months

found that fluoride exposure levels were lower than the known toxicity level and did not exceed limits for dental fluorosis (*22*). A prospective study in the United States of more than 10 000 fluoride varnish applications in children aged 0–5 years observed no treatment-related adverse events (*23*).

WHO guidelines

The 1994 WHO report on fluorides and oral health provides a comprehensive review of the role of fluorides in preventing dental caries, and considers various aspects such as history, pharmacology, preventive effects, risks and side-effects (*20*). The key recommendations from the report remain consistent with current recommendations, highlighting the enduring significance of fluorides as a valuable tool for preventing dental caries.

The 2022 WHO briefing note on prevention and treatment of dental caries emphasizes the use of mercury-free products and minimal intervention, aligning with the Minamata Convention on Mercury Elimination. The note highlights fluoride varnish as a recommended approach, suitable for various populations, including those in urban, rural, remote, and vulnerable areas. Fluoride varnish is recognized for its simplicity, effectiveness, wide acceptance, without need for specialist dental training for its application for (*24*).

The 2019 WHO implementation manual on ending childhood dental caries highlights brushing teeth with fluoride-containing toothpaste and application of fluoride varnish as key interventions for preventing and treating early childhood caries (*25*).

The 2011 World Health Assembly resolution on oral health (*26*) and the 2022 draft global strategy on oral health (*27*) stress the urgent need to intensify preventive efforts, particularly for dental caries. These documents highlight the limited access to oral health promotion and prevention programmes, including the use of fluorides for caries prevention. Essential prevention methods, such as water fluoridation, community-based initiatives, topical fluoride applications and access to good-quality fluoride toothpaste, are often unavailable or unaffordable for many people. To address this issue, the draft global oral health action plan was prepared and proposes a series of global targets focused on achieving optimal fluoride levels for population oral health. Additionally, the action plan aims to improve the availability and affordability of fluoride medicines for oral health and includes a target that 50% of countries should include dental preparations listed in the WHO Model Lists in their national essential medicines lists by 2030 (*28*).

Costs/cost–effectiveness

Evidence on the cost and cost–effectiveness of fluoride formulations for prevention of dental caries is limited, primarily consisting of studies conducted in school-based programmes.

A 2020 scoping literature review aimed to identify evidence on the cost–effectiveness of school-based interventions for caries prevention globally (*29*). The review included 15 studies, nine published after 2011 and 11 from high-income countries. Almost 80% of the studies assessed the cost–effectiveness of topical fluoride therapies and fissure sealants. The review found evidence to suggest that school-based caries preventive methods were cost-effective and in some cases cost-saving. Evidence from low- and middle-income countries was lacking.

A study in Chile compared the cost–effectiveness of seven caries prevention programmes among schoolchildren from a societal perspective, namely water fluoridation, salt fluoridation, dental sealants, milk fluoridation, fluoride mouthrinse, fluoride gel and supervised toothbrushing with fluoride toothpaste (*30*). Four programmes showed net savings per diseased tooth averted: salt fluoridation (US$ 16.21); water fluoridation (US$ 14.89); milk fluoridation (US$ 14.78); and fluoride mouthrinse (US$ 8.63). The remaining programmes were associated with costs per diseased tooth averted: fluoride gel (US$ 21.30); dental sealants (US$ 11.56); and supervised toothbrushing with fluoride toothpaste (US$ 8.55).

A modelling study assessed the lifelong costs of caries with and without fluoride use based on German epidemiological data (*31*). Effectiveness and costs for seven fluoride regimes were evaluated, including fluoridated salt, weekly home application of fluoride gel, fluoride toothpaste, professional biannual fluoride applications, and various combinations of these. All fluoride regimes resulted in lower lifetime dental restoration costs (fillings, endodontics, crowns and bridges) than the scenario of no fluoride use.

A cluster-randomized trial assessed the efficacy and costs of fluoride varnish application for caries prevention in a high-risk population of 513 South African children (*32*). In addition to supervised toothbrushing with fluoride toothpaste, participants were randomly allocated to receive fluoride varnish application every 3 months or no additional intervention (control) and followed for 24 months. Dental restorations were received or required in 10.2% of teeth in each treatment group. No significant difference was seen between treatment groups for tooth extractions (3.9% versus 4.1% in the fluoride varnish and control groups, respectively). Fluoride varnish was associated with high initial costs, but follow-up costs were comparable in both groups, resulting in fluoride varnish being significantly more expensive than no additional intervention (control).

A retrospective study evaluated caries increment and performed a cost analysis of a school-based programme of biannual fluoride applications for adolescents 12 to 15 years in Sweden (*33*). The programme was introduced in selected public dental clinics in 2003 and extended to all clinics within the region in 2008. Caries data for three groups of participants were compared: two intervention groups (with participants born in 1993 or 1998) who received

fluoride varnish and a control group (with participants born in 1993) who did not receive fluoride varnish. The implementation of the school-based fluoride varnish programme was associated with significantly lower caries prevalence and caries increment in 15-year-olds. Over 4 years, the estimated cost per participant was about €44.

Cost–effectiveness and estimated net monetary benefits of a programme of one to five visits for fluoride varnish application were evaluated in a study of children aged 9 to 30 months in Thailand (*34*). From the provider's perspective, one to three visits for fluoride varnish application decreased decayed, missing and filled primary teeth and saved costs compared with no visit, one visit and two visits. From the patient's perspective, the estimated net monetary benefits were positive for up to three visits, although no differences were seen in the incremental cost-effectiveness ratios.

A cost–effectiveness analysis estimated the average cost–effectiveness ratio of dental sealants versus fluoride varnish in a school-based setting (*35*). Over a 4-year period, treatment costs for sealants and varnish were US$ 104.25 and US$ 44.96 per child, respectively. The higher cost of sealants was due primarily to differences in labour (30 minutes of a dentist and dental assistant per sealant application compared with 5 minutes from a school health aide per varnish application). The corresponding average cost–effectiveness ratios were US$ 137 and US$ 102 per carious lesion prevented, respectively. Varnish was more cost-effective than sealants, although the difference was not statistically significant.

Availability

The applications reported that fluoride gel, mouthrinse (higher strength) and varnish are available as prescription products or via medical/dental distributors for professional use, but it highlighted that availability was often limited in public oral health centres. Lower strength fluoride mouthrinse is available as an over-the-counter product.

Procurement of supplies for school-based oral health programmes is generally undertaken by the programme organizers (ministries of health and/or education, or other agencies or organizations).

Committee recommendations

The Expert Committee acknowledged the large global burden of dental caries and noted the work undertaken by WHO in developing a global oral health action plan, in which a target has been set that 50% of countries will include essential dental preparations on the EML/EMLc in their national essential medicines lists by 2030.

The Committee recalled the request of the 2021 Expert Committee for WHO to identify and define alternative fluoride-containing formulations for use in the prevention of dental caries.

The Committee considered that the evidence presented in the applications for fluoride gel, mouthrinse and varnish supported the effectiveness and safety of these products in the prevention of dental caries. The Committee also noted that that school-based fluoride programmes had been shown to be a cost-effective public health intervention in some settings.

The Expert Committee therefore recommended the inclusion of gel, mouthrinse and varnish as specific formulations of fluoride on the core list of the EML and EMLc for prevention of dental caries.

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Resin-based composites – addition – EML and EMLc

Resin-based composites	ATC code: not applicable

Proposal

Addition of resin-based composites on the core list of the EML and EMLc for the prevention and treatment of dental caries in adults and children.

Applicant

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Noncommunicable Diseases

EML/EMLc

EML and EMLc

Section

30 Dental medicines and preparations

Dose form(s) & strengths(s)

Low-viscosity: single-use applicator or multi-use bottle (of any type for use as dental sealant)

High-viscosity: single-use capsule or multi-use syringe (of any type for use as dental filling material)

Core/complementary

Core

Individual/square box listing

Individual

Background

Resin-based composites have not previously been considered for inclusion on the Model Lists.

Glass ionomer cement was added to the Model Lists in 2021 as a dental sealant and filling material for the prevention and treatment of dental caries. The Expert Committee took into consideration that dental sealants, including

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glass ionomer cement, have been shown to be highly effective in the prevention and treatment dental caries. The main advantage of glass ionomer cement over other sealants was the simplicity of application, making it suitable for use in atraumatic restorative treatment by dentists and other health professionals in primary care, and community and field settings outside of specialized dental clinics. The Committee noted that while other types of sealants or fillings, such as resin-based products, are at least as effective as glass ionomer cement sealants and may have better mechanical properties (e.g. adherence to the tooth), they require more specialized expertise and application techniques and conditions. Glass ionomer cement was considered particularly suitable for people who are unable to tolerate conventional invasive dental treatment, such as young children, elderly people and patients with mental health conditions who may have difficulty cooperating (*1*).

Public health relevance

The WHO global oral health status report, using the latest available data of the Global Burden of Disease Study 2019, estimates that oral diseases affect close to 3.5 billion people worldwide. Dental caries is the most widespread oral disease with more than 2.5 billion untreated cases. This includes more than 2 billion estimated cases of caries in permanent teeth (global average prevalence of 29%) and 514 million estimated cases of caries in primary (deciduous) teeth (global average prevalence of 43%). Among the 194 WHO Member States, 134 have prevalence figures greater than 40% for caries in primary teeth. More than three quarters of cases of untreated caries teeth are found in middle-income countries. Over the past 30 years cases of untreated caries have increased and surpassed the demographic population growth during the same period (*2*).

Untreated dental caries may cause pain and infection, and may lead to systemic infections requiring hospitalization and complex treatment. The high prevalence and severity of untreated dental caries in children can contribute to low body mass index and stunting (*3–5*). Additionally, dental caries results in significant absenteeism in schools and workplaces (*6,7*). Good oral health is essential for healthy aging (*8*).

The burden of dental caries varies significantly across populations within and between countries, with a clear socioeconomic gradient showing higher disease burden in deprived and disadvantaged communities, who also have limited access to prevention and oral health services (*2,9*). Caries affects people throughout their lives, with varying patterns of burden across age groups – starting in early childhood, increasing notably in adolescence and continuing to rise in adulthood (*10*).

Summary of evidence: benefits

Resin-based composites as sealants

A 2017 Cochrane systematic review of 38 randomized controlled trials (7924 participants) evaluated the effectiveness of dental sealants for preventing dental caries in children and adolescents (*11*). For the comparison of resin-based composite sealants versus no sealant, there was moderate quality evidence that resin-based sealants were superior to no sealant for preventing caries in first permanent molars in children aged 5–10 years at 2 years of follow-up (odds ratio (OR) 0.12, 95% confidence interval (CI) 0.08 to 0.97; seven randomized controlled trials, 1322 participants). The superior effect was maintained over 48 and 54 months of follow-up, however the quality and quantity of the evidence declined. For comparisons of glass ionomer sealants versus resin sealants, the trials identified in the review reported inconclusive results for relative effectiveness, although they generally indicated that resin-based sealants had better retention rates at 24 months follow-up and beyond.

A 2022 Cochrane systematic review of nine randomized controlled trials (1120 participants) evaluated the effectiveness of different dental sealants for preventing dental caries in primary teeth of children aged 18 months to 8 years (*12*). Data were not pooled due to differences in study design (e.g. age of participants and duration of follow-up). The incidence of development of new caries lesions was typically low across the different sealant types evaluated; however, the authors concluded that the certainty of the evidence for the comparisons and outcome of caries incidence was low or very low. A study with 200 participants reported an advantage of resin-based sealants over glass ionomer sealants for complete or partial retention at 24 months (OR 0.20, 95% CI 0.11 to 0.36) (*13*).

A 2020 Cochrane systematic review of 11 randomized controlled trials (3374 participants) compared pit and fissure sealants versus fluoride varnish for preventing dental caries in permanent teeth of children and adolescents (*14*). For the comparison of resin-based sealants versus fluoride varnish, it was uncertain whether one was better than the other in preventing caries in first permanent molars at 2–3 years of follow up (OR 0.67, 95% CI 0.37 to 1.19; four randomized controlled trials, 1683 participants). There was low-certainty evidence from one study (542 participants) of a small advantage for resin-based sealant over fluoride varnish for the outcomes of decayed, missing and filled permanent surfaces increment at 2 years (mean difference (MD) –0.09, 95% CI –0.15 to –0.03) and decayed, missing and filled permanent teeth increment at 2 years (MD –0.08, 95% CI –0.14 to –0.02) (*15*). There was very low-certainty evidence from one study (75 participants) of a benefit for sealant at 4 years in preventing caries (risk ratio (RR) 0.42, 95% CI 0.21 to 0.84) and at 9 years (RR 0.48, 95% CI 0.29 to 0.79; 75 children) (*16*).

Resin-based composites as filling material

A 2021 Cochrane systematic review of eight randomized controlled trials compared the efficacy as measured by restoration failure or survival at 3 years follow-up of direct composite resin fillings versus amalgam fillings for permanent posterior teeth (*17*). Data were combined from two parallel-group trials (921 participants) for the primary meta-analyses. There was low-certainty evidence that composite resin restorations had a greater risk of failure compared with amalgam restorations (RR 1.89, 95% CI 1.52 to 2.35), and were at higher risk of secondary caries (RR 2.14, 95% CI 1.67 to 2.74). There was also low certainty evidence that composite resin restorations were not more likely to result in restoration fracture (RR 0.87, 95% CI 0.46 to 1.64). The authors noted that composite resin materials have improved substantially in the years since the trials informing the primary analyses were conducted, and that the global phase-down of dental amalgam with the Minamata Convention on Mercury was an important consideration for decision-making when choosing materials for dental restorations.

A 2015 systematic review of 17 clinical studies evaluated the long-term clinical performance of composite resin restorations placed in anterior teeth (*18*). Among a total of 1821 restorations evaluated, the total failure rate was 24.1%. Annual failure rates varied from 0 to 4.1%, and survival rates varied from 53.3% to 100.0% across the studies.

Summary of evidence: harms

The 2021 Cochrane systematic review comparing composite resin fillings with amalgam fillings for permanent posterior teeth found very low-certainty evidence suggesting that there may be no clinically important differences in the safety profile of amalgam compared with composite resin dental restorations (*17*).

A 2015 systematic literature review examined allergic reactions to dental materials, considering both patients and providers. In the case of resin-based composites, the main potential allergen is the metacrylate compound. However, reports of allergic reactions specifically to resin-based composite fillings or dental sealants were rare. Reactions are typically localized, such as erythema (redness) of the surrounding gum, and subside after the removal of the resin-based composite material (*19*).

A study based on data from the Norwegian Mother and Child Cohort Study found no increased risk for adverse birth outcomes associated with placement of resin-based composite fillings during pregnancy (*20*).

WHO guidelines

WHO plays an important role in global coordination of the work on phasing down the use of dental amalgam and the introduction of good-quality alternative materials for restorative dental care (*21*).

A 2022 WHO briefing note on the prevention and treatment of dental caries with mercury-free products and minimal intervention provided updated guidance on resin-based composites (*22*). The publication lists the following benefits of using resin-based composites:

- effective against caries, with good durability in small-to-moderate restorations, and more durable than glass ionomer cement for large, multisurface, load-bearing restorations;
- minimally invasive and protective of more of the natural tooth structure than conventional methods;
- improved health and quality of life through reductions in infection, pain, tooth damage and the need to fill future cavities, thereby reducing financial burdens for individuals and health systems, and reducing school and work absenteeism;
- aesthetic benefits, as composite resin can match the colour and translucency of natural teeth;
- environmental and public health benefits as a mercury-free alternative to dental amalgam;
- safe, cost-effective and potentially widely available; and
- suitable for use in primary care facilities by trained dentists.

The 2011 World Health Assembly resolution on oral health (*23*) and the 2022 draft global strategy on oral health (*24*) highlight the urgent need to intensify preventive efforts, particularly for dental caries. To address this issue, the draft global oral health action plan was prepared, which includes a target that 50% of countries will include dental preparations that are listed in the WHO Model Lists on their national essential medicines lists by 2030 (*25*).

Costs/cost–effectiveness

Evidence on the cost and cost–effectiveness of resin-based composites as dental sealant and filling material is limited.

A study in Chile modelled the cost–effectiveness of different caries preventive programmes versus no intervention from a societal perspective (*26*). Health outcomes were measured as dental caries averted over a 6-year period. Costs were estimated as direct treatment costs, programmes costs and costs of parental productivity losses as a result of each dental caries prevention programme. Four programmes (salt fluoridation, water fluoridation, milk fluoridation and fluoridated mouthrinses) showed net social savings for dental caries averted. Programmes using fluoride gel application, dental sealants and supervised toothbrushing were associated with costs per diseased tooth averted of US$ 21.30, US$ 11.56 and US$ 8.55, respectively.

A multicountry randomized controlled trial evaluated the cost–effectiveness of glass ionomer cement versus resin composites in the treatment of dental caries from a payers perspective (*27*). Overall costs were lower for glass hybrid than resin composites in Croatia, Serbia and Türkiye, but differences in costs between interventions were minimal in Italy. The overall survival time for restorations over 3 years was not significantly different between interventions.

A cost-comparison study of dental filling procedures using amalgam and resin composite fillings was done in nine European countries (*28*). Mean unit costs for dental amalgam and resin composite fillings were €2.03 and €4.75, respectively.

Availability

Resin-based composites are available through medical and dental retailers for professional use and are reported to be available globally.

For public dental services, procurement of supplies such as resin-based composite is generally undertaken by the service administrators (e.g. health ministry or other agencies).

Committee recommendations

The Expert Committee acknowledged the large global burden of dental caries and noted the work undertaken by WHO in developing a global oral health action plan, in which targets have been set that by 2030, 50% of countries will include essential dental preparations that are on the EML/EMLc in their national essential medicines lists, and 90% of countries will have implemented measures to phase down or will have phased out the use of dental amalgam as stipulated in the Minamata Convention on Mercury.

The Committee noted that the available evidence indicated that resin-based composites were effective and safe for use as dental sealants (low-viscosity forms) and as filling materials (high-viscosity forms) in the prevention and treatment of dental caries. The Committee also noted that resin-based composites may have functional and aesthetic advantages compared with glass ionomer cement, however they required more specialized expertise and facilities for application. The Committee noted that the evidence suggested that resin-based composites were not as effective as dental amalgam when used as a filling material but considered that the availability of alternatives to dental amalgam was important to enable parties to the Minamata Convention on Mercury to achieve the mandated phase down of dental amalgam use to reduce environmental mercury pollution.

The Committee noted that limited information was available on the cost and cost–effectiveness of resin-based composites. They may be more expensive than other prevention and treatment options. The Committee considered that

having more treatment options available could increase access and affordability at the country level.

The Expert Committee therefore recommended the inclusion of resin-based composites on the core list of the EML and EMLc for use as sealant and filling material in the prevention and treatment of dental caries.

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Acknowledgements

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Annex 1

WHO Model List of Essential Medicines – 23rd List (2023)

Explanatory notes

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

Where the [c] symbol is placed next to an individual medicine or strength of medicine on the core list it signifies that there is a specific indication for restricting its use to children.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

Where the *[c]* symbol is placed next to an individual medicine or strength of medicine on the complementary list it signifies that the medicine(s) require(s) specialist diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training for their use in children.

The **square box symbol** (□) is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the Anatomical Therapeutic Chemical (ATC) classification, which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Not all square box listings are applicable to medicine selection for children. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines. However, the selection and use of quality-assured generics and biosimilars of essential medicines at country level is recommended.

National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The ⟦a⟧ symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine can be found in Table 1.1.

The presence of an entry on the Essential Medicines List carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that, when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO website https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/quality-assurance.

Medicines and dosage forms are listed in alphabetical order within each section and the order of listing does not imply preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of The International Pharmacopoeia. https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES

1.1 General anaesthetics and oxygen

1.1.1 *Inhalational medicines*

halothane	**Inhalation.**
isoflurane	**Inhalation.**
nitrous oxide	**Inhalation.**
oxygen	**Inhalation** (medical gas).
sevoflurane	**Inhalation.**

1.1.2 *Injectable medicines*

ketamine	**Injection:** 50 mg/mL (as hydrochloride) in 10 mL vial.
☐ propofol Therapeutic alternatives: – thiopental	**Injection:** 10 mg/mL; 20 mg/mL.

1.2 Local anaesthetics

☐ bupivacaine Therapeutic alternatives to be reviewed	**Injection:** 0.25%; 0.5% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4 mL ampoule to be mixed with 7.5% glucose solution.
☐ lidocaine Therapeutic alternatives to be reviewed	**Injection:** 1%; 2% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 5% (hydrochloride) in 2 mL ampoule to be mixed with 7.5% glucose solution. **Topical forms:** 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	**Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000. **Injection:** 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.

Complementary List

ephedrine	*Injection: 30 mg/mL (hydrochloride) in 1 mL ampoule.* *(For use in spinal anaesthesia during delivery, to prevent hypotension).*

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES *(continued)*	

1.3 Preoperative medication and sedation for short-term procedures

atropine	**Injection:** 1 mg (sulfate) in 1 mL ampoule.
□ midazolam Therapeutic alternatives to be reviewed	**Injection:** 1 mg/mL. **Oral liquid:** 2 mg/mL [c] . **Tablet:** 7.5 mg; 15 mg.
morphine	**Injection:** 10 mg (sulfate or hydrochloride) in 1 mL ampoule.

1.4 Medical gases

oxygen*	**Inhalation** For use in the management of hypoxaemia. * No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE	

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

acetylsalicylic acid	**Suppository:** 50 mg to 150 mg. **Tablet:** 100 mg to 500 mg.
ibuprofen [a]	**Oral liquid:** 100 mg/5 mL [c] , 200 mg/5 mL. **Tablet:** 200 mg; 400 mg; 600 mg. [a] Not in children less than 3 months.
paracetamol* (acetaminophen)	**Oral liquid:** 120 mg/5 mL or 125 mg/5 mL**, 250 mg/5 mL [c] . **The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided. **Suppository:** 100 mg, 250 mg [c] . **Tablet:** 250 mg, 325 mg, 500 mg. **Tablet (dispersible):** 100 mg, 250 mg [c] . * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*

2.2 Opioid analgesics

codeine	**Tablet:** 30 mg (phosphate).
fentanyl*	**Transdermal patch:** 12 micrograms/hr; 25 micrograms/hr; 50 micrograms/hr; 75 micrograms/hr; 100 micrograms/hr * For the management of cancer pain
☐ morphine Therapeutic alternatives: – hydrormorphone – oxycodone	**Granules (slow release; to mix with water):** 20 mg to 200 mg (morphine sulfate). **Injection:** 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule. **Oral liquid:** 10 mg/5 mL (morphine hydrochloride or morphine sulfate). **Tablet (slow release):** 10 mg to 200mg (morphine hydrochloride or morphine sulfate). **Tablet (immediate release):** 10 mg (morphine sulfate).

Complementary list

*methadone**	***Tablet:** 5 mg; 10 mg (hydrochloride)* ***Oral liquid:** 5 mg/5 mL; 10 mg/5 mL (hydrochloride)* ***Concentrate for oral liquid:** 5 mg/mL; 10 mg/mL (hydrochloride)* * For the management of cancer pain.*

2.3 Medicines for other common symptoms in palliative care

amitriptyline	**Tablet:** 10 mg; 25 mg; 75 mg.
cyclizine [c]	**Injection:** 50 mg/mL. **Tablet:** 50 mg.
dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule. **Oral liquid:** 2 mg/5 mL. **Tablet:** 2 mg [c] ; 4 mg.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*

diazepam	**Injection:** 5 mg/mL. **Oral liquid:** 2 mg/5 mL. **Rectal gel:** 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system. **Rectal solution:** 2 mg/mL in 1.25 mL, 2.5 mL rectal tube; 4 mg/mL in 2.5 mL rectal tube. **Tablet:** 5 mg; 10 mg.
docusate sodium	**Capsule:** 100 mg. **Oral liquid:** 50 mg/5 mL.
fluoxetine	**Solid oral dosage form:** 20 mg (as hydrochloride).
haloperidol	**Injection:** 5 mg in 1 mL ampoule. **Oral liquid:** 2 mg/mL. **Solid oral dosage form:** 0.5 mg; 2mg; 5 mg.
hyoscine butylbromide	**Injection:** 20 mg/mL.
hyoscine hydrobromide [c]	**Injection:** 400 micrograms/mL; 600 micrograms/mL. **Transdermal patches:** 1 mg/72 hours.
lactulose [c]	**Oral liquid:** 3.1 to 3.7 g/5 mL.
loperamide	**Solid oral dosage form:** 2 mg.
metoclopramide	**Injection:** 5 mg/mL (hydrochloride) in 2 mL ampoule. **Oral liquid:** 5 mg/5 mL. **Solid oral dosage form:** 10 mg (hydrochloride).
midazolam	**Injection:** 1 mg/mL; 5 mg/mL. **Oral liquid:** 2mg/mL [c] . **Solid oral dosage form:** 7.5 mg; 15 mg.
☐ ondansetron [a] Therapeutic alternatives: – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg base/mL in 2 mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base. [a] > 1 month.
senna	**Oral liquid:** 7.5 mg/5 mL.

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS

dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.
epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
hydrocortisone	**Powder for injection:** 100 mg (as sodium succinate) in vial.

◻ loratadine*

Therapeutic alternatives:
– cetirizine
– fexofenadine

Oral liquid: 1 mg/mL.

Tablet: 10 mg.

* There may be a role for sedating antihistamines for limited indications (EMLc).

◻ prednisolone

Therapeutic alternatives:
– prednisone

Oral liquid: 5 mg/mL [c] .

Tablet: 5 mg; 25 mg.

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS

4.1 Non-specific

charcoal, activated	**Powder.**

4.2 Specific

acetylcysteine	**Injection:** 200 mg/mL in 10 mL ampoule. **Oral liquid:** 10% [c] ; 20% [c] .
atropine	**Injection:** 1 mg (sulfate) in 1 mL ampoule.
calcium gluconate	**Injection:** 100 mg/mL in 10 mL ampoule.
methylthioninium chloride (methylene blue)	**Injection:** 10 mg/mL in 10 mL ampoule.
naloxone	**Injection:** 400 micrograms (hydrochloride) in 1 mL ampoule.
penicillamine	**Solid oral dosage form:** 250 mg.
potassium ferric hexacyano-ferrate(II) -2H$_2$O (Prussian blue)	**Powder for oral administration.**
sodium nitrite	**Injection:** 30 mg/mL in 10 mL ampoule.
sodium thiosulfate	**Injection:** 250 mg/mL in 50 mL ampoule.

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS *(continued)*

Complementary List

deferoxamine	**Powder for injection:** *500 mg (mesilate) in vial.*
dimercaprol	**Injection in oil:** *50 mg/mL in 2 mL ampoule.*
fomepizole	**Injection:** *5 mg/mL (sulfate) in 20 mL ampoule or 1 g/mL (base) in 1.5 mL ampoule.*
sodium calcium edetate	**Injection:** *200 mg/mL in 5 mL ampoule.*
succimer	**Solid oral dosage form:** *100 mg.*

5. MEDICINES FOR DISEASES OF THE NERVOUS SYSTEM

5.1 Antiseizure medicines

carbamazepine	**Oral liquid:** 100 mg/5 mL.
	Tablet (chewable): 100 mg; 200 mg.
	Tablet (scored): 100 mg; 200 mg; 400 mg.
diazepam	**Rectal gel:** 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system.
	Rectal solution: 2 mg/mL in 1.25 mL, 2.5 mL rectal tube; 4 mg/mL in 2.5 mL rectal tube.
lamotrigine*	**Tablet:** 25 mg; 50 mg; 100 mg; 200 mg.
	Tablet (chewable, dispersible): 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg.
	* For use as adjunctive therapy for treatment-resistant partial or generalized seizures.
levetiracetam	**Oral solution:** 100 mg/mL.
	Tablet: 250 mg; 500 mg; 750 mg; 1000 mg.
☐ lorazepam Therapeutic alternatives: – diazepam (injection) – midazolam (injection)	**Injection:** 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.
magnesium sulfate*	**Injection:** 0.5 g/mL in 2 mL ampoule (equivalent to 1 g in 2 mL; 50% weight/volume); 0.5 g/mL in 10 mL ampoule (equivalent to 5 g in 10 mL; 50% weight/volume).
	* For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.

5. MEDICINES FOR DISEASES OF THE NERVOUS SYSTEM *(continued)*

midazolam	**Solution for oromucosal administration:** 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL, 2 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL pre-filled syringe.
	Injection*: 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial.
	* For buccal administration when solution for oromucosal administration is not available.
phenobarbital	**Injection:** 30 mg/mL or 60 mg/mL **[c]** ; 200 mg/mL (sodium).
	Oral liquid: 15 mg/5 mL.
	Tablet: 15 mg to 100 mg.
phenytoin	**Injection:** 50 mg/mL (phenytoin sodium).
	Oral liquid: 30 mg/5 mL (phenytoin).
	Solid oral dosage form: 25 mg; 50 mg; 100 mg (phenytoin sodium).
	Tablet (chewable): 50 mg (phenytoin).
valproic acid (sodium valproate)*	**Oral liquid:** 200 mg/5 mL.
	Tablet (crushable): 100 mg.
* *Avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.*	**Tablet (enteric-coated):** 200 mg; 500 mg.

Complementary List

ethosuximide	*Capsule: 250 mg.*
	Oral liquid: 250 mg/5 mL.
levetiracetam	*Concentrate solution for infusion: 500 mg/5 mL in 5 mL vial.*
	Solution for infusion: 5 mg/mL; 10 mg/mL; 15 mg/mL in 100 mL bag.

5. MEDICINES FOR DISEASES OF THE NERVOUS SYSTEM *(continued)*

valproic acid (sodium valproate) *	***Injection:*** *100 mg/mL in 3 mL, 4 mL, 10 mL ampoule.*

* Avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.

5.2 Medicines for multiple sclerosis

Complementary List

cladribine	***Tablet:*** *10 mg.*
glatiramer acetate	***Injection (subcutaneous):*** *20 mg/mL; 40 mg/mL in pre-filled syringe.*
rituximab*	***Injection (intravenous):*** *500 mg/50 mL in 50 mL vial.*

* including quality-assured biosimilars

5.3 Medicines for parkinsonism

☐ biperiden	**Injection:** 5 mg (lactate) in 1 mL ampoule.
Therapeutic alternatives:	**Tablet:** 2 mg (hydrochloride).
– trihexyphenidyl	
levodopa + ☐ carbidopa	**Tablet:** 100 mg + 10 mg; 100 mg + 25 mg; 250 mg + 25 mg.
Therapeutic alternatives:	
– benserazide (for carbidopa)	

6. ANTI-INFECTIVE MEDICINES

6.1 Anthelminthics

6.1.1 *Intestinal anthelminthics*

albendazole	**Tablet (chewable, scored):** 400 mg.
ivermectin	**Tablet:** 3 mg.
levamisole	**Tablet:** 50 mg; 150 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 500 mg.
	Tablet (scored): 600 mg.
pyrantel	**Tablet (chewable):** 250 mg (as embonate or pamoate).

6.1.2 *Antifilarials*

albendazole	**Tablet (chewable, scored):** 400 mg.
diethylcarbamazine	**Tablet:** 50 mg; 100 mg (dihydrogen citrate).
ivermectin	**Tablet:** 3 mg.

6.1.3 *Antischistosomals and other antitrematode medicines*

praziquantel	**Tablet:** 150 mg, 500 mg.
	Tablet (scored): 600 mg.
triclabendazole	**Tablet (scored):** 250 mg.

Complementary List

oxamniquine*	*Capsule:* 250 mg.
	Oral liquid: 250 mg/5 mL.
	* For use when praziquantel treatment fails.

6.1.4 *Cysticidal medicines*

Complementary List

albendazole	*Tablet (chewable):* 200 mg [c] .
	Tablet (chewable, scored): 400 mg.
mebendazole	*Tablet (chewable):* 100 mg [c] , 500 mg.
praziquantel	*Tablet:* 150 mg, 500 mg.
	Tablet (scored): 600 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics was developed – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

ACCESS GROUP ANTIBIOTICS
This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

WATCH GROUP ANTIBIOTICS
This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

RESERVE GROUP ANTIBIOTICS
This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably carbapenem resistant Enterobacteriaceae. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.1 *Access group antibiotics*

| amikacin | **Injection:** 50 mg/mL (as sulfate) [c] ; 250 mg/mL (as sulfate) in 2 mL vial. |

	FIRST CHOICE	**SECOND CHOICE**
	– *High-risk febrile neutropenia*	– *Sepsis in neonates and children* [c]
	– *Pyelonephritis or prostatitis (severe)*	

amoxicillin	**Powder for injection:** 250 mg; 500 mg; 1 g (as sodium) in vial.
	Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (as trihydrate) [c] .
	Solid oral dosage form: 250 mg; 500 mg; 1g (as trihydrate).
	Tablet (dispersible, scored): 250 mg; 500 mg (as trihydrate) [c] .

	FIRST CHOICE	**SECOND CHOICE**
	– *Community acquired pneumonia (mild to moderate)*	– *Acute bacterial meningitis*
	– *Community acquired pneumonia (severe)* [c]	
	– *Complicated severe acute malnutrition* [c]	
	– *Exacerbations of COPD*	
	– *Otitis media*	
	– *Pharyngitis*	
	– *Progressive apical dental abscess*	
	– *Sepsis in neonates and children* [c]	
	– *Sinusitis*	
	– *Uncomplicated severe acute malnutrition* [c]	

6.   ANTI-INFECTIVE MEDICINES *(continued)*

amoxicillin + clavulanic acid	**Powder for injection:** 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial.
	Powder for oral liquid: 125 mg (as trihydrate) + 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL [c] .
	Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt); 875 mg (as trihydrate) + 125 mg (as potassium salt).
	Tablet (dispersible): 200 mg (as trihydrate) + 28.5 mg (as potassium salt) [c] ; 250 mg (as trihydrate) + 62.5 mg (as potassium salt) [c] .

FIRST CHOICE	**SECOND CHOICE**
– *Community acquired pneumonia (severe)* [c]	– *Bone and joint infections*
– *Complicated intraabdominal infections (mild to moderate)*	– *Community-acquired pneumonia (mild to moderate)*
– *Exacerbations of COPD*	– *Community acquired pneumonia (severe)*
– *Hospital acquired pneumonia*	– *Otitis media*
– *Low-risk febrile neutropenia*	– *Surgical prophylaxis*
– *Lower urinary tract infections*	
– *Sinusitis*	
– *Skin and soft tissue infections*	

ampicillin	**Powder for injection:** 500 mg; 1 g (as sodium) in vial.

FIRST CHOICE	**SECOND CHOICE**
– *Community acquired pneumonia (severe)* [c]	– *Acute bacterial meningitis*
– *Complicated intraabdominal infections* [c]	
– *Complicated severe acute malnutrition* [c]	
– *Sepsis in neonates and children* [c]	

6. ANTI-INFECTIVE MEDICINES *(continued)*

benzathine benzylpenicillin	**Powder for injection:** 1.2 million IU (≈ 900 mg) in vial [c] ; 2.4 million IU (≈ 1.8 g) in vial.

FIRST CHOICE	SECOND CHOICE
– *Syphilis*	

benzylpenicillin	**Powder for injection:** 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)* [c]	– *Acute bacterial meningitis*
– *Complicated severe acute malnutrition* [c]	
– *Sepsis in neonates and children* [c]	
– *Syphilis*	

cefalexin	**Powder for oral liquid:** 125 mg/5 mL; 250 mg/5 mL (anhydrous).
	Solid oral dosage form: 250 mg; 500 mg (as monohydrate).
	Tablet (dispersible): 125 mg [c] ; 250 mg [c] .

FIRST CHOICE	SECOND CHOICE
– *Skin and soft tissue infections*	– *Exacerbations of COPD*
	– *Pharyngitis*

cefazolin [a]	**Powder for injection:** 1 g (as sodium salt) in vial.
	[a] > 1 month.

FIRST CHOICE	SECOND CHOICE
– *Surgical prophylaxis*	– *Bone and joint infections*

chloramphenicol	**Oily suspension for injection*:** 0.5 g/mL (as sodium succinate) in 2 mL ampoule.
	* Only for the presumptive treatment of epidemic meningitis in children older than 2 years and in adults.
	Powder for injection: 1 g (sodium succinate) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

clindamycin

Capsule: 150 mg (as hydrochloride).

Injection: 150 mg/mL (as phosphate); 600 mg/4 mL (as phosphate); 900 mg/6 mL (as phosphate).

Oral liquid: 75 mg/5 mL (as palmitate hydrochloride) **[c]** .

FIRST CHOICE	SECOND CHOICE
– Necrotizing fasciitis	*– Bone and joint infections*

☐ cloxacillin*

Therapeutic alternatives:
– 4th level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)

Capsule: 250 mg **[c]** , 500 mg; 1 g (as sodium).

Powder for injection: 250 mg **[c]** , 500 mg (as sodium) in vial.

Powder for oral liquid: 125 mg/5 mL, 250 mg/5 mL (as sodium) **[c]** .

* cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.

FIRST CHOICE	SECOND CHOICE
– Bone and joint infections	*– Sepsis in neonates and children* **[c]**
– Skin and soft tissue infections	

doxycycline **[a]**

Oral liquid: 50 mg/5 mL (calcium) **[c]** .

Powder for oral liquid: 25 mg/5 mL (monohydrate) **[c]** .

Powder for injection: 100 mg in vial.

Solid oral dosage form: 50 mg **[c]** ; 100 mg (as hyclate).

Tablet (dispersible): 100 mg (as monohydrate) **[c]** .

[a] Use in children <8 years only for life-threatening infections when no alternative exists.

FIRST CHOICE	SECOND CHOICE
– Cholera	*– Cholera* **[c]**
– Sexually transmitted infection due to Chlamydia trachomatis	*– Community acquired pneumonia (mild to moderate)*
	– Exacerbations of COPD

6. ANTI-INFECTIVE MEDICINES *(continued)*

gentamicin	**Injection:** 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.	
	FIRST CHOICE	**SECOND CHOICE**
	– *Acute bacterial meningitis in neonates* [c]	– *Gonorrhoea*
	– *Community acquired pneumonia (severe)* [c]	– *Surgical prophylaxis*
	– *Complicated intraabdominal infections* [c]	
	– *Complicated severe acute malnutrition* [c]	
	– *Sepsis in neonates and children* [c]	

metronidazole	**Injection:** 500 mg in 100 mL vial.	
	Oral liquid: 200 mg/5 mL (as benzoate).	
	Suppository: 500 mg; 1 g.	
	Tablet: 200 mg; 250 mg; 400 mg; 500 mg.	
	FIRST CHOICE	**SECOND CHOICE**
	– *C. difficile infection*	– *Complicated intraabdominal infections (mild to moderate)*
	– *Complicated intraabdominal infections (mild to moderate)*	
	– *Complicated intrabdominal infections (severe)*	
	– *Necrotizing fasciitis*	
	– *Surgical prophylaxis*	
	– *Trichomoniasis*	

nitrofurantoin	**Oral liquid:** 25 mg/5 mL [c] .	
	Solid oral dosage form: 50 mg [c] ; 100 mg.	
	FIRST CHOICE	**SECOND CHOICE**
	– *Lower urinary tract infections*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

phenoxymethylpenicillin	**Powder for oral liquid:** 250 mg/5 mL (as potassium). **Solid oral dosage form:** 250 mg; 500 mg (as potassium).	
	FIRST CHOICE	**SECOND CHOICE**
	– *Community acquired pneumonia (mild to moderate)* – *Pharyngitis* – *Progressive apical dental abscess*	

procaine benzylpenicillin*	**Powder for injection:** 1 g (=1 million IU); 3 g (=3 million IU) in vial. * Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.	
	FIRST CHOICE	**SECOND CHOICE**
	– *Syphilis (congenital)* [c]	– *Syphilis*

spectinomycin	**Powder for injection:** 2 g (as hydrochloride) in vial.	
	FIRST CHOICE	**SECOND CHOICE**
		– *Gonorrhoea*

sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg. **Tablet (dispersible):** 100 mg + 20 mg [c] .	
	FIRST CHOICE	**SECOND CHOICE**
	– *Lower urinary tract infections*	– *Acute invasive diarrhoea / bacterial dysentery*

trimethoprim	**Tablet:** 100 mg; 200 mg. **Oral liquid:** 50 mg/5 mL [c] .	
	FIRST CHOICE	**SECOND CHOICE**
	– *Lower urinary tract infections*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.2 *Watch group antibiotics*

azithromycin

Solid oral dosage form: 250 mg; 500 mg (anhydrous).

Powder for oral liquid: 200 mg/5 mL (anhydrous) [c] .

FIRST CHOICE	SECOND CHOICE
– *Cholera*	– *Acute invasive bacterial diarrhoea / dysentery*
– *Enteric fever*	– *Gonorrhoea*
– *Gonorrhoea*	
– *Sexually transmitted infection due to Chlamydia trachomatis*	
– *Trachoma*	
– *Yaws*	

cefixime

Powder for oral liquid: 100 mg/5 mL [c] .

Solid oral dosage form: 200 mg; 400 mg (as trihydrate).

FIRST CHOICE	SECOND CHOICE
	– *Acute invasive bacterial diarrhoea / dysentery*
	– *Gonorrhoea*

cefotaxime*

Powder for injection: 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis*	– *Bone and joint infections*
– *Community acquired pneumonia (severe)*	– *Pyelonephritis or prostatitis (mild to moderate)*
– *Complicated intraabdominal infections (mild to moderate)*	– *Sepsis in neonates and children* [c]
– *Complicated intraabdominal infections (severe)*	
– *Hospital acquired pneumonia*	
– *Pyelonephritis or prostatitis (severe)*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

ceftriaxone* [a]   **Powder for injection:** 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] > 41 weeks corrected gestational age.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis*	– *Acute invasive bacterial diarrhoea / dysentery*
– *Community acquired pneumonia (severe)*	– *Bone and joint infections*
– *Complicated intraabdominal infections (mild to moderate)*	– *Pyelonephritis or prostatitis (mild to moderate)*
– *Complicated intrabdominal infections (severe)*	– *Sepsis in neonates and children* [c]
– *Endophthalmitis*	
– *Enteric fever*	
– *Gonorrhoea*	
– *Hospital acquired pneumonia*	
– *Necrotizing fasciitis*	
– *Pyelonephritis or prostatitis (severe)*	

cefuroxime   **Powder for injection:** 250 mg; 750 mg; 1.5 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Surgical prophylaxis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

ciprofloxacin	**Oral liquid:** 250 mg/5 mL (anhydrous) [c] .
	Solution for IV infusion: 2 mg/mL (as hyclate) [c] .
	Solid oral dosage form: 100 mg [c] ; 250 mg; 500 mg (as hydrochloride).

FIRST CHOICE	SECOND CHOICE
– *Acute invasive bacterial diarrhoea / dysentery*	– *Cholera*
– *Enteric fever*	– *Complicated intraabdominal infections (mild to moderate)*
– *Low-risk febrile neutropenia*	
– *Pyelonephritis or prostatitis (mild to moderate)*	

☐ clarithromycin†	**Powder for oral liquid:** 125 mg/5 mL; 250 mg/5 mL.
Therapeutic alternatives:	**Powder for injection:** 500 mg in vial.
– erythromycin*	**Solid oral dosage form:** 250 mg [c] ; 500 mg.
* as second choice treatment for pharyngitis in children (EMLc only)	† clarithromycin is also listed for use in combination regimens for eradication of *H. pylori* in adults.

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (severe)*	– *Pharyngitis*

| piperacillin + tazobactam | **Powder for injection:** 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial. |

FIRST CHOICE	SECOND CHOICE
– *Complicated intraabdominal infections (severe)*	
– *High-risk febrile neutropenia*	
– *Hospital acquired pneumonia*	
– *Necrotizing fasciitis*	

| vancomycin | **Capsule:** 125 mg; 250 mg (as hydrochloride). |
| | * vancomycin powder for injection may also be used for oral administration |

FIRST CHOICE	SECOND CHOICE
	– *C. difficile infection*

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

ceftazidime	**Powder for injection:** *250 mg; 1 g (as pentahydrate) in vial.*

FIRST CHOICE	**SECOND CHOICE**
– *Endophthalmitis*	

☐ *meropenem** [a]
Therapeutic alternatives*:
– *imipenem + cilastatin*

* *complicated intraabdominal infections and high-risk febrile neutropenia only. Meropenem is the preferred choice for acute bacterial meningitis in neonates.*

Powder for injection: *500 mg (as trihydrate); 1 g (as trihydrate) in vial.*
[a] > 3 months.

FIRST CHOICE	**SECOND CHOICE**
	– *Acute bacterial meningitis in neonates* [c]
	– *Complicated intraabdominal infections (severe)*
	– *High-risk febrile neutropenia*

vancomycin	**Powder for injection:** *250 mg; 500 mg; 1 g (as hydrochloride) in vial.*

FIRST CHOICE	**SECOND CHOICE**
– *Endophthalmitis*	– *High-risk febrile neutropenia*
– *Necrotizing fasciitis*	

6.2.3 Reserve group antibiotics

Complementary List

cefiderocol	**Powder for injection:** *1 g (as sulfate tosylate) in vial.*
ceftazidime + avibactam	**Powder for injection:** *2 g + 0.5 g in vial.*
ceftolozane + tazobactam	**Powder for injection:** *1 g + 0.5 g in vial.*
colistin	**Powder for injection:** *1 million IU (as colistemethate sodium) (equivalent to 34 mg colistin base activity) in vial.*
fosfomycin	**Powder for injection:** *2 g; 4 g (as sodium) in vial.*
☐ *linezolid* *Therapeutic alternatives:* – *tedizolid phosphate*	**Injection for intravenous administration:** *2 mg/mL in 300 mL bag.* **Powder for oral liquid:** *100 mg/5 mL.* **Tablet:** *600 mg.* **Tablet (dispersible):** *150 mg* [c].

6. ANTI-INFECTIVE MEDICINES *(continued)*	
meropenem + vaborbactam	*Powder for injection: 1 g (as trihydrate) + 1 g in vial.*
plazomicin	*Injection: 500 mg/10 mL.*
polymyxin B	*Powder for injection: 500 000 IU (equivalent to 50 mg polymyxin B base) in vial.*

6.2.4 Antileprosy medicines

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	**Solid oral dosage form:** 50 mg; 100 mg.
dapsone	**Tablet:** 25 mg; 50 mg; 100 mg.
rifampicin	**Oral liquid:** 20 mg/mL **[c]** . **Solid oral dosage form:** 150 mg; 300 mg.

6.2.5 Antituberculosis medicines

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

ethambutol	**Tablet:** 100 mg; 400 mg (hydrochloride). **Tablet (dispersible):** 100 mg **[c]** .
ethambutol + isoniazid + pyrazinamide + rifampicin	**Tablet:** 275 mg + 75 mg + 400 mg + 150 mg.
ethambutol + isoniazid + rifampicin	**Tablet:** 275 mg + 75 mg + 150 mg.
ethionamide	**Tablet:** 250 mg. **Tablet (dispersible):** 125 mg **[c]** .
isoniazid	**Tablet:** 100 mg; 300 mg. **Tablet (dispersible):** 100 mg **[c]** .
isoniazid + pyrazinamide + rifampicin	**Tablet (dispersible):** 50 mg + 150 mg + 75 mg **[c]** .
isoniazid + rifampicin	**Tablet:** 75 mg + 150 mg; 150 mg + 300 mg. **Tablet (dispersible):** 50 mg + 75 mg **[c]** .

6. ANTI-INFECTIVE MEDICINES *(continued)*

isoniazid + rifapentine   **Tablet (scored):** 300 mg + 300 mg.

moxifloxacin   **Tablet:** 400 mg.

pyrazinamide   **Tablet:** 400 mg; 500 mg
Tablet (dispersible): 150 mg.

rifabutin   **Solid oral dosage form:** 150 mg.*
* For use only in patients with HIV receiving protease inhibitors.

rifampicin   **Oral liquid:** 20 mg/mL **[c]** .
Solid oral dosage form: 150 mg; 300 mg.

rifapentine   **Tablet:** 150 mg; 300 mg.

Complementary List

Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.

amikacin   *Injection: 250 mg/mL (as sulfate) in 2 mL vial.*

amoxicillin +   *Powder for oral liquid: 250 mg (as trihydrate) + 62.5 mg*
clavulanic acid*   *(as potassium salt)/5mL* **[c]** *.*
Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt).
* For use only in combination with meropenem or imipenem+cilastatin.

bedaquiline   *Tablet: 20 mg* **[c]** *; 100 mg.*

clofazimine   *Solid oral dosage form: 50 mg; 100 mg.*

☐ cycloserine   *Solid oral dosage form: 125 mg* **[c]** *; 250 mg.*
Therapeutic alternatives:
– terizidone

delamanid   *Tablet (dispersible): 25 mg* **[c]** *.*
Tablet: 50 mg.

☐ ethionamide   *Tablet: 250 mg.*
Therapeutic alternatives: *Tablet (dispersible): 125 mg* **[c]** *.*
– protionamide

levofloxacin   *Tablet: 250mg; 500 mg; 750 mg.*
Tablet (dispersible): 100 mg **[c]** *.*

linezolid   *Tablet: 600 mg.*
Tablet (dispersible): 150 mg **[c]** *.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

☐ *meropenem*

Therapeutic alternatives:
– imipenem + cilastatin

Powder for injection: 500 mg (as trihydrate);
1 g (as trihydrate) in vial.

moxifloxacin

Tablet: 400 mg.
Tablet (dispersible): 100 mg [c] *.*

p-aminosalicylate sodium

Powder for oral solution: 5.52 g in sachet (equivalent to 4 g
p-aminosalicylic acid).

pretomanid

Tablet: 200 mg.

streptomycin [c]

Powder for injection: 1 g (as sulfate) in vial.

6.3 Antifungal medicines

amphotericin B*

Powder for injection: 50 mg (liposomal complex) in vial.

Powder for injection: 50 mg (as sodium deoxycholate) in vial.

* Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.

clotrimazole

Vaginal cream: 1%; 10%.

Vaginal tablet: 100 mg; 500 mg.

fluconazole

Capsule: 50 mg.

Injection: 2 mg/mL in vial.

Oral liquid: 50 mg/5 mL.

Powder for oral liquid: 50 mg/5 mL [c] .

flucytosine

Capsule: 250 mg.

Infusion: 2.5 g in 250 mL.

griseofulvin

Oral liquid: 125 mg/5 mL [c] .

Solid oral dosage form: 125 mg; 250 mg.

itraconazole*

Capsule: 100 mg.

Oral liquid: 10 mg/mL.

* For treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by *T. marneffei* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients.

6. ANTI-INFECTIVE MEDICINES *(continued)*	
nystatin	**Lozenge:** 100 000 IU.
	Oral liquid: 100 000 IU/mL [c] .
	Pessary: 100 000 IU.
	Solid oral dosage form: 500 000 IU.
voriconazole*	**Tablet:** 50 mg; 200 mg
	Powder for injection: 200 mg in vial
	Powder for oral liquid: 40 mg/mL
	* For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.
Complementary List	
☐ *micafungin* *Therapeutic alternatives:* *– anidulafungin* *– caspofungin*	***Powder for injection:*** *50 mg (as sodium); 100 mg (as sodium) in vial.*
potassium iodide	***Saturated solution.***

6.4 Antiviral medicines

6.4.1 Antiherpes medicines

☐ aciclovir Therapeutic alternatives: – valaciclovir (oral)	**Oral liquid:** 200 mg/5 mL [c] .
	Powder for injection: 250 mg (as sodium salt) in vial.
	Tablet: 200 mg.

6.4.2 Antiretrovirals

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission, pre-exposure prophylaxsis (where indicated) and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.2.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

abacavir	**Tablet:** 300 mg (as sulfate).
lamivudine	**Oral liquid:** 50 mg/5 mL [c] . **Tablet:** 150 mg.
tenofovir disoproxil fumarate†	**Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil). † also indicated for pre-exposure prophylaxis.
zidovudine	**Capsule:** 250 mg. **Oral liquid:** 50 mg/5 mL. **Solution for IV infusion:** 10 mg/mL in 20 mL vial. **Tablet:** 300 mg.

6.4.2.2 *Non-nucleoside reverse transcriptase inhibitors*

efavirenz	**Tablet:** 600 mg.
nevirapine [a]	**Oral liquid:** 50 mg/5 mL. **Tablet:** 50 mg (dispersible); 200 mg. [a] > 6 weeks

6.4.2.3 *Protease inhibitors*

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

atazanavir + ritonavir	**Tablet (heat stable):** 300 mg (as sulfate) + 100 mg.
darunavir [a]	**Tablet:** 75 mg; 400 mg; 600 mg; 800 mg [a] > 3 years
lopinavir + ritonavir	**Solid oral dosage form:** 40 mg + 10 mg [c] . **Tablet (heat stable):** 100 mg + 25 mg; 200 mg + 50 mg.
ritonavir	**Tablet (heat stable):** 25 mg; 100 mg.

6.4.2.4 *Integrase inhibitors*

dolutegravir [a]	**Tablet (dispersible, scored):** 10 mg [c] . [a] ≥ 4 weeks and ≥ 3 kg **Tablet:** 50 mg [a] ≥ 25 kg

6. ANTI-INFECTIVE MEDICINES *(continued)*

raltegravir* **Granules for oral suspension:** 100 mg in sachet.

Tablet (chewable): 25 mg.

Tablet: 400 mg.

* For use in pregnant women and in second-line regimens in accordance with WHO treatemnt guidelines.

6.4.2.5 *Fixed-dose combinations of antiretroviral medicines*

abacavir + lamivudine **Tablet (dispersible, scored):** 120 mg (as sulfate) + 60 mg.

dolutegravir + lamivudine + tenofovir **Tablet:** 50 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)

efavirenz + ☐ emtricitabine + tenofovir **Tablet:** 600 mg + 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).

Therapeutic alternatives:
– lamivudine (for emtricitabine)

efavirenz + lamivudine + tenofovir **Tablet:** 400 mg + 300 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)

☐ emtricitabine + tenofovir† **Tablet:** 200 mg + 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).

Therapeutic alternatives:
– lamivudine (for emtricitabine) † combination also indicated for pre-exposure prophylaxis

lamivudine + zidovudine **Tablet:** 30 mg + 60 mg **[c]** ; 150 mg + 300 mg.

6.4.2.6 *Medicines for prevention of HIV-related opportunistic infections*

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim **Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg.

6.4.3 *Other antivirals*

ribavirin* **Injection for intravenous administration:** 800 mg; 1 g in 10 mL phosphate buffer solution.

Solid oral dosage form: 200 mg; 400 mg; 600 mg.

* For the treatment of viral haemorrhagic fevers.

valganciclovir* **Tablet:** 450 mg.

* For the treatment of cytomegalovirus retinitis (CMVr).

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary list

oseltamivir*	**Capsule:** *30 mg; 45 mg; 75 mg (as phosphate).*
	* *Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.*
valganciclovir* [c]	**Powder for oral solution:** *50 mg/mL*
	Tablet: *450 mg.*
	* *For the treatment of cytomegalovirus retinitis (CMVr).*

6.4.4 Antihepatitis medicines

6.4.4.1 Medicines for hepatitis B

6.4.4.1.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

entecavir	**Oral liquid:** 0.05 mg/mL
	Tablet: 0.5 mg; 1 mg
tenofovir disoproxil fumarate	**Tablet:** 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil).

6.4.4.2 Medicines for hepatitis C

Pangenotypic direct-acting antivirals should be considered as therapeutic alternatives for the purposes of selection and procurement at national level.

6.4.4.2.1 □ Pangenotypic direct-acting antiviral combinations

daclatasvir*	**Tablet:** 30 mg; 60 mg (as hydrochloride).
	* Pangenotypic when used in combination with sofosbuvir.
daclatasvir + sofosbuvir	**Tablet:** 60 mg + 400 mg.
glecaprevir + pibrentasvir	**Tablet:** 100 mg + 40 mg.
	Granules: 50 mg + 20 mg in sachet [c] .
ravidasvir*	**Tablet:** 200 mg.
	* Pangenotypic when used in combination with sofosbuvir
sofosbuvir*	**Tablet:** 200 mg; 400 mg.
	* Pangenotypic when used in combination with daclatasvir or ravidasvir
sofosbuvir + velpatasvir	**Tablet:** 200 mg + 50 mg [c] ; 400 mg + 100 mg.

6.4.4.2.2 Non-pangenotypic direct-acting antiviral combinations

ledipasvir + sofosbuvir	**Tablet:** 90 mg + 400 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.4.2.3 *Other antivirals for hepatitis C*

ribavirin*	**Injection for intravenous administration:** 800 mg; 1 g in 10 mL phosphate buffer solution.
	Solid oral dosage form: 200 mg; 400 mg; 600 mg.
	* For the treatment of hepatitis C, in combination with direct acting anti-viral medicines.

6.5 Antiprotozoal medicines

6.5.1 *Antiamoebic and antigiardiasis medicines*

diloxanide [a]	**Tablet:** 500 mg (furoate).
	[a] > 25 kg.

☐ metronidazole	**Injection:** 500 mg in 100 mL vial.
Therapeutic alternatives:	**Oral liquid:** 200 mg/5 mL (as benzoate).
– tinidazole	**Tablet:** 200 mg; 250 mg; 400 mg; 500 mg.

6.5.2 *Antileishmaniasis medicines*

amphotericin B*	**Powder for injection:** 50 mg (liposomal complex) in vial.
	Powder for injection: 50 mg (as sodium deoxycholate) in vial.
	* Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.

meglumine antimoniate	**Injection:** 1.5 g/5 mL in 5 mL ampoule.
miltefosine	**Solid oral dosage form:** 10 mg; 50 mg.
paromomycin	**Solution for intramuscular injection:** 750 mg of paromomycin base (as sulfate).
sodium stibogluconate	**Injection:** 100 mg/mL in 30 mL vial.

6.5.3 *Antimalarial medicines*

6.5.3.1 *For curative treatment*

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs) in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.

amodiaquine*	**Tablet:** 153 mg or 200 mg (as hydrochloride).
	* To be used in combination with artesunate 50 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

artemether*	**Oily injection:** 80 mg/mL in 1 mL ampoule.
	* For use in the management of severe malaria.
artemether + lumefantrine*	**Tablet:** 20 mg + 120 mg.
	Tablet (dispersible): 20 mg + 120 mg [c] .
	* Not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	**Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria.
	Rectal dosage form: 50 mg [c] ; 100 mg [c] ; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care) [c] .
	Tablet: 50 mg.
	* To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.
artesunate + amodiaquine*	**Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg.
	* Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.
artesunate + mefloquine	**Tablet:** 25 mg + 55 mg; 100 mg + 220 mg.
artesunate + pyronaridine tetraphosphate [a]	**Granules:** 20 mg + 60 mg [c] .
	Tablet: 60 mg + 180 mg.
	[a] > 5 kg
chloroquine*	**Oral liquid:** 50 mg/5 mL (as phosphate or sulfate).
	Tablet: 100 mg; 150 mg (as phosphate or sulfate).
	* For use only for the treatment of *Plasmodium vivax* infection.
dihydroartemisinin + piperaquine phosphate [a]	**Tablet:** 20 mg + 160 mg; 40 mg + 320 mg.
	[a] > 5 kg
doxycycline*	**Capsule:** 100 mg (as hydrochloride or hyclate).
	Tablet (dispersible): 100 mg (as monohydrate).
	* For use only in combination with quinine.
mefloquine*	**Tablet:** 250 mg (as hydrochloride).
	* To be used in combination with artesunate 50 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*	

primaquine* **Tablet:** 7.5 mg; 15 mg (as diphosphate).

* Only for use to achieve radical cure of *Plasmodium vivax* and *Plasmodium ovale* infections, given for 14 days.

quinine* **Injection:** 300 mg/mL (hydrochloride) in 2 mL ampoule.

Tablet: 300 mg (sulfate) or 300 mg (bisulfate).

* For use only in the management of severe malaria and should be used in combination with doxycycline.

sulfadoxine + pyrimethamine* **Tablet:** 500 mg + 25 mg.

* Only in combination with artesunate 50 mg.

6.5.3.2 *For chemoprevention*

amodiaquine – sulfadoxine + pyrimethamine [c] **Co-packaged dispersible tablets:**

amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1];

amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].

chloroquine* **Oral liquid:** 50 mg/5 mL (as phosphate or sulfate).

Tablet: 150 mg (as phosphate or sulfate).

* For use only in central American regions, for *Plasmodium vivax* infections.

doxycycline [a] **Solid oral dosage form:** 100 mg (as hydrochloride or hyclate).

[a] > 8 years.

mefloquine [a] **Tablet:** 250 mg (as hydrochloride).

[a] > 5 kg or > 3 months.

proguanil* **Tablet:** 100 mg (as hydrochloride).

* For use only in combination with chloroquine.

sulfadoxine + pyrimethamine **Tablet:** 250 mg + 12.5 mg [c] ; 500 mg + 25 mg.

6.5.4 *Antipneumocystosis and antitoxoplasmosis medicines*

pyrimethamine **Tablet:** 25 mg.

sulfadiazine **Tablet:** 500 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule.
	Oral liquid: 200 mg + 40 mg/5 mL [c] .
	Tablet: 100 mg + 20 mg; 400 mg + 80 mg [c] ; 800 mg + 160 mg
	Tablet (dispersible): 100 mg + 20 mg [c] .

Complementary List

pentamidine — *Tablet: 200 mg; 300 mg (as isethionate).*

6.5.5 Antitrypanosomal medicines

6.5.5.1 African trypanosomiasis

fexinidazole* **Tablet:** 600 mg

* For the treatment of 1st and 2nd stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.

Medicines for the treatment of 1st stage African trypanosomiasis

pentamidine* **Powder for injection:** 300 mg (as isetionate) in vial.

* To be used for the treatment of *Trypanosoma brucei gambiense* infection.

suramin sodium* **Powder for injection:** 1 g in vial.

* To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine* **Injection:** 200 mg/mL (hydrochloride) in 50 mL bottle.

* To be used for the treatment of *Trypanosoma brucei gambiense* infection.

melarsoprol **Injection:** 180 mg/5 mL in 5 mL ampoule (3.6% solution).

nifurtimox* **Tablet (scored):** 30 mg; 120 mg.

* Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.

Complementary List

melarsoprol [c] — *Injection: 180 mg/5 mL in 5 mL ampoule (3.6% solution).*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.5.2 *American trypanosomiasis*

benznidazole	**Tablet:** 12.5 mg [c] **Tablet (scored):** 50 mg; 100 mg.
nifurtimox	**Tablet:** 30 mg; 120 mg.

6.6 Medicines for ectoparasitic infections

ivermectin	**Tablet:** 3 mg

6.7 Medicines for Ebola virus disease

ansuvimab	**Powder for injection:** 400 mg
atoltivimab + maftivimab + odesivimab	**Injection:** 241.7 mg + 241.7 mg + 241.7 mg in 14.5 mL vial

6.8 Medicines for COVID-19

WHO recommends that effective and safe therapeutics for prevention and treatment of COVID-19 should be considered as essential medicines in the context of the public health emergency. WHO recommendations are revised and updated regularly in WHO living guidelines for therapeutics for the treatment and prevention of COVID-19.

Selection of essential therapeutics for COVID-19 at the national level should be informed by recommendations in these guidelines, and consideration of the latest evidence, epidemiology and national priorities.

The latest WHO Therapeutics and COVID-19: living guideline is available online at: https://app.magicapp.org/#/guideline/nBkO1E

The latest WHO Drugs to prevent COVID-19: living guideline is available online at: https://app.magicapp.org/#/guideline/L6RxYL

7. ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

acetylsalicylic acid	**Tablet:** 300 mg to 500 mg.
ibuprofen [c]	**Oral liquid:** 100 mg/5 mL [c] . **Tablet:** 200 mg; 400 mg.

7. ANTIMIGRAINE MEDICINES *(continued)*

paracetamol (acetaminophen)	**Oral liquid:** 120 mg/5 mL or 125 mg/5 mL*, 250 mg/5 mL [c] .
	* The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
	Suppository: 250 mg [c] .
	Tablet: 250 mg, 325 mg, 500 mg.
	Tablet (dispersible): 100 mg, 250 mg [c] .
sumatriptan	**Tablet:** 50 mg

7.2 For prophylaxis

☐ propranolol Therapeutic alternatives to be reviewed	**Tablet:** 20 mg; 40 mg (hydrochloride).

8. IMMUNOMODULATORS AND ANTINEOPLASTICS

8.1 Immunomodulators for non-malignant disease

Complementary List

☐ *adalimumab** *Therapeutic alternatives*:* *– certolizumab pegol* *– etanercept* *– golimumab* *– infliximab* ** including quality-assured biosimilars*	***Injection:*** *10 mg/0.2 mL* [c] *; 20 mg/0.4 mL* [c] *; 40 mg/0.8 mL; 40 mg/0.4 mL.*
azathioprine	***Oral liquid:*** *10 mg/mL* [c] *.* ***Powder for injection:*** *50 mg* [c] *; 100 mg (as sodium salt) in vial.* ***Tablet:*** *25 mg* [c] *.* ***Tablet (scored):*** *50 mg.*
ciclosporin	***Capsule:*** *25 mg.* ***Concentrate for injection:*** *50 mg/mL in 1 mL ampoule.* ***Oral liquid:*** *100 mg/mL* [c] *.*
tacrolimus	***Capsule (immediate-release):*** *0.5 mg; 0.75 mg; 1 mg; 2 mg; 5 mg.* ***Granules for oral supsension:*** *0.2 mg; 1 mg.* ***Injection:*** *5 mg/mL in 1 mL vial.*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2 Antineoplastics and supportive medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

8.2.1 *Cytotoxic medicines*

Complementary List

arsenic trioxide	**Concentrate for solution for infusion:** *1 mg/mL; 2 mg/mL.*
	– *Acute promyelocytic leukaemia*
asparaginase*	**Powder for injection:** *10 000 IU in vial.*
* *including quality-assured biosimilars*	– *Acute lymphoblastic leukaemia*
bendamustine	**Injection:** *45 mg/0.5 mL; 180 mg/2 mL.*
	– *Chronic lymphocytic leukaemia*
	– *Follicular lymphoma*
bleomycin	**Powder for injection:** *15 000 IU (as sulfate) in vial.*
	– *Hodgkin lymphoma*
	– *Kaposi sarcoma*
	– *Ovarian germ cell tumour*
	– *Testicular germ cell tumour*
calcium folinate (leucovorin calcium)	**Injection:** *3 mg/mL in 10 mL ampoule; 7.5 mg/mL in 2 mL ampoule; 10 mg/mL in 5 mL ampoule.*
	Tablet: *5 mg; 15 mg; 25 mg.*
	– *Burkitt lymphoma*
	– *Early stage colon cancer*
	– *Early stage rectal cancer*
	– *Gestational trophoblastic neoplasia*
	– *Metastatic colorectal cancer*
	– *Osteosarcoma*
capecitabine	**Tablet:** *150 mg; 500 mg.*
	– *Early stage colon cancer*
	– *Early stage rectal cancer*
	– *Metastatic breast cancer*
	– *Metastatic colorectal cancer*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

carboplatin	***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.*

    – Cervical cancer
    – Early stage breast cancer
    – Epithelial ovarian cancer
    – Head and neck cancer (as a radio-sensitizer)
    – Low-grade glioma
    – Nasopharyngeal cancer
    – Nephroblastoma (Wilms tumour)
    – Non-small cell lung cancer
    – Osteosarcoma
    – Ovarian germ cell tumour
    – Retinoblastoma
    – Testicular germ cell tumour

chlorambucil	***Tablet:*** *2 mg.*

    – Chronic lymphocytic leukaemia

cisplatin	***Injection:*** *10 mg/10 mL; 20 mg/20 mL; 50 mg/50 mL; 100 mg/100 mL.*

    – Cervical cancer
    – Head and neck cancer (as a radio-sensitizer)
    – Low-grade glioma
    – Nasopharyngeal cancer (as a radio-sensitizer)
    – Non-small cell lung cancer
    – Osteosarcoma
    – Ovarian germ cell tumour
    – Testicular germ cell tumour

cyclophosphamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.*
	Solid oral dosage form: *25 mg, 50 mg.*

    – Acute lymphoblastic leukaemia
    – Anaplastic large cell lymphoma
    – Burkitt lymphoma
    – Chronic lymphocytic leukaemia
    – Diffuse large B-cell lymphoma
    – Early stage breast cancer
    – Ewing sarcoma
    – Follicular lymphoma
    – Gestational trophoblastic neoplasia
    – Hodgkin lymphoma
    – Low-grade glioma
    – Metastatic breast cancer
    – Multiple myeloma
    – Nephroblastoma (Wilms tumour)
    – Rhabdomyosarcoma

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	

cytarabine	***Injection:*** *100 mg in vial.*
	Powder for injection: *100 mg in vial.*
	– Acute lymphoblastic leukaemia *– Acute myeloid leukaemia* *– Acute promyelocytic leukaemia* *– Anaplastic large cell lymphoma* *– Burkitt lymphoma* *– Langerhans cell histiocytosis*
dacarbazine	***Powder for injection:*** *100 mg; 200 mg in vial.*
	– Hodgkin lymphoma
dactinomycin	***Powder for injection:*** *500 micrograms in vial.*
	– Ewing sarcoma *– Gestational trophoblastic neoplasia* *– Nephroblastoma (Wilms tumour)* *– Rhabdomyosarcoma*
daunorubicin	***Injection:*** *2 mg/mL; 5 mg/mL (as hydrochloride) in vial.*
	Powder for injection: *20 mg; 50 mg (as hydrochloride) in vial.*
	– Acute lymphoblastic leukaemia *– Acute myeloid leukaemia* *– Acute promyelocytic leukaemia*
docetaxel	***Injection:*** *20 mg/mL; 40 mg/mL.*
	– Early stage breast cancer *– Metastatic breast cancer* *– Metastatic prostate cancer*
doxorubicin	***Injection:*** *2 mg/mL (hydrochloride) in vial.*
	Powder for injection: *10 mg; 50 mg (hydrochloride) in vial.*
	– Acute lymphoblastic leukaemia *– Anaplastic large cell lymphoma* *– Burkitt lymphoma* *– Diffuse large B-cell lymphoma* *– Early stage breast cancer* *– Ewing sarcoma* *– Follicular lymphoma* *– Hodgkin lymphoma* *– Kaposi sarcoma* *– Metastatic breast cancer* *– Multiple myeloma* *– Nephroblastoma (Wilms tumour)* *– Osteosarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

doxorubicin (as pegylated liposomal)	***Injection:*** *2 mg/mL (hydrochloride) in 10 mL, 25 mL vial.* – *Kaposi sarcoma*
etoposide	***Capsule:*** *50 mg, 100 mg.* ***Injection:*** *20 mg/mL in 5 mL ampoule.* ***Powder for injection:*** *100 mg (as phosphate) in vial.* – *Acute lymphoblastic leukaemia* – *Acute myeloid leukaemia* – *Anaplastic large cell lymphoma* – *Burkitt lymphoma* – *Ewing sarcoma* – *Gestational trophoblastic neoplasia* – *Hodgkin lymphoma* – *Nephroblastoma (Wilms tumour)* – *Non-small cell lung cancer* – *Osteosarcoma* – *Ovarian germ cell tumour* – *Retinoblastoma* – *Testicular germ cell tumour*
fludarabine	***Powder for injection:*** *50 mg (phosphate) in vial.* ***Tablet:*** *10 mg* – *Chronic lymphocytic leukaemia.*
fluorouracil	***Injection:*** *50 mg/mL in vial.* – *Early stage breast cancer* – *Early stage colon cancer* – *Early stage rectal cancer* – *Metastatic colorectal cancer* – *Nasopharyngeal cancer*
gemcitabine	***Powder for injection:*** *200 mg; 1 g in vial.* – *Epithelial ovarian cancer* – *Non-small cell lung cancer*
hydroxycarbamide (hydroxyurea)	***Solid oral dosage form:*** *100 mg* [c] *; 200 mg; 300 mg; 400 mg; 500 mg; 1 g.* – *Chronic myeloid leukaemia*

| 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)* |

ifosfamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.*
	– *Anaplastic large cell lymphoma*
	– *Burkitt lymphoma*
	– *Ewing sarcoma*
	– *Nephroblastoma (Wilms tumour)*
	– *Ovarian germ cell tumour*
	– *Osteosarcoma*
	– *Rhabdomyosarcoma*
	– *Testicular germ cell tumour*
irinotecan	***Injection:*** *40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.*
	– *Metastatic colorectal cancer*
	– *Nephroblastoma (Wilms tumour)*
	– *Rhabdomyosarcoma*
melphalan	***Tablet:*** *2 mg.*
	Powder for injection: *50 mg in vial.*
	– *Multiple myeloma*
mercaptopurine	***Tablet:*** *50 mg.*
	Oral liquid: *20 mg/mL* **[c]** *.*
	– *Acute lymphoblastic leukaemia*
	– *Acute promyelocytic leukaemia*
	– *Langerhans cell histiocytosis*
methotrexate	***Concentrated injection:*** *1000 mg/10 mL.*
	Injection: *50 mg/2 mL.*
	Powder for injection: *50 mg (as sodium) in vial.*
	Tablet: *2.5 mg (as sodium).*
	– *Acute lymphoblastic leukaemia*
	– *Acute promyelocytic leukaemia*
	– *Anaplastic large cell lymphoma*
	– *Burkitt lymphoma*
	– *Early stage breast cancer*
	– *Gestational trophoblastic neoplasia*
	– *Langerhans cell histiocytosis*
	– *Osteosarcoma*
oxaliplatin	***Injection:*** *50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; 200 mg/40 mL in 40 mL vial.*
	Powder for injection: *50 mg; 100 mg in vial.*
	– *Early stage colon cancer*
	– *Metastatic colorectal cancer*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

paclitaxel	***Injection:*** *6 mg/mL in vial.*

– *Cervical cancer*
– *Epithelial ovarian cancer*
– *Early stage breast cancer*
– *Metastatic breast cancer*
– *Kaposi sarcoma*
– *Nasopharyngeal cancer*
– *Non-small cell lung cancer*
– *Ovarian germ cell tumour*

pegaspargase*	***Injection:*** *3750 units/5 mL in vial.*
* including quality-assured biosimilars	***Powder for injection:*** *3750 units in vial.*

– *Acute lymphoblastic leukaemia*

procarbazine [c] ***Capsule:*** *50 mg (as hydrochloride).*

– *Hodgkin lymphoma*

realgar-Indigo naturalis formulation ***Tablet:*** *270 mg (containing tetra-arsenic tetra-sulfide 30 mg).*

– *Acute promyelocytic leukaemia*

tioguanine [c] ***Solid oral dosage form:*** *40 mg.*

– *Acute lymphoblastic leukaemia*

vinblastine	***Injection:*** *10 mg/10 mL (sulfate) in vial.*
	Powder for injection: *10 mg (sulfate) in vial.*

– *Anaplastic large cell lymphoma*
– *Hodgkin lymphoma*
– *Kaposi sarcoma*
– *Langerhans cell histiocytosis*
– *Low-grade glioma*
– *Ovarian germ cell tumour*
– *Testicular germ cell tumour*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

vincristine **Injection:** *1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial.*

Powder for injection: *1 mg; 5 mg (sulfate) in vial.*

– *Acute lymphoblastic leukaemia*
– *Burkitt lymphoma*
– *Diffuse large B-cell lymphoma*
– *Ewing sarcoma*
– *Follicular lymphoma*
– *Gestational trophoblastic neoplasia*
– *Hodgkin lymphoma*
– *Kaposi sarcoma*
– *Langerhans cell histiocytosis*
– *Low-grade glioma*
– *Nephroblastoma (Wilms tumour)*
– *Retinoblastoma*
– *Rhabdomyosarcoma*

vinorelbine **Capsule:** *20 mg; 30 mg; 80 mg.*

Injection: *10 mg/mL in 1 mL, 5 mL vial.*

– *Non-small cell lung cancer*
– *Metastatic breast cancer*
– *Rhabdomyosarcoma*

8.2.2 Targeted therapies

Complementary List

all-trans retinoid acid (ATRA) **Capsule:** *10 mg.*
– *Acute promyelocytic leukaemia.*

bortezomib **Powder for injection:** *3.5 mg in vial.*
– *Multiple myeloma*

dasatinib **Tablet:** *20 mg; 50 mg; 70 mg; 80 mg; 100 mg; 140 mg.*
– *Imatinib-resistant chronic myeloid leukaemia*

☐ *erlotinib* **Tablet:** *100 mg, 150 mg.*
Therapeutic alternatives: – *EGFR mutation-positive advanced non-small cell*
– *afatinib*   *lung cancer*
– *gefitinib*

everolimus **Tablet:** *2.5 mg; 5 mg; 7.5 mg; 10 mg.*

Tablet (dispersible): *2 mg; 3 mg; 5 mg.*
– *Subependymal giant cell astrocytoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

ibrutinib	**Capsule:** 140 mg.
	– *Relapsed/refractory chronic lymphocytic leukaemia*
imatinib	**Solid oral dosage form:** 100 mg; 400 mg.
	– *Chronic myeloid leukaemia*
	– *Gastrointestinal stromal tumour*
	– *Philadelphia chromosome positive acute lymphoblastic leukaemia*
nilotinib	**Capsule:** 150 mg; 200 mg.
	– *Imatinib-resistant chronic myeloid leukaemia*
rituximab* ** including quality-assured biosimilars*	**Injection (intravenous):** 100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial.
	– *Burkitt lymphoma*
	– *Diffuse large B-cell lymphoma*
	– *Chronic lymphocytic leukaemia*
	– *Follicular lymphoma*
trastuzumab* ** including quality-assured biosimilars*	**Powder for injection:** 60 mg; 150 mg; 440 mg in vial.
	– *Early stage HER2 positive breast cancer*
	– *Metastatic HER2 positive breast cancer*

8.2.3 *Immunomodulators*

Complementary List

filgrastim* ** including quality-assured biosimilars*	**Injection:** 120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe.
	Injection: 300 micrograms/mL in 1 mL vial; 480 micrograms/1.6 mL in 1.6 mL vial.
	– *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.*
	– *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy*
	– *To facilitate administration of dose dense chemotherapy regimens*
lenalidomide	**Capsule:** 25 mg.
	– *Multiple myeloma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	

☐ *nivolumab**

Concentrate solution for infusion: *10 mg/mL.*

    – *Metastatic melanoma*

Therapeutic alternatives*:
– pembrolizumab
* including quality-assured
  biosimilars

pegfilgrastim*

Injection: *6 mg/0.6 mL in pre-filled syringe.*

    – *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy*
    – *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy*
    – *To facilitate administration of dose dense chemotherapy regimens*

* including quality-assured
  biosimilars

thalidomide

Capsule: *50 mg.*

    – *Multiple myeloma*

8.2.4 *Hormones and antihormones*

Complementary List

☐ *abiraterone*

Tablet: *250 mg; 500 mg.*

    – *Metastatic castration-resistant prostate cancer*

Therapeutic alternatives:
– enzalutamide

☐ *anastrozole*

Tablet: *1 mg.*

    – *Early stage breast cancer*
    – *Metastatic breast cancer*

Therapeutic alternatives:
– 4th level ATC chemical
  subgroup (L02BG
  Aromatase inhibitors)

☐ *bicalutamide*

Tablet: *50 mg.*

    – *Metastatic prostate cancer*

Therapeutic alternatives:
– flutamide
– nilutamide

dexamethasone

Injection: *4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.*

Oral liquid: *2 mg/5 mL* [c] *.*

Tablet: *2 mg* [c] *; 4 mg.*

    – *Acute lymphoblastic leukaemia*
    – *Anaplastic large cell lymphoma*
    – *Burkitt lymphoma*
    – *Multiple myeloma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

hydrocortisone **Powder for injection:** *100 mg (as sodium succinate) in vial.*

  – *Acute lymphoblastic leukaemia*
  – *Burkitt lymphoma*

☐ *leuprorelin* **Injection:** *7.5 mg; 22.5 mg in pre-filled syringe.*

Therapeutic alternatives:
– *goserelin*
– *triptorelin*

  – *Early stage breast cancer*
  – *Metastatic prostate cancer.*

methylprednisolone **[c]** **Injection:** *40 mg/mL (as sodium succinate) in 1 mL single-dose vial and 5 mL multi-dose vials; 80 mg/mL (as sodium succinate) in 1 mL single-dose vial.*

  – *Acute lymphoblastic leukamia*
  – *Burkitt lymphoma*

☐ *prednisolone* **Oral liquid:** *5 mg/mL* **[c]**

Therapeutic alternatives: **Tablet:** *5 mg; 25 mg.*
– *prednisone*

  – *Acute lymphoblastic leukaemia*
  – *Anaplastic large cell lymphoma*
  – *Burkitt lymphoma*
  – *Chronic lymphocytic leukaemia*
  – *Diffuse large B-cell lymphoma*
  – *Follicular lymphoma*
  – *Hodgkin lymphoma*
  – *Langerhans cell histiocytosis*
  – *Metastatic castration-resitsant prostate cancer*
  – *Multiple myeloma*

tamoxifen **Tablet:** *10 mg; 20 mg (as citrate).*

  – *Early stage breast cancer*
  – *Metastatic breast cancer.*

8.2.5 *Supportive medicines*

Complementary List

allopurinol **[c]** **Tablet:** *100 mg; 300 mg.*

  – *Tumour lysis syndrome*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	
mesna	***Injection:*** *100 mg/mL in 4 mL and 10 mL ampoules.*
	Tablet: *400 mg; 600 mg.*
	– *Burkitt lymphoma*
	– *Ewing sarcoma*
	– *Nephroblastoma (Wilms tumour)*
	– *Ovarian germ cell tumour*
	– *Osteosarcoma*
	– *Rhabdomyosarcoma*
	– *Testicular germ cell tumour*
rasburicase	***Powder and solvent for solution for infusion:*** *1.5 mg; 7.5 mg in vial.*
	– *Tumour lysis syndrome*
zoledronic acid	***Concentrate solution for infusion:*** *4 mg/5 mL in 5 mL vial.*
	Solution for infusion: *4 mg/100 mL in 100 mL bottle.*
	– *Malignancy-related bone disease*

9. THERAPEUTIC FOODS	
ready-to-use therapeutic food [c]	**Biscuit or paste***
	* of nutritional composition as determined by the UN joint statement on the community-based management of severe acute malnutrition and Codex alimentarius guidelines.

10. MEDICINES AFFECTING THE BLOOD	

10.1 Antianaemia medicines

ferrous salt	**Oral liquid:** equivalent to 25 mg iron (as sulfate)/mL.
	Tablet: equivalent to 60 mg iron.
ferrous salt + folic acid	**Tablet:** equivalent to 60 mg elemental iron + 400 micrograms folic acid.*
	* nutritional supplement for use during pregnancy
	Tablet: equivalent to 60 mg elemental iron + 2.8 mg folic acid.**
	**for weekly iron and folic acid supplementation
folic acid	**Tablet:** 400 micrograms*; 1 mg; 5 mg.
	* periconceptual use for prevention of first occurrence of neural tube defects
hydroxocobalamin	**Injection:** 1 mg/mL (as acetate, as hydrochloride or as sulfate) in 1 mL ampoule.

10. MEDICINES AFFECTING THE BLOOD *(continued)*

Complementary List

☐ *erythropoiesis-stimulating agents**

Therapeutic alternatives:
– *epoetin alfa, beta and theta*
– *darbepoetin alfa*
– *methoxy polyethylene glycol-epoetin beta*

* *including quality-assured biosimilars*

Injection: pre-filled syringe

1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8 mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL.

10.2 Medicines affecting coagulation

☐ dabigatran

Therapeutic alternatives:
– apixaban
– edoxaban
– rivaroxaban

Capsule: 110 mg; 150 mg.

☐ enoxaparin*

Therapeutic alternatives*:
– dalteparin
– nadroparin

* *including quality-assured biosimilars*

Injection: ampoule or pre-filled syringe

20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.

heparin sodium

Injection: 1000 IU/mL; 5000 IU/mL; 20 000 IU/mL in 1 mL ampoule.

phytomenadione

Injection: 1 mg/mL [c] ; 10 mg/mL in ampoule.
Tablet: 10 mg.

protamine sulfate

Injection: 10 mg/mL in 5 mL ampoule.

tranexamic acid

Injection: 100 mg/mL in 10 mL ampoule.

☐ warfarin

Therapeutic alternatives to be reviewed

Tablet: 1 mg; 2 mg; 5 mg (sodium).

Complementary List

desmopressin [c]

Injection: *4 micrograms/mL (as acetate) in 1 mL ampoule.*
Nasal spray: *10 micrograms (as acetate) per dose.*

heparin sodium [c]

Injection: *1000 IU/mL; 5000 IU/mL in 1 mL ampoule.*

10. MEDICINES AFFECTING THE BLOOD *(continued)*

protamine sulfate **[c]**	**Injection:** *10 mg/mL in 5 mL ampoule.*
☐ *warfarin* **[c]** *Therapeutic alternatives* *to be reviewed*	**Tablet:** *0.5 mg; 1 mg; 2 mg; 5 mg (sodium).*

10.3 Other medicines for haemoglobinopathies

☐ deferasirox Therapeutic alternatives: – deferiprone	**Tablet (dispersible):** 100 mg; 125 mg; 250 mg; 400 mg; 500 mg. **Tablet (film-coated):** 90 mg; 180 mg; 360 mg.

> ***Complementary List***

deferoxamine	**Powder for injection:** *500 mg (mesilate) in vial.*
hydroxycarbamide *(hydroxyurea)*	**Solid oral dosage form:** *100 mg* **[c]** *; 200 mg; 500 mg; 1 g.*

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

☐ cryoprecipitate, pathogen-reduced Therapeutic alternatives: – cryoprecipitate (not pathogen-reduced)	**Injection:** frozen liquid in bag or lyophilized powder in vial containing: – > 50 IU Factor VIII – > 100 IU vWF – > 140 mg clottable fibrinogen per unit
fresh-frozen plasma	
platelets	
red blood cells	
whole blood	

11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES *(continued)*

11.2.1 *Human immunoglobulins*

anti-D immunoglobulin	**Injection:** 250 micrograms in single-dose vial.
anti-rabies immunoglobulin	**Injection:** 150 IU/mL in vial.
anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.

Complementary List

normal immunoglobulin **Intramuscular administration:** *16% protein solution.*
Subcutaneous administration: *15%; 16% protein solution.*
  – Primary immune deficiency
*I*ntravenous administration:* *5%; 10% protein solution.*
  – Primary immune deficiency
  – Kawasaki disease
  – Langerhans cell histiocytosis

11.2.2 *Blood coagulation factors*

Complementary List

coagulation factor VIII **Powder for injection:** *250 IU; 500 IU; 1000 IU in vial.*

☐ *coagulation factor IX* **Powder for injection:** *500 IU/vial; 1000 IU/vial.*
Therapeutic alternatives:
– coagulation factor IX complex

11.3 Plasma substitutes

☐ dextran 70 **Injectable solution:** 6%.
Therapeutic alternatives:
– Polygeline injectable
   solution 3.5%

12. CARDIOVASCULAR MEDICINES

12.1 Antianginal medicines

☐ bisoprolol **Tablet:** 1.25 mg; 5 mg.
Therapeutic alternatives:
– carvedilol
– metoprolol

12. CARDIOVASCULAR MEDICINES *(continued)*	
glyceryl trinitrate	**Tablet (sublingual):** 500 micrograms.
isosorbide dinitrate	**Tablet (sublingual):** 5 mg.
verapamil	**Tablet:** 40 mg; 80 mg (hydrochloride).

12.2 Antiarrhythmic medicines

☐ bisoprolol	**Tablet:** 1.25 mg; 5 mg.
Therapeutic alternatives: – carvedilol – metoprolol	
digoxin	**Injection:** 250 micrograms/mL in 2 mL ampoule. **Oral liquid:** 50 micrograms/mL. **Tablet:** 62.5 micrograms; 250 micrograms.
epinephrine (adrenaline)	**Injection:** 100 micrograms/mL (as acid tartrate or hydrochloride) in 10 mL ampoule.
lidocaine	**Injection:** 20 mg/mL (hydrochloride) in 5 mL ampoule.
verapamil	**Injection:** 2.5 mg/mL (hydrochloride) in 2 mL ampoule. **Tablet:** 40 mg; 80 mg (hydrochloride).

Complementary List

amiodarone	*Injection: 50 mg/mL (hydrochloride) in 3 mL ampoule.* *Tablet: 100 mg; 200 mg; 400 mg (hydrochloride).*

12.3 Antihypertensive medicines

☐ amlodipine	**Tablet:** 5 mg (as maleate, mesylate or besylate).
Therapeutic alternatives: – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives)	
☐ bisoprolol	**Tablet:** 1.25 mg; 5 mg.
Therapeutic alternatives: – atenolol* – carvedilol – metoprolol	* atenolol should not be used as a first-line agent in uncomplicated hypertension in patients > 60 years

12. CARDIOVASCULAR MEDICINES *(continued)*

☐ enalapril

Therapeutic alternatives:
– 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain)

Oral liquid: 1 mg/mL (as hydrogen maleate) [c] .

Tablet: 2.5 mg; 5 mg; 10 mg (as hydrogen maleate).

hydralazine*

Powder for injection: 20 mg (hydrochloride) in ampoule.

Tablet: 25 mg; 50 mg (hydrochloride).

* Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.

☐ hydrochlorothiazide

Therapeutic alternatives:
– chlorothiazide
– chlorthalidone
– indapamide

Oral liquid: 50 mg/5 mL.

Solid oral dosage form: 12.5 mg; 25 mg.

☐ lisinopril + ☐ amlodipine

Therapeutic alternatives:
– 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril)
– 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)

Tablet: 10 mg + 5 mg; 20 mg + 5 mg; 20 mg + 10 mg.

☐ lisinopril + ☐ hydrochlorothiazide

Therapeutic alternatives:
– 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for lisinopril)
– chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)

Tablet: 10 mg + 12.5 mg; 20 mg + 12.5 mg; 20 mg + 25 mg.

☐ losartan

Therapeutic alternatives:
– 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain)

Tablet: 25 mg; 50 mg; 100 mg.

12. CARDIOVASCULAR MEDICINES *(continued)*

methyldopa*	**Tablet:** 250 mg.

* Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.

☐ telmisartan +
☐ amlodipine

Tablet: 40 mg + 5 mg; 80 mg + 5 mg; 80 mg + 10 mg.

Therapeutic alternatives:
– 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan)
– 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)

☐ telmisartan +
☐ hydrochlorothiazide

Tablet: 40 mg + 12.5 mg; 80 mg + 12.5 mg; 80 mg + 25 mg.

Therapeutic alternatives:
– 4th level ATC chemical subgroup (C09CA Angiotensin II receptor blockers (ARBs), plain) (for telmisartan)
– chlorthalidone, chlorothiazide, indapamide (for hydrochlorothiazide)

Complementary List

sodium nitroprusside   ***Powder for infusion:*** *50 mg in ampoule.*

12.4 Medicines used in heart failure

☐ bisoprolol   **Tablet:** 1.25 mg; 5 mg.
Therapeutic alternatives:
– carvedilol
– metoprolol

digoxin   **Injection:** 250 micrograms/mL in 2 mL ampoule.

Oral liquid: 50 micrograms/mL.

Tablet: 62.5 micrograms; 250 micrograms.

☐ enalapril   **Tablet:** 2.5 mg; 5 mg; 10 mg (as hydrogen maleate).
Therapeutic alternatives:
– 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain)

12. CARDIOVASCULAR MEDICINES *(continued)*

☐ furosemide

Therapeutic alternatives:
– bumetanide
– torasemide

Injection: 10 mg/mL in 2 mL, 5 mL ampoule.
Oral liquid: 20 mg/5 mL; 50 mg/5 mL [c].
Tablet: 20 mg; 40 mg.

☐ hydrochlorothiazide

Therapeutic alternatives:
– chlorothiazide
– chlorthalidone
– indapamide

Oral liquid: 50 mg/5 mL.
Solid oral dosage form: 25 mg.

☐ losartan

Therapeutic alternatives:
– 4th level ATC chemical
  subgroup (C09CA
  Angiotensin II receptor
  blockers (ARBs), plain)

Tablet: 25 mg; 50 mg; 100 mg.

spironolactone

Tablet: 25 mg.

Complementary List

digoxin [c]

Injection: *100 micrograms/mL in 1 mL ampoule;
250 micrograms/mL in 2 mL ampoule.*
Oral liquid: *50 micrograms/mL.*
Tablet: *62.5 micrograms; 125 micrograms;
250 micrograms.*

dopamine

Injection: *40 mg/mL (hydrochloride) in 5 mL vial.*

12.5 Antithrombotic medicines

12.5.1 *Anti-platelet medicines*

acetylsalicylic acid

Tablet: 100 mg.

clopidogrel

Tablet: 75 mg; 300 mg.

12.5.2 *Thrombolytic medicines*

Complementary List

alteplase

Powder for injection: *10 mg; 20 mg; 50 mg in vial*

streptokinase

Powder for injection: *1.5 million IU in vial.*

12. CARDIOVASCULAR MEDICINES *(continued)*

12.6 Lipid-lowering agents

☐ simvastatin*

Therapeutic alternatives:

– atorvastatin
– fluvastatin
– lovastatin
– pravastatin

Tablet: 5 mg; 10 mg; 20 mg; 40 mg.

* For use in high-risk patients.

12.7 Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease

acetylsalicylic acid +
☐ atorvastatin + ☐ ramipril

Therapeutic alternatives:

– fluvastatin, lovastatin,
  pravastatin, simvastatin (for
  atorvastatin)
– 4th level ATC chemical
  subgroup (C09AA ACE
  inhibitors, plain) (for ramipril)

Tablet: 100 mg + 20 mg + 2.5 mg; 100 mg + 20 mg +
5 mg; 100 mg + 20 mg + 10 mg; 100 mg + 40 mg +
2.5 mg; 100 mg + 40 mg + 5 mg; 100 mg + 40 mg +
10 mg.

acetylsalicylic acid +
☐ simvastatin +
☐ ramipril + ☐ atenolol +
☐ hydrochlorothiazide

Therapeutic alternatives:

– atorvastatin, fluvastatin,
  lovastatin, pravastatin (for
  simvastatin)
– 4th level ATC chemical
  subgroup (C09AA ACE
  inhibitors, plain) (for ramipril)
– bisoprolol, carvedilol,
  metoprolol (for atenolol)
– chlorthalidone,
  chlorothiazide, indapamide
  (for hydrochlorothiazide)

Tablet: 100 mg + 20 mg + 5 mg + 50 mg + 12.5 mg.

12. CARDIOVASCULAR MEDICINES *(continued)*

☐ atorvastatin + ☐ perindopril + ☐ amlodipine Therapeutic alternatives: – fluvastatin, lovastatin, pravastatin, simvastatin (for atorvastatin) – 4th level ATC chemical subgroup (C09AA ACE inhibitors, plain) (for perindopril) – 4th level ATC chemical subgroup (C08CA Dihydropyridine derivatives) (for amlodipine)	**Tablet:** 20 mg + 5 mg + 5 mg; 20 mg + 10 mg + 10 mg; 40 mg + 5 mg + 5 mg; 40 mg + 10 mg + 10 mg.

13. DERMATOLOGICAL MEDICINES

13.1 Antifungal medicines

☐ miconazole Therapeutic alternatives: – 4th level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations	**Cream or ointment:** 2% (nitrate).
selenium sulfide	**Detergent-based suspension:** 2%.
sodium thiosulfate	**Solution:** 15%.
terbinafine	**Cream or ointment:** 1% (hydrochloride).

13.2 Anti-infective medicines

mupirocin	**Cream:** 2% (as calcium). **Ointment:** 2%.
potassium permanganate	**Aqueous solution:** 1:10 000.
silver sulfadiazine [a]	**Cream:** 1%. [a] > 2 months.

13. DERMATOLOGICAL MEDICINES *(continued)*

13.3 Anti-inflammatory and antipruritic medicines

☐ betamethasone a | **Cream or ointment:** 0.1% (as valerate).

Therapeutic alternatives:
– 4th level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))

a Hydrocortisone preferred in neonates.

calamine | **Lotion.**

☐ hydrocortisone | **Cream or ointment:** 1% (acetate).

Therapeutic alternatives:
– 4th level ATC chemical subgroup (D07AA Corticosteroids, weak (group I))

13.4 Medicines affecting skin differentiation and proliferation

benzoyl peroxide | **Cream or lotion:** 5%.

☐ calcipotriol | **Cream or ointment:** 50 micrograms/mL (0.005%).

Therapeutic alternatives:
– calcitriol
– tacalcitol

Lotion: 50 micrograms/mL (0.005%).

coal tar | **Solution:** 5%.

fluorouracil | **Ointment:** 5%.

☐ podophyllum resin | **Solution:** 10% to 25%.

Therapeutic alternatives:
– podophyllotoxin

salicylic acid | **Solution:** 5%.

urea | **Cream or ointment:** 5%; 10%.

  Complementary List

  methotrexate | ***Tablet:*** *2.5 mg; 10 mg (as sodium).*

13.5 Scabicides and pediculicides

☐ benzyl benzoate a | **Lotion:** 25%.

Therapeutic alternatives:
– precipitated sulfur topical ointment

a > 2 years.

13. DERMATOLOGICAL MEDICINES *(continued)*	
permethrin	**Cream:** 5%.
	Lotion: 1%.

14. DIAGNOSTIC AGENTS	

14.1 Ophthalmic medicines

fluorescein	**Eye drops:** 1% (sodium salt).
☐ tropicamide Therapeutic alternatives: – atropine – cyclopentolate	**Eye drops:** 0.5%.

14.2 Radiocontrast media

☐ amidotrizoate Therapeutic alternatives to be reviewed	**Injection:** 140 mg to 420 mg iodine/mL (as sodium or meglumine salt) in 20 mL ampoule.
barium sulfate	**Aqueous suspension.**
☐ iohexol Therapeutic alternatives to be reviewed	**Injection:** 140 mg to 350 mg iodine/mL in 5 mL; 10 mL; 20 mL ampoule.

Complementary List

barium sulfate [c]	*Aqueous suspension.*
☐ *meglumine iotroxate* *Therapeutic alternatives to be reviewed*	*Solution: 5 g to 8 g iodine in 100 mL to 250 mL.*

15. ANTISEPTICS AND DISINFECTANTS	

15.1 Antiseptics

☐ chlorhexidine Therapeutic alternatives to be reviewed	**Solution:** 5% (digluconate).
☐ ethanol Therapeutic alternatives: – propanol	**Solution:** 70% (denatured).

15. ANTISEPTICS AND DISINFECTANTS *(continued)*

☐ povidone iodine

Solution: 10% (equivalent to 1% available iodine).

Therapeutic alternatives:
– iodine

15.2 Disinfectants

alcohol based hand rub

Solution: containing ethanol 80% volume/volume.

Solution: containing isopropyl alcohol 75% volume/volume.

chlorine base compound

Liquid: (0.1% available chlorine) for solution.

Powder: (0.1% available chlorine) for solution.

Solid: (0.1% available chlorine) for solution.

☐ chloroxylenol

Solution: 4.8%.

Therapeutic alternatives:
– 4th level ATC chemical subgroup (D08AE Phenol and derivatives)

glutaral

Solution: 2%.

16. DIURETICS

amiloride

Tablet: 5 mg (hydrochloride).

☐ furosemide

Injection: 10 mg/mL in 2 mL, 5 mL ampoule.

Therapeutic alternatives:
– bumetanide
– torasemide

Oral liquid: 20 mg/5 mL; 50 mg/5 mL [c].

Tablet: 20 mg; 40 mg.

☐ hydrochlorothiazide

Solid oral dosage form: 25 mg.

Therapeutic alternatives:
– chlorothiazide
– chlortalidone
– indapamide

mannitol

Injectable solution: 10%; 20%.

spironolactone

Tablet: 25 mg.

Complementary List

☐ *hydrochlorothiazide* [c]

Tablet (scored): 25 mg.

Therapeutic alternatives:
– chlorothiazide
– chlortalidone

16. DIURETICS *(continued)*

mannitol [c]	***Injectable solution:*** *10%; 20%.*
spironolactone [c]	***Oral liquid:*** *5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.* ***Tablet:*** *25 mg.*

17. GASTROINTESTINAL MEDICINES

Complementary List

pancreatic enzymes [c]	*Age-appropriate formulations and doses including lipase, protease and amylase.*

17.1 Antiulcer medicines

☐ omeprazole Therapeutic alternatives: – 4th level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	**Powder for injection:** 40 mg in vial **Powder for oral liquid:** 20 mg; 40 mg sachets. **Solid oral dosage form:** 10 mg; 20 mg; 40 mg.
☐ ranitidine Therapeutic alternatives: – 4th level ATC chemical subgroup (A02BA H$_2$-receptor antagonists) excluding combinations	**Injection:** 25 mg/mL (as hydrochloride) in 2 mL ampoule. **Oral liquid:** 75 mg/5 mL (as hydrochloride). **Tablet:** 150 mg (as hydrochloride).

17.2 Antiemetic medicines

dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule. **Oral liquid:** 0.5 mg/5 mL; 2 mg/5 mL. **Solid oral dosage form:** 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.
metoclopramide [a]	**Injection:** 5 mg/mL (hydrochloride) in 2 mL ampoule. **Oral liquid:** 5 mg/5 mL [c]. **Tablet:** 10 mg (hydrochloride). [a] Not in neonates.
☐ ondansetron [a] Therapeutic alternatives: – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg base/mL in 2 mL ampoule (as hydrochloride). **Oral liquid:** 4 mg base/5 mL. **Solid oral dosage form:** Eq 4 mg base; Eq 8 mg base; Eq 24 mg base. [a] > 1 month.

17. GASTROINTESTINAL MEDICINES *(continued)*

Complementary list

aprepitant	**Capsule:** *80 mg; 125 mg; 165 mg.*
	Powder for oral suspension: *125 mg in sachet.*

17.3 Anti-inflammatory medicines

☐ sulfasalazine	**Retention enema.**
Therapeutic alternatives:	**Suppository:** 500 mg.
– mesalazine	**Tablet:** 500 mg.

Complementary List

hydrocortisone	**Retention enema:** *100 mg/60 mL.*
	Suppository: *25 mg (acetate).*
prednisolone	**Retention enema:** *20 mg/100 mL (as sodium phosphate).*

17.4 Laxatives

☐ senna	**Tablet:** 7.5 mg (sennosides) (or traditional dosage forms).
Therapeutic alternatives:	
– bisacodyl	

17.5 Medicines used in diarrhoea

oral rehydration salts – zinc sulfate [c]	**Co-package containing:**
	ORS powder for dilution (see Section 17.5.1) – zinc sulfate **solid oral dosage form** 20 mg (see Section 17.5.2)

17. GASTROINTESTINAL MEDICINES *(continued)*

17.5.1 *Oral rehydration*

oral rehydration salts	**Powder for dilution** in 200 mL; 500 mL; 1 L.

glucose:	75 mEq
sodium:	75 mEq or mmol/L
chloride:	65 mEq or mmol/L
potassium:	20 mEq or mmol/L
citrate:	10 mmol/L
osmolarity:	245 mOsm/L
glucose:	13.5 g/L
sodium chloride:	2.6 g/L
potassium chloride:	1.5 g/L
trisodium citrate dihydrate*:	2.9 g/L

* trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

17.5.2 *Medicines for diarrhoea*

zinc sulfate*	**Solid oral dosage form:** 20 mg.

* In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

18. MEDICINES FOR ENDOCRINE DISORDERS

18.1 Adrenal hormones and synthetic substitutes

fludrocortisone	**Tablet:** 100 micrograms (acetate).
hydrocortisone	**Tablet:** 5 mg; 10 mg; 20 mg.

18.2 Androgens

Complementary List

testosterone	*Injection: 200 mg (enanthate) in 1 mL ampoule.*

18.3 Estrogens

18.4 Progestogens

☐ medroxyprogesterone acetate	**Tablet:** 5 mg.

Therapeutic alternatives:
– norethisterone

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

18.5 Medicines for diabetes

18.5.1 *Insulins*

insulin injection (soluble)*

* *including quality-assured biosimilars*

Injection: 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.

intermediate-acting insulin*

* *including quality-assured biosimilars*

Injection: 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen (as compound insulin zinc suspension or isophane insulin).

☐ long-acting insulin analogues*

Therapeutic alternatives:

– insulin degludec
– insulin detemir
– insulin glargine

* *including quality-assured biosimilars*

Injection: 100 IU/mL in 3 mL cartridge or pre-filled pen.

18.5.2 *Oral hypoglycaemic agents*

☐ empagliflozin

Therapeutic alternatives:

– canagliflozin
– dapagliflozin

Tablet: 10 mg; 25 mg.

☐ gliclazide*

Therapeutic alternatives:

– 4th level ATC chemical subgroup (A10BB Sulfonylureas)

Solid oral dosage form: (controlled-release tablets) 30 mg; 60 mg; 80 mg.

* glibenclamide not suitable above 60 years.

metformin

Tablet: 500 mg (hydrochloride).

   Complementary List

   metformin [c]

Tablet: *500 mg (hydrochloride).*

18.6 Medicines for hypoglycaemia

glucagon

Injection: 1 mg/mL.

   Complementary List

   diazoxide [c]

Oral liquid: *50 mg/mL.*
Tablet: *50 mg.*

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

18.7 Thyroid hormones and antithyroid medicines

levothyroxine	**Tablet:** 25 micrograms [c] ; 50 micrograms; 100 micrograms (sodium salt).
potassium iodide	**Tablet:** 60 mg.

☐ methimazole

Tablet: 5mg, 10mg, 20mg.

Therapeutic alternatives:
– carbimazole (depending on
  local availability)

propylthiouracil*

Tablet: 50 mg.

* For use when alternative first-line treatment is not appropriate or
  available; and in patients during the first trimester of pregnancy.

> *Complementary List*

> *Lugol's solution* [c]   ***Oral liquid:*** *about 130 mg total iodine/mL.*

> ☐ *methimazole* [c]   ***Tablet:*** *5mg, 10mg, 20mg.*
> *Therapeutic alternatives:*
> *– carbimazole (depending*
>   *on local availability)*

> *potassium iodide* [c]   ***Tablet:*** *60 mg.*

> *propylthiouracil** [c]   ***Tablet:*** *50 mg.*
> * *For use when alternative first-line treatment is not appropriate*
>   *or available.*

18.8 Medicines for disorders of the pituitary hormone system

☐ cabergoline

Tablet: 0.5 mg; 1 mg.

Therapeutic alternatives:
– bromocriptine

> *Complementary List*

> *octreotide*   ***Injection (immediate-release):*** *0.05 mg/mL; 0.1 mg/mL;*
> *0.5 mg/mL (as acetate) in 1 mL vial.*
>
> ***Injection (modified-release):*** *20 mg (as acetate) in vial*
> *plus diluent.*

19. IMMUNOLOGICALS

19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

tuberculin, purified protein
derivative (PPD)

Injection.

19.2 Sera, immunoglobulins and monoclonal antibodies

All plasma fractions should comply with the WHO requirements.

anti-rabies virus
monoclonal antibodies*

** including quality-assured
 biosimilars*

Injection: 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL
in 2.5 mL vial (human).

Injection: 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL,
2.5 mL and 5 mL vial (murine).

antivenom
immunoglobulin*

Injection.

* Exact type to be defined locally.

diphtheria antitoxin

Injection: 10 000 IU; 20 000 IU in vial.

equine rabies
immunoglobulin

Injection: 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL
in vial.

19. IMMUNOLOGICALS *(continued)*

19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers based on recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at March 2023. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at: https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

WHO noted the need for vaccines used in children to be polyvalent.

Recommendations for all

BCG vaccine
diphtheria vaccine
Haemophilus influenzae type b vaccine
hepatitis B vaccine
human papilloma virus (HPV) vaccine
measles vaccine
pertussis vaccine
pneumococcal vaccine
poliomyelitis vaccine
rotavirus vaccine
rubella vaccine
tetanus vaccine

Recommendations for certain regions

Japanese encephalitis vaccine
tick-borne encephalitis vaccine
yellow fever vaccine

19. IMMUNOLOGICALS *(continued)*

Recommendations for some high-risk populations

cholera vaccine
dengue vaccine
hepatitis A vaccine
meningococcal meningitis vaccine
rabies vaccine
typhoid vaccine

Recommendations for immunization programmes with certain characteristics

influenza vaccine (seasonal)
mumps vaccine
varicella vaccine

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS

☐ atracurium Therapeutic alternatives to be reviewed	**Injection:** 10 mg/mL (besylate).
neostigmine	**Injection:** 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule. **Tablet:** 15 mg (bromide).
suxamethonium	**Injection:** 50 mg/mL (chloride) in 2 mL ampoule. **Powder for injection:** (chloride), in vial.
☐ vecuronium **[c]** Therapeutic alternatives: – atracurium	**Powder for injection:** 10 mg (bromide) in vial.

   Complementary List

pyridostigmine	***Injection:*** *1 mg in 1 mL ampoule.* ***Tablet:*** *60 mg (bromide).*
☐ *vecuronium* *Therapeutic alternatives to be reviewed*	***Powder for injection:*** *10 mg (bromide) in vial.*

21. OPHTHALMOLOGICAL PREPARATIONS

21.1 Anti-infective agents

aciclovir	**Ointment:** 3% w/w.
azithromycin	**Solution (eye drops):** 1.5%. – *Trachoma*
erythromycin	**Ointment:** 0.5% [c] . – *Infections due to Chlamydia trachomatis or Neisseria gonorrhoea*

□ gentamicin

Solution (eye drops): 0.3% (sulfate).

Therapeutic alternatives:
– amikacin
– kanamycin
– netilmicin
– tobramycin

    – *Bacterial blepharitis*
    – *Bacterial conjunctivitis*

natamycin

Suspension (eye drops): 5%
    – *Fungal keratitis*

□ ofloxacin

Solution (eye drops): 0.3%.

Therapeutic alternatives:
– 4th level ATC chemical subgroup (S01AE Fluoroquinolones)

    – *Bacterial conjunctivitis*
    – *Bacterial keratitis*

□ tetracycline

Eye ointment: 1% (hydrochloride).

Therapeutic alternatives:
– chlortetracycline
– oxytetracycline

    – *Bacterial blepharitis*
    – *Bacterial conjunctivitis*
    – *Bacterial keratitis*
    – *Trachoma*

21.2 Anti-inflammatory agents

□ prednisolone

Solution (eye drops): 0.5% (sodium phosphate).

Therapeutic alternatives to be reviewed

21.3 Local anaesthetics

□ tetracaine [a]

Solution (eye drops): 0.5% (hydrochloride).

Therapeutic alternatives:
– 4th level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations

[a] Not in preterm neonates.

21. OPHTHALMOLOGICAL PREPARATIONS *(continued)*

21.4 Miotics and antiglaucoma medicines

acetazolamide	**Tablet:** 250 mg.
latanoprost	**Solution (eye drops):** 50 micrograms/mL.

☐ pilocarpine

Solution (eye drops): 2%; 4% (hydrochloride or nitrate).

Therapeutic alternatives:
– carbachol

☐ timolol

Solution (eye drops): 0.25%; 0.5% (as hydrogen maleate).

Therapeutic alternatives:
– 4th level ATC chemical subgroup (S01ED Beta blocking agents) excluding combinations

21.5 Mydriatics

☐ atropine a

Solution (eye drops): 0.1%; 0.5%; 1% (sulfate).

Therapeutic alternatives*:
– cyclopentolate hydrochloride
– homatropine hydrobromide

a > 3 months.

* *EMLc only*

Complementary List

epinephrine (adrenaline)	***Solution (eye drops):** 2% (as hydrochloride).*

21.6 Anti-vascular endothelial growth factor (VEGF) preparations

Complementary List

bevacizumab*	***Injection:** 25 mg/mL.*

* *including quality-assured biosimilars*

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE

22.1 Contraceptives

22.1.1 *Oral hormonal contraceptives*

☐ ethinylestradiol +
☐ levonorgestrel

Tablet: 30 micrograms + 150 micrograms.

Therapeutic alternatives to be reviewed

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*

☐ ethinylestradiol + ☐ norethisterone Therapeutic alternatives to be reviewed	**Tablet:** 35 micrograms + 1 mg.
levonorgestrel	**Tablet:** 30 micrograms; 750 micrograms (pack of two); 1.5 mg.
ulipristal	**Tablet:** 30 mg (as acetate)

22.1.2 *Injectable hormonal contraceptives*

estradiol cypionate + medroxyprogesterone acetate	**Injection:** 5 mg + 25 mg.
medroxyprogesterone acetate	**Injection (intramuscular):** 150 mg mL in 1 mL vial. **Injection (subcutaneous):** 104 mg/0.65 mL in pre-filled syringe or single-dose injection delivery system.
norethisterone enantate	**Oily solution:** 200 mg/mL in 1 mL ampoule.

22.1.3 *Intrauterine devices*

copper-containing device	
levonorgestrel-releasing intrauterine system	**Intrauterine system:** with reservoir containing 52 mg of levonorestrel

22.1.4 *Barrier methods*

condoms

diaphragms

22.1.5 *Implantable contraceptives*

etonogestrel-releasing implant	**Single-rod etonogestrel-releasing implant:** containing 68 mg of etonogestrel.
levonorgestrel-releasing implant	**Two-rod levonorgestrel-releasing implant:** each rod containing 75 mg of levonorgestrel (150 mg total).

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*	

22.1.6 *Intravaginal contraceptives*

ethinylestradiol + etonogestrel	**Vaginal ring:** containing 2.7 mg + 11.7 mg
progesterone vaginal ring*	**Progesterone-releasing vaginal ring:** containing 2.074 g of micronized progesterone.
	* For use in women actively breastfeeding at least 4 times per day.

22.2 Ovulation inducers

Complementary List

clomifene	***Tablet:*** *50 mg (citrate).*
☐ *letrozole*	***Solid oral dosage form:*** *2.5 mg.*
Therapeutic alternatives: *– anastrozole*	

22.3 Uterotonics

carbetocin	**Injection (heat stable):** 100 micrograms/mL
☐ ergometrine Therapeutic alternatives: – methylergometrine	**Injection:** 200 micrograms (hydrogen maleate) in 1 mL ampoule.
mifepristone – misoprostol	**Tablet** 200 mg – **tablet** 200 micrograms.
Where permitted under national law and where culturally acceptable.	**Co-package containing:** mifepristone 200 mg tablet [1] and misoprostol 200 micrograms tablet [4] – Management of intrauterine fetal demise; – Management of induced abortion
misoprostol	**Tablet:** 200 micrograms. – Management of incomplete abortion and miscarriage; – Prevention and treatment of postpartum haemorrhage where oxytocin is not available or cannot be safely used
	Vaginal tablet: 25 micrograms.*
	* Only for use for induction of labour where appropriate facilities are available.
oxytocin	**Injection:** 10 IU in 1 mL.

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*

22.4 Antioxytocics (tocolytics)

nifedipine	**Immediate-release capsule:** 10 mg.

22.5 Other medicines administered to the mother

dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.

multiple micronutrient supplement*	**Tablet containing:**	
	Vitamin A (retinol acetate)	800 micrograms retinol activity equivalent
	Vitamin C (ascorbic acid)	70 mg
	Vitamin D (cholecalciferol)	5 micrograms (200 IU)
	Vitamin E (alpha tocopherol succinate)	10 mg alpha tocopherol equivalent
	Vitamin B1 (thiamine mononitrate)	1.4 mg
	Vitamin B2 (riboflavin)	1.4 mg
	Vitamin B3 (niacinamide)	18 mg niacin equivalent
	Vitamin B6 (pyridoxine hydrochloride)	1.9 mg
	Folic acid (folic acid)	680 micrograms dietary folate equivalent (400 micrograms)
	Vitamin B12 (cyanocobalamin)	2.6 micrograms
	Iron (ferrous fumarate)	30 mg
	Iodine (potassium iodide)	150 micrograms
	Zinc (zinc oxide)	15 mg
	Selenium (sodium selenite)	65 micrograms
	Copper (cupric oxide)	2 mg

* For use in specific contexts. Refer to current WHO recommendations.

tranexamic acid	**Injection:** 100 mg/mL in 10 mL ampoule

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*

22.6 Medicines administered to the neonate [c]

caffeine citrate [c]	**Injection:** 20 mg/mL (equivalent to 10 mg caffeine base/mL).
	Oral liquid: 20 mg/mL (equivalent to 10 mg caffeine base/mL).
chlorhexidine [c]	**Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).

Complementary List

☐ *ibuprofen* [c]   *Solution for injection: 5 mg/mL.*
Therapeutic alternatives:
– indometacin

☐ *prostaglandin E1* [c]   *Solution for injection: 0.5 mg/mL in alcohol.*
Therapeutic alternatives:
– prostaglandin E2

surfactant [c]   ***Suspension for intratracheal instillation:*** *25 mg/mL or 80 mg/mL.*

23. PERITONEAL DIALYSIS SOLUTION

Complementary List

intraperitoneal dialysis solution   **Parenteral solution:** *of appropriate composition*

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

24.1 Medicines for psychotic disorders

☐ fluphenazine   **Injection:** 25 mg (decanoate or enantate) in 1 mL ampoule.
Therapeutic alternatives:
– haloperidol decanonate
– zuclopenthixol decanonate

☐ haloperidol   **Tablet:** 2 mg; 5 mg.
Therapeutic alternatives:
– chlorpromazine

haloperidol   **Injection:** 5 mg/mL in 1 mL ampoule.

olanzapine   **Powder for injection:** 10 mg in vial.

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*

☐ paliperidone

Therapeutic alternatives:
– risperidone injection

Injection (prolonged-release): 25 mg; 50 mg; 75 mg; 100 mg; 150 mg (as palmitate) in pre-filled syringe

☐ risperidone

Therapeutic alternatives:
– aripiprazole
– olanzapine
– paliperidone
– quetiapine

Solid oral dosage form: 0.25 mg to 6.0 mg.

Complementary List

clozapine

Solid oral dosage form: 25 to 200 mg.

24.2 Medicines for mood disorders

24.2.1 *Medicines for depressive disorders*

amitriptyline

Tablet: 25 mg; 75mg (hydrochloride).

☐ fluoxetine

Therapeutic alternatives:
– citalopram
– escitalopram
– fluvoxamine
– paroxetine
– sertraline

Solid oral dosage form: 20 mg (as hydrochloride).

24.2.2 *Medicines for bipolar disorders*

carbamazepine

Tablet (scored): 100 mg; 200 mg; 400 mg.

lithium carbonate

Solid oral dosage form: 300 mg.

☐ quetiapine

Therapeutic alternatives:
– aripiprazole
– olanzapine
– paliperidone

Tablet (immediate-release): 25 mg; 100 mg; 150 mg; 200 mg; 300 mg.

Tablet (modified-release): 50 mg; 150 mg; 200 mg; 300 mg; 400 mg.

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*

valproic acid (sodium valproate)*	**Tablet (enteric-coated):** 200 mg; 500 mg.

* *avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.*

24.3 Medicines for anxiety disorders

☐ diazepam*

Therapeutic alternatives:
– lorazepam

Tablet (scored): 2 mg; 5 mg.

* For short-term emergency management of acute and severe anxiety symptoms only.

☐ fluoxetine

Therapeutic alternatives:
– citalopram
– escitalopram
– fluvoxamine
– paroxetine
– sertraline

Solid oral dosage form: 20 mg (as hydrochloride).

24.4 Medicines for obsessive compulsive disorders

clomipramine

Capsule: 10 mg; 25 mg (hydrochloride).

☐ fluoxetine

Therapeutic alternatives:
– citalopram
– escitalopram
– fluvoxamine
– paroxetine
– sertraline

Solid oral dosage form: 20 mg (as hydrochloride).

24.5 Medicines for disorders due to psychoactive substance use

24.5.1 *Medicines for alcohol use disorders*

acamprosate calcium

Tablet: 333 mg.

naltrexone

Injection suspension (extended-release): 380 mg in vial.
Tablet: 50 mg.

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS *(continued)*

24.5.2 *Medicines for nicotine use disorders*

bupropion	**Tablet (sustained-release):** 150 mg (hydrochloride)
nicotine replacement therapy (NRT)	**Chewing gum:** 2 mg; 4 mg (as polacrilex). **Lozenge:** 2 mg; 4 mg. **Oral spray:** 1 mg per actuation. **Transdermal patch:** 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.
varenicline	**Tablet:** 0.5 mg; 1 mg.

24.5.3 *Medicines for opioid use disorders*

Complementary List

☐ *methadone**

Therapeutic alternatives:
  – buprenorphine

***Concentrate for oral liquid:** 5 mg/mL; 10 mg/mL (hydrochloride).*

***Oral liquid:** 5 mg/5 mL; 10 mg/5 mL (hydrochloride).*

*   *The medicines should only be used within an established support programme.*

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic medicines and medicines for chronic obstructive pulmonary disease

☐ budesonide

Therapeutic alternatives:
– beclometasone
– ciclesonide
– flunisolide
– fluticasone
– mometasone

Inhalation (aerosol): 100 micrograms per dose; 200 micrograms per dose.

☐ budesonide +
☐ formoterol

Therapeutic alternatives:
– beclometasone + formoterol
– budesonide + salmeterol
– fluticasone + formoterol
– fluticasone furoate + vilanterol
– mometasone + formoterol

Dry powder inhaler: 100 micrograms + 6 micrograms per dose; 200 micrograms + 6 micrograms per dose

epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
ipratropium bromide	**Inhalation (aerosol):** 20 micrograms/metered dose.

25. MEDICINES ACTING ON THE RESPIRATORY TRACT *(continued)*

☐ salbutamol Therapeutic alternatives: – terbutaline	**Inhalation (aerosol):** 100 micrograms (as sulfate) per dose. **Injection:** 50 micrograms/mL (as sulfate) in 5 mL ampoule. **Metered dose inhaler (aerosol):** 100 micrograms (as sulfate) per dose. **Respirator solution for use in nebulizers:** 5 mg/mL (as sulfate).
☐ tiotropium Therapeutic alternatives: – aclidinium – glycopyrronium – umeclidinium	**Powder for inhalaton, capsule:** 18 micrograms **Inhalation solution:** 1.25 micrograms; 2.5 micrograms per actuation

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES

26.1 Oral

oral rehydration salts	See section 17.5.1.
potassium chloride	**Powder for solution.**

26.2 Parenteral

glucose	**Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	**Injectable solution:** 4% glucose, 0.18% sodium chloride (equivalent to Na+ 30 mmol/L, Cl- 30 mmol/L). **Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na+ 150 mmol/L and Cl- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na+ 75 mmol/L and Cl- 75 mmol/L) **[c]** .
potassium chloride	**Solution:** 11.2% in 20 mL ampoule (equivalent to K+ 1.5 mmol/mL, Cl- 1.5 mmol/mL). **Solution for dilution:** 7.5% (equivalent to K 1 mmol/mL and Cl 1 mmol/mL) **[c]** ; 15% (equivalent to K 2 mmol/mL and Cl 2 mmol/mL) **[c]** .
sodium chloride	**Injectable solution:** 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L).

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES *(continued)*

sodium hydrogen carbonate	**Injectable solution:** 1.4% isotonic (equivalent to Na+ 167 mmol/L, HCO_3^- 167 mmol/L).
	Solution: 8.4% in 10 mL ampoule (equivalent to Na+ 1000 mmol/L, HCO_3^- 1000 mmol/L).
sodium lactate, compound solution	**Injectable solution.**

26.3 Miscellaneous

water for injection	2 mL; 5 mL; 10 mL ampoules.

27. VITAMINS AND MINERALS

ascorbic acid	**Tablet:** 50 mg.
calcium	**Tablet:** 500 mg (elemental).
☐ colecalciferol [c] Therapeutic alternatives: – ergocalciferol	**Oral liquid:** 400 IU/mL. **Solid oral dosage form:** 400 IU; 1000 IU.
☐ ergocalciferol Therapeutic alternatives: – colecalciferol	**Oral liquid:** 250 micrograms/mL (10 000 IU/mL). **Solid oral dosage form:** 1.25 mg (50 000 IU).
iodine	**Capsule:** 190 mg. **Iodized oil:** 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.
multiple micronutrient powder [c]	**Sachets containing:** – iron (elemental) 12.5 mg (as coated ferrous fumarate) – zinc (elemental) 5 mg – vitamin A 300 micrograms – with or without other micronutrients at recommended daily values
nicotinamide	**Tablet:** 50 mg.
pyridoxine	**Tablet:** 25 mg (hydrochloride).

27. VITAMINS AND MINERALS *(continued)*	
retinol	**Capsule:** 50 000 IU; 100 000 IU; 200 000 IU (as palmitate).
	Oral oily solution: 100 000 IU/mL (as palmitate) in multidose dispenser.
	Tablet (sugar-coated): 10 000 IU (as palmitate).
	Water-miscible injection: 100 000 IU (as palmitate) in 2 mL ampoule.
riboflavin	**Tablet:** 5 mg.
thiamine	**Tablet:** 50 mg (hydrochloride).
Complementary List	
calcium gluconate	*Injection: 100 mg/mL in 10 mL ampoule.*

28. EAR, NOSE AND THROAT MEDICINES	
acetic acid [c]	**Topical:** 2%, in alcohol.
☐ budesonide [c] Therapeutic alternatives to be reviewed	**Nasal spray:** 100 micrograms per dose.
☐ ciprofloxacin [c] Therapeutic alternatives: – ofloxacin	**Solution (ear drops):** 0.3% (as hydrochloride).
☐ xylometazoline [a] [c] Therapeutic alternatives to be reviewed	**Nasal spray:** 0.05%. [a] Not in children less than 3 months.

29. MEDICINES FOR DISEASES OF JOINTS	

29.1 Medicines used to treat gout

allopurinol	**Tablet:** 100 mg.

29.2 Disease-modifying anti-rheumatic drugs (DMARDs)

chloroquine	**Tablet:** 100 mg; 150 mg (as phosphate or sulfate).
Complementary List	
azathioprine	*Tablet: 50 mg.*
hydroxychloroquine	*Solid oral dosage form: 200 mg (as sulfate).*
methotrexate	*Tablet: 2.5 mg (as sodium).*

29. MEDICINES FOR DISEASES OF JOINTS *(continued)*

penicillamine	**Solid oral dosage form:** 250 mg.
sulfasalazine	**Tablet:** 500 mg.

29.3 Medicines for juvenile joint diseases

Complementary List

acetylsalicylic acid*
(acute or chronic use)

Suppository: 50 mg to 150 mg.

Tablet: 100 mg to 500 mg.

* For use for rheumatic fever, juvenile arthritis, Kawasaki disease.

☐ adalimumab*

Therapeutic alternatives:
– certolizumab pegol
– etanercept
– golimumab
– infliximab

** including quality-assured
  biosimilars*

Injection: 10 mg/0.2 mL [c] ; 20 mg/0.4 mL [c] ;
40 mg/0.8 mL; 40 mg/0.4 mL.

methotrexate **Tablet:** 2.5 mg (as sodium).

☐ triamcinolone
hexacetonide

Therapeutic alternatives:
– triamcinolone acetonide

Injection: 20 mg/mL in vial.

30. DENTAL MEDICINES AND PREPARATIONS

fluoride

Gel: containing 2500 to 12 500 ppm fluoride (any type).

Mouthrinse: containing 230 to 900 ppm fluoride (any type).

Toothpaste, cream or gel: containing 1000 to 1500 ppm fluoride (any type).

Varnish: containing 22 500 ppm fluoride (any type).

glass ionomer cement

Single-use capsules: 0.4 g powder + 0.09 mL liquid.

Multi-use bottle: powder + liquid.

Powder (fluoro-alumino-silicate glass) contains: 25-50% silicate, 20-40% aluminium oxide, 1-20% fluoride, 15-40% metal oxide, 0-15% phosphate, remainder are polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7-25% polybasic carboxylic acid, 45-60% polyacrylic acid.

resin-based composite
(low-viscosity)*

Single-use applicator or multi-use bottle

* of any type for use as dental sealant.

30. DENTAL MEDICINES AND PREPARATIONS *(continued)*	
resin-based composite (high-viscosity)*	**Single-use capsule or multi-use syringe** * of any type for use as dental filling material
silver diamine fluoride	**Solution:** 38% w/v.

Table 1.1: Medicines with age or weight restrictions

artesunate + pyronaridine tetraphosphate	> 5 kg
atropine	> 3 months
benzyl benzoate	> 2 years
betamethasone topical preparations	hydrocortisone preferred in neonates
cefazolin	> 1 month
ceftriaxone	> 41 weeks corrected gestational age
darunavir	> 3 years
dihydroartemisinin + piperaquine phosphate	> 5 kg
diloxanide	> 25 kg
dolutegravir	≥ 4 weeks and ≥ 3 kg (10 mg dispersible tablet) ≥ 25 kg (50 mg tablet)
doxycycline	> 8 years (except for serious infections e.g. cholera)
ibuprofen	> 3 months (except IV form for patent ductus arteriosus)
mefloquine	> 5 kg or > 3 months
metoclopramide	Not in neonates
nevirapine	> 6 weeks
ondansetron	> 1 month
silver sulfadiazine	> 2 months
tetracaine	Not in preterm neonates
xylometazoline	> 3 months

Table 1.2: Explanation of dosage forms

A. Principal dosage forms used in EML – oral administration

Term	Definition
Solid oral dosage form	Refers to tablets or capsules or other solid dosage forms such as 'melts' that are immediate-release preparations. It implies that there is no difference in clinical efficacy or safety between the available dosage forms, and countries should therefore choose the form(s) to be listed depending on quality and availability. The term 'solid oral dosage form' is never intended to allow any type of modified-release tablet.
Tablets	Refers to: • uncoated or coated (film-coated or sugar-coated) tablets that are intended to be swallowed whole; • unscored and scored*; • tablets that are intended to be chewed before being swallowed; • tablets that are intended to be dispersed or dissolved in water or another suitable liquid before being swallowed; • tablets that are intended to be crushed before being swallowed. The term 'tablet' without qualification is never intended to allow any type of modified-release tablet.
Tablets (qualified)	Refers to a specific type of tablet: **chewable** - tablets that are intended to be chewed before being swallowed; **dispersible** - tablets that are intended to be dispersed in water or another suitable liquid before being swallowed; **soluble** - tablets that are intended to be dissolved in water or another suitable liquid before being swallowed; **crushable** - tablets that are intended to be crushed before being swallowed; **scored** - tablets bearing a break mark or marks where sub-division is intended in order to provide doses of less than one tablet; **sublingual** - tablets that are intended to be placed beneath the tongue.

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*   Scored tablets may be divided for ease of swallowing, provided that dose is a whole number of tablets.

Table 1.2 *continued*

Term	Definition
	The term 'tablet' is *always* qualified with an additional term (in parentheses) in entries where one of the following types of tablet is intended: **gastro-resistant** (such tablets may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.
Capsules	Refers to hard or soft capsules.
	The term 'capsule' without qualification is *never* intended to allow any type of modified-release capsule.
Capsules (qualified)	The term 'capsule' with qualification refers to **gastro-resistant** (such capsules may sometimes be described as enteric-coated or as delayed-release), **prolonged-release** or another modified-release form.
Granules	Preparations that are issued to patient as granules to be swallowed without further preparation, to be chewed, or to be taken in or with water or another suitable liquid.
	The term 'granules' without further qualification is never intended to allow any type of modified-release granules.
Oral powder	Preparations that are issued to patient as powder (usually as single-dose) to be taken in or with water or another suitable liquid.
Oral liquid	Liquid preparations intended to be *swallowed* i.e. oral solutions, suspensions, emulsions and oral drops, including those constituted from powders or granules, but not those preparations intended for *oromucosal administration* e.g. gargles and mouthwashes.
	Oral liquids presented as powders or granules may offer benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

B. Principal dosage forms used in EML – parenteral administration

Term	Definition
Injection	Refers to solutions, suspensions and emulsions including those constituted from powders or concentrated solutions.
Injection (qualified)	Route of administration is indicated in parentheses where relevant.
Injection (oily)	The term 'injection' is qualified by '(oily)' in relevant entries.
Intravenous infusion	Refers to solutions and emulsions including those constituted from powders or concentrated solutions.

C. Other dosage forms

Mode of administration	Term to be used
To the eye	Eye drops, eye ointments.
Topical	For liquids: lotions, paints. For semi-solids: cream, ointment.
Rectal	Suppositories, gel or solution.
Vaginal	Pessaries or vaginal tablets.
Inhalation	Powder for inhalation, pressurized inhalation, nebulizer.

Annex 2

WHO Model List of Essential Medicines for Children – 9th List (2023)

Explanatory notes

This Model List is intended for use for children up to and including 12 years of age

The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost–effectiveness in a variety of settings.

The **square box symbol** (□) is intended to indicate therapeutic alternatives to the listed medicine that may be considered for selection in national essential medicines lists. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the Anatomical Therapeutic Chemical (ATC) classification, which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines. However, the selection and use of quality-assured generics and biosimilars of essential medicines at country level is recommended.

National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.

The format and numbering of the 23rd WHO Model List of Essential Medicines is used for the 9th WHO Model Essential List for Children. Some sections have been deleted because they contain medicines that are not relevant for children.

The a symbol indicates that there is an age or weight restriction on use of the medicine; details for each medicine are in Table 1.1 of Annex 1.

The presence of an entry on the Essential Medicines List for Children carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines website https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines/quality-assurance.

Medicines and dosage forms are listed in alphabetical order within each section and the order of listing does not imply preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The main terms used for dosage forms in the Essential Medicines List can be found in Table 1.2 of Annex 1.

Definitions of many of these terms and pharmaceutical quality requirements applicable to the different categories are published in the current edition of *The International Pharmacopoeia* https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia.

1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES

1.1 General anaesthetics and oxygen

1.1.1 *Inhalational medicines*

halothane	**Inhalation.**
isoflurane	**Inhalation.**
nitrous oxide	**Inhalation.**
oxygen	**Inhalation** (medical gas).
sevoflurane	**Inhalation.**

1.1.2 *Injectable medicines*

ketamine	**Injection:** 50 mg/mL (as hydrochloride) in 10 mL vial.
☐ propofol* Therapeutic alternatives: – thiopental	**Injection:** 10 mg/mL; 20 mg/mL.

1.2 Local anaesthetics

☐ bupivacaine Therapeutic alternatives to be reviewed	**Injection:** 0.25%; 0.5% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 0.5% (hydrochloride) in 4 mL ampoule to be mixed with 7.5% glucose solution.
☐ lidocaine Therapeutic alternatives to be reviewed	**Injection:** 1%; 2% (hydrochloride) in vial. **Injection for spinal anaesthesia:** 5% (hydrochloride) in 2 mL ampoule to be mixed with 7.5% glucose solution. **Topical forms:** 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	**Dental cartridge:** 2% (hydrochloride) + epinephrine 1:80 000. **Injection:** 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial.

1.3 Preoperative medication and sedation for short-term procedures

atropine	**Injection:** 1 mg (sulfate) in 1mL ampoule.
☐ midazolam Therapeutic alternatives to be reviewed	**Injection:** 1 mg/mL. **Oral liquid:** 2 mg/mL. **Tablet:** 7.5 mg; 15 mg.
morphine	**Injection**: 10 mg (sulfate or hydrochloride) in 1mL ampoule.

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1. ANAESTHETICS, PREOPERATIVE MEDICINES AND MEDICAL GASES *(continued)*

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1.4 Medical gases

oxygen*	**Inhalation**
	For use in the management of hypoxaemia.
	* No more than 30% oxygen should be used to initiate resuscitation of neonates less than or equal to 32 weeks of gestation.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

ibuprofen [a]	**Oral liquid:** 100 mg/5 mL; 200 mg/5 mL.
	Tablet: 200 mg; 400 mg; 600 mg.
	[a] Not in children less than 3 months.
paracetamol* (acetaminophen)	**Oral liquid:** 120 mg/5 mL or 125 mg/5 mL**; 250 mg/5 mL.
	**The presence of both 120 mg/5 mL and 125 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
	Suppository: 100 mg; 250 mg.
	Tablet: 250 mg; 325 mg; 500 mg.
	Tablet (dispersible): 100 mg; 250 mg.
	* Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.

2.2 Opioid analgesics

☐ morphine Therapeutic alternatives: – hydrormorphone – oxycodone	**Granules (slow release; to mix with water):** 20 mg to 200 mg (morphine sulfate).
	Injection: 10 mg (morphine hydrochloride or morphine sulfate) in 1 mL ampoule.
	Oral liquid: 10 mg/5 mL (morphine hydrochloride or morphine sulfate).
	Tablet (slow release): 10 mg to 200mg (morphine hydrochloride or morphine sulfate).
	Tablet (immediate release): 10 mg (morphine sulfate).

Complementary list

*methadone**	*Tablet:* 5 mg; 10 mg (hydrochloride).
	Oral liquid: 5 mg/5 mL; 10 mg/5 mL (hydrochloride).
	Concentrate for oral liquid: 5 mg/mL; 10 mg/mL (hydrochloride)
	* For the management of cancer pain.

2. MEDICINES FOR PAIN AND PALLIATIVE CARE *(continued)*

2.3 Medicines for other symptoms common in palliative care

amitriptyline	**Tablet:** 10 mg; 25 mg.
cyclizine	**Injection:** 50 mg/mL.
	Tablet: 50 mg.
dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.
	Oral liquid: 2 mg/5 mL.
	Tablet: 2 mg.
diazepam	**Injection:** 5 mg/mL.
	Oral liquid: 2 mg/5 mL.
	Rectal gel: 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system.
	Rectal solution: 2 mg/mL in 1.25 mL, 2.5 mL rectal tubes; 4 mg/mL in 2.5 mL rectal tube.
	Tablet: 5 mg; 10 mg.
docusate sodium	**Capsule:** 100 mg.
	Oral liquid: 50 mg/5 mL.
hyoscine hydrobromide	**Injection:** 400 micrograms/mL; 600 micrograms/mL. **Transdermal patches**: 1 mg/72 hours.
lactulose	**Oral liquid:** 3.1 to 3.7 g/5 mL.
midazolam	**Injection:** 1 mg/mL; 5 mg/mL.
	Oral liquid: 2mg/mL.
	Solid oral dosage form: 7.5 mg; 15 mg.
☐ ondansetron [a] Therapeutic alternatives – dolasetron – granisetron – palonosetron – tropisetron	**Injection:** 2 mg base/mL in 2 mL ampoule (as hydrochloride).
	Oral liquid: 4 mg base/5 mL.
	Solid oral dosage form: Eq 4 mg base; Eq 8 mg base.
	[a] > 1 month.
senna	**Oral liquid:** 7.5 mg/5 mL.

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS

dexamethasone	**Injection:** 4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.
epinephrine (adrenaline)	**Injection:** 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.
hydrocortisone	**Powder for injection:** 100 mg (as sodium succinate) in vial.

☐ loratadine*

Therapeutic alternatives:
– cetirizine
– fexofenadine

Oral liquid: 1 mg/mL.

Tablet: 10 mg.

* *There may be a role for sedating antihistamines for limited indications.*

☐ prednisolone

Therapeutic alternatives:
– prednisone

Oral liquid: 5 mg/mL.

Tablet: 5 mg; 25 mg.

4. ANTIDOTES AND OTHER SUBSTANCES USED IN POISONINGS

4.1 Non-specific

charcoal, activated	**Powder.**

4.2 Specific

acetylcysteine	**Injection:** 200 mg/mL in 10 mL ampoule. **Oral liquid:** 10%; 20%.
atropine	**Injection:** 1 mg (sulfate) in 1 mL ampoule.
calcium gluconate	**Injection:** 100 mg/mL in 10 mL ampoule.
naloxone	**Injection:** 400 micrograms (hydrochloride) in 1 mL ampoule.

Complementary List

deferoxamine	*Powder for injection: 500 mg (mesilate) in vial.*
dimercaprol	*Injection in oil: 50 mg/mL in 2 mL ampoule.*
fomepizole	*Injection: 5 mg/mL (sulfate) in 20 mL ampoule or 1 g/mL (base) in 1.5 mL ampoule.*
sodium calcium edetate	*Injection: 200 mg/mL in 5 mL ampoule.*
succimer	*Solid oral dosage form: 100 mg.*

5. MEDICINES FOR DISEASES OF THE NERVOUS SYSTEM

5.1 Antiseizure medicines

carbamazepine	**Oral liquid:** 100 mg/5 mL.
	Tablet (chewable): 100 mg; 200 mg.
	Tablet (scored): 100 mg; 200 mg; 400 mg.
diazepam	**Rectal gel:** 5 mg/mL in 0.5 mL, 2 mL, 4 mL rectal delivery system.
	Rectal solution: 2 mg/mL in 1.25 mL, 2.5 mL rectal tubes; 4 mg/mL in 2.5 mL rectal tube.
lamotrigine*	**Tablet:** 25 mg; 50 mg; 100 mg; 200 mg.
	Tablet (chewable, dispersible): 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg.
	* For use as adjunctive therapy for treatment-resistant partial or generalized seizures.
levetiracetam	**Oral solution:** 100 mg/mL.
	Tablet: 250 mg; 500 mg; 750 mg; 1000 mg.
☐ lorazepam Therapeutic alternatives: – diazepam (injection) – midazolam (injection)	**Injection:** 2 mg/mL in 1 mL ampoule; 4 mg/mL in 1 mL ampoule.
midazolam	**Solution for oromucosal administration:** 5 mg/mL in 0.5 mL, 1 mL, 1.5 mL, 2 mL pre-filled syringe; 10 mg/mL in 0.25 mL, 0.5 mL, 0.75 mL, 1 mL pre-filled syringe.
	Injection*: 1 mg/mL in 5 mL vial; 5 mg/mL in 1 mL or 3 mL vial.
	* For buccal administration when solution for oromucosal administration is not available.
phenobarbital	**Injection:** 30 mg/mL or 60 mg/mL; 200 mg/mL (sodium).
	Oral liquid: 15 mg/5 mL.
	Tablet: 15 mg to 100 mg.
phenytoin	**Injection:** 50 mg/mL (phenytoin sodium).
	Oral liquid: 30 mg/5 mL (phenytoin).
	Solid oral dosage form: 25 mg; 50 mg; 100 mg (phenytoin sodium).
	Tablet (chewable): 50 mg (phenytoin).

5. MEDICINES FOR DISEASES OF THE NERVOUS SYSTEM *(continued)*

valproic acid
(sodium valproate)*

* *avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.*

Oral liquid: 200 mg/5 mL.

Tablet (crushable): 100 mg.

Tablet (enteric-coated): 200 mg; 500 mg.

Complementary List

ethosuximide

Capsule: *250 mg.*

Oral liquid: *250 mg/5 mL.*

levetiracetam

Concentrate solution for infusion: *500 mg/5mL in 5 mL vial.*

Solution for infusion: *5 mg/mL; 10 mg/mL; 15 mg/mL in 100 mL bag.*

valproic acid (sodium valproate)*

* *avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.*

Injection: *100 mg/mL in 3 mL, 4 mL, 10 mL ampoule.*

5.2 Medicines for multiple sclerosis

5.3 Medicines for parkinsonism

6. ANTI-INFECTIVE MEDICINES

6.1 Anthelminthics

6.1.1 *Intestinal anthelminthics*

albendazole	**Tablet (chewable, scored):** 400 mg.
ivermectin	**Tablet:** 3 mg.
levamisole	**Tablet:** 50 mg (as hydrochloride).
mebendazole	**Tablet (chewable):** 100 mg; 500 mg.
niclosamide	**Tablet (chewable):** 500 mg.
praziquantel	**Tablet:** 150 mg; 500 mg.
	Tablet (scored): 600 mg.
pyrantel	**Tablet (chewable):** 250 mg (as embonate or pamoate).

6.1.2 *Antifilarials*

albendazole	**Tablet (chewable, scored):** 400 mg.
diethylcarbamazine	**Tablet:** 50 mg; 100 mg (dihydrogen citrate).
ivermectin	**Tablet:** 3 mg.

6.1.3 *Antischistosomals and other antitrematode medicines*

praziquantel	**Tablet:** 150 mg; 500 mg.
	Tablet (scored): 600 mg.
triclabendazole	**Tablet (scored):** 250 mg.

Complementary List

oxamniquine*	***Capsule:** 250 mg.*
	***Oral liquid:** 250 mg/5 mL.*
	* For use when praziquantel treatment fails.

6.1.4 *Cysticidal medicines*
Complementary List

albendazole	***Tablet (chewable):** 200 mg.*
	***Tablet (chewable, scored):** 400 mg.*
mebendazole	***Tablet (chewable):** 100 mg; 500 mg.*
praziquantel	***Tablet:** 150 mg; 500 mg.*
	***Tablet (scored):** 600 mg.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics has been developed by WHO – where antibiotics are classified into different groups to emphasize the importance of their appropriate use.

ACCESS GROUP ANTIBIOTICS

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model Lists.

RESERVE GROUP ANTIBIOTICS

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.1 *Access group antibiotics*

amikacin	**Injection:** 50 mg/mL (as sulfate); 250 mg/mL (as sulfate) in 2 mL vial.

FIRST CHOICE	SECOND CHOICE
– *High-risk febrile neutropenia* – *Pyelonephritis (severe)*	– *Sepsis in neonates and children*

amoxicillin	**Powder for injection:** 250 mg; 500 mg; 1 g (as sodium) in vial. **Powder for oral liquid:** 125 mg/5 mL; 250 mg/5 mL (as trihydrate). **Solid oral dosage form:** 250 mg; 500 mg (as trihydrate). **Tablet (dispersible, scored):** 250 mg; 500 mg (as trihydrate).

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (mild to moderate)* – *Community acquired pneumonia (severe)* – *Complicated severe acute malnutrition* – *Otitis media* – *Pharyngitis* – *Progressive apical dental abscess* – *Sepsis in neonates and children* – *Sinusitis* – *Uncomplicated severe acute malnutrition*	– *Acute bacterial meningitis*

6. ANTI-INFECTIVE MEDICINES *(continued)*

amoxicillin + clavulanic acid	**Powder for injection:** 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial.
	Powder for oral liquid: 125 mg (as trihydrate) + 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL.
	Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt).
	Tablet (dispersible): 200 mg (as trihydrate) + 28.5 mg (as potassium salt); 250 mg (as trihydrate) + 62.5 mg (as potassium salt).

FIRST CHOICE	**SECOND CHOICE**
– *Community acquired pneumonia (severe)*	– *Bone and joint infections*
– *Complicated intraabdominal infections (mild to moderate)*	– *Community acquired pneumonia (mild to moderate)*
– *Hospital acquired pneumonia*	– *Community acquired pneumonia (severe)*
– *Low-risk febrile neutropenia*	– *Otitis media*
– *Lower urinary tract infections*	– *Surgical prophylaxis*
– *Sinusitis*	
– *Skin and soft tissue infections*	

| ampicillin | **Powder for injection:** 500 mg; 1 g (as sodium) in vial. |

FIRST CHOICE	**SECOND CHOICE**
– *Community acquired pneumonia (severe)*	– *Acute bacterial meningitis*
– *Complicated intraabdominal infections*	
– *Complicated severe acute malnutrition*	
– *Sepsis in neonates and children*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

benzathine benzylpenicillin	**Powder for injection:** 1.2 million IU (≈ 900 mg) in vial; 2.4 million IU (≈ 1.8 g) in vial.	
	FIRST CHOICE	**SECOND CHOICE**
	– Syphilis (congenital)	

benzylpenicillin	**Powder for injection:** 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.	
	FIRST CHOICE	**SECOND CHOICE**
	– Community acquired pneumonia (severe)	*– Acute bacterial meningitis*
	– Complicated severe acute malnutrition	
	– Sepsis in neonates and children	
	– Syphilis (congenital)	

cefalexin	**Powder for oral liquid:** 125 mg/5 mL; 250 mg/5 mL (anhydrous).	
	Solid oral dosage form: 250 mg (as monohydrate).	
	Tablet (dispersible): 125 mg; 250 mg.	
	FIRST CHOICE	**SECOND CHOICE**
	– Skin and soft tissue infections	*– Pharyngitis*

cefazolin [a]	Powder for injection: 1 g (as sodium salt) in vial.	
	[a] > 1 month.	
	FIRST CHOICE	**SECOND CHOICE**
	– Surgical prophylaxis	*– Bone and joint infections*

chloramphenicol	**Oily suspension for injection*:** 0.5 g/mL (as sodium succinate) in 2 mL ampoule.	
	* Only for the presumptive treatment of epidemic meningitis in children older than 2 years.	
	Powder for injection: 1 g (sodium succinate) in vial.	
	FIRST CHOICE	**SECOND CHOICE**
		– Acute bacterial meningitis

6. ANTI-INFECTIVE MEDICINES *(continued)*

clindamycin

Capsule: 150 mg (as hydrochloride).

Injection: 150 mg/mL (as phosphate).

Powder for oral liquid: 75 mg/5 mL (as palmitate hydrochloride).

FIRST CHOICE	SECOND CHOICE
– Necrotizing fasciitis	*– Bone and joint infections*

☐ cloxacillin*

Therapeutic alternatives:
– 4ᵗʰ level ATC chemical subgroup (J01CF Beta-lactamase resistant penicillins)

Capsule: 250 mg; 500 mg; 1 g (as sodium).

Powder for injection: 250 mg; 500 mg (as sodium) in vial.

Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (as sodium).

* cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.

FIRST CHOICE	SECOND CHOICE
– Bone and joint infections	*– Sepsis in neonates and children*
– Skin and soft tissue infections	

doxycycline [a]

Oral liquid: 50 mg/5 mL (calcium).

Powder for oral liquid: 25 mg/5 mL (monohydrate).

Powder for injection: 100 mg in vial.

Solid oral dosage form: 50 mg; 100 mg (as hyclate).

Tablet (dispersible): 100 mg (as monohydrate).

[a] Use in children <8 years only for life-threatening infections when no alternative exists.

FIRST CHOICE	SECOND CHOICE
	– Cholera
	– Community acquired pneumonia (mild to moderate)

6. ANTI-INFECTIVE MEDICINES *(continued)*

gentamicin	**Injection:** 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.	
	FIRST CHOICE	**SECOND CHOICE**
	– *Acute bacterial meningitis in neonates*	– *Surgical prophylaxis*
	– *Community acquired pneumonia (severe)*	
	– *Complicated intra-abdominal infections*	
	– *Complicated severe acute malnutrition*	
	– *Sepsis in neonates and children*	

metronidazole	**Injection:** 500 mg in 100 mL vial. **Oral liquid:** 200 mg/5 mL (as benzoate). **Tablet:** 200 mg; 250 mg; 400 mg; 500 mg.	
	FIRST CHOICE	**SECOND CHOICE**
	– *C. difficile infection*	– *Complicated intra-abdominal infections (mild to moderate)*
	– *Complicated intra-abdominal infections (mild to moderate)*	
	– *Complicated intra-abdominal infections (severe)*	
	– *Necrotizing fasciitis*	
	– *Surgical prophylaxis*	

nitrofurantoin	**Oral liquid:** 25 mg/5 mL. **Solid oral dosage form:** 50 mg; 100 mg.	
	FIRST CHOICE	**SECOND CHOICE**
	– *Lower urinary tract infections*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

phenoxymethylpenicillin	**Powder for oral liquid:** 250 mg/5 mL (as potassium).
	Solid oral dosage form: 250 mg (as potassium).

FIRST CHOICE	SECOND CHOICE
– *Community acquired pneumonia (mild to moderate)*	
– *Pharyngitis*	
– *Progressive apical dental abscess*	

procaine benzylpenicillin*	**Powder for injection:** 1 g (=1 million IU); 3 g (=3 million IU) in vial.
	* Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis / sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.

FIRST CHOICE	SECOND CHOICE
– *Syphilis (congenital)*	

sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule.
	Oral liquid: 200 mg + 40 mg/5 mL.
	Tablet: 100 mg + 20 mg; 400 mg + 80 mg.
	Tablet (dispersible): 100 mg + 20 mg.

FIRST CHOICE	SECOND CHOICE
– *Lower urinary tract infections*	– *Acute invasive bacterial diarrhoea / dysentery*

trimethoprim	**Tablet:** 100 mg; 200 mg.
	Oral liquid: 50 mg/5 mL.

FIRST CHOICE	SECOND CHOICE
– *Lower urinary tract infections*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.2 *Watch group antibiotics*

azithromycin

Solid oral dosage form: 250 mg; 500 mg (anhydrous).

Powder for oral liquid: 200 mg/5 mL (anhydrous).

FIRST CHOICE	SECOND CHOICE
– *Cholera*	– *Acute invasive bacterial diarrhoea / dysentery*
– *Enteric fever*	
– *Trachoma*	
– *Yaws*	

cefixime

Powder for oral liquid: 100 mg/5 mL.

Solid oral dosage form: 200 mg; 400 mg (as trihydrate).

FIRST CHOICE	SECOND CHOICE
	– *Acute invasive bacterial diarrhoea / dysentery*

cefotaxime*

Powder for injection: 250 mg; 500 mg; 1 g; 2 g (as sodium) in vial.

* 3rd generation cephalosporin of choice for use in hospitalized neonates.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis*	– *Bone and joint infections*
– *Community acquired pneumonia (severe)*	– *Pyelonephritis (mild to moderate)*
– *Complicated intraabdominal infections (mild to moderate)*	– *Sepsis in neonates and children*
– *Complicated intraabdominal infections (severe)*	
– *Hospital acquired pneumonia*	
– *Pyelonephritis (severe)*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

ceftriaxone* [a]	**Powder for injection:** 250 mg; 500 mg; 1 g (as sodium) in vial.

* Do not administer with calcium and avoid in infants with hyperbilirubinaemia.

[a] > 41 weeks corrected gestational age.

FIRST CHOICE	SECOND CHOICE
– *Acute bacterial meningitis*	– *Acute invasive bacterial diarrhoea / dysentery*
– *Community acquired pneumonia (severe)*	– *Bone and joint infections*
– *Complicated intraabdominal infections (mild to moderate)*	– *Pyelohepnritis or prostatitis (mild to moderate)*
– *Complicated intraabdominal infections (severe)*	– *Sepsis in neonates and children*
– *Endophthalmitis*	
– *Enteric fever*	
– *Hospital acquired pneumonia*	
– *Necrotizing fasciitis*	
– *Pyelonephritis (severe)*	

cefuroxime	**Powder for injection:** 250 mg; 750 mg; 1.5 g (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
	– *Surgical prophylaxis*

ciprofloxacin	**Oral liquid:** 250 mg/5 mL (anhydrous). **Solution for IV infusion:** 2 mg/mL (as hyclate). **Solid oral dosage form:** 100 mg; 250 mg (as hydrochloride).

FIRST CHOICE	SECOND CHOICE
– *Acute invasive bacterial diarrhoea / dysentery*	– *Cholera*
– *Enteric fever*	– *Complicated intra-abdominal infections (mild to moderate)*
– *Low-risk febrile neutropenia*	
– *Pyelonephritis (mild to moderate)*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

☐ clarithromycin	**Powder for oral liquid:** 125 mg/5 mL; 250 mg/5 mL.
Therapeutic alternatives: – erythromycin	**Powder for injection:** 500 mg in vial. **Solid oral dosage form:** 250 mg.

FIRST CHOICE	SECOND CHOICE
	– *Pharyngitis*

piperacillin + tazobactam	**Powder for injection:** 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial.

FIRST CHOICE	SECOND CHOICE
– *Complicated intra-abdominal infections (severe)* – *High-risk febrile neutropenia* – *Hospital acquired pneumonia* – *Necrotizing fasciitis*	

vancomycin	Capsule: 125 mg; 250 mg (as hydrochloride).
	* vancomycin powder for injection may also be used for oral administration.

FIRST CHOICE	SECOND CHOICE
	– *C. difficile infection*

Complementary List

ceftazidime	***Powder for injection:*** *250 mg; 1 g (as pentahydrate) in vial.*

FIRST CHOICE	SECOND CHOICE
– *Endophthalmitis*	

6. ANTI-INFECTIVE MEDICINES *(continued)*

☐ *meropenem** [a] *Therapeutic alternatives*:* *– imipenem + cilastatin* * *complicated intra-abdominal infections and high-risk febrile neutropenia only. Meropenem is the preferred choice for acute bacterial meningitis in neonates.*	***Powder for injection:*** *500 mg (as trihydrate); 1 g (as trihydrate) in vial* [a] > 3 months.

FIRST CHOICE	**SECOND CHOICE** *– Acute bacterial meningitis in neonates* *– Complicated intra-abdominal infections (severe)* *– High-risk febrile neutropenia*

vancomycin	***Powder for injection:*** *250 mg; 500 mg; 1 g (as hydrochloride) in vial.*

FIRST CHOICE *– Endophthalmitis* *– Necrotizing fasciitis*	**SECOND CHOICE** *– High-risk febrile neutropenia*

6.2.3 Reserve group antibiotics

Complementary List

ceftazidime + avibactam	***Powder for injection:*** *2 g + 0.5 g in vial.*
ceftolozane + tazobactam	***Powder for injection:*** *1 g + 0.5 g in vial.*
colistin	***Powder for injection:*** *1 million IU (as colistemethate sodium) (equivalent to 34 mg colistin base activity) in vial.*
fosfomycin	***Powder for injection:*** *2 g; 4 g (as sodium) in vial.*
linezolid	***Injection for intravenous administration:*** *2 mg/mL in 300 mL bag.* ***Powder for oral liquid:*** *100 mg/5 mL.* ***Tablet (dispersible):*** *150 mg.*
polymyxin B	***Powder for injection:*** *500 000 IU (equivalent to 50 mg polymyxin B base) in vial.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.2.4 *Antileprosy medicines*

Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour-coded blister packs (MDT blister packs) containing standard two-medicine (paucibacillary leprosy) or three-medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.

clofazimine	**Solid oral dosage form:** 50 mg; 100 mg.
dapsone	**Tablet:** 25 mg; 50 mg; 100 mg.
rifampicin	**Oral liquid:** 20 mg/mL. **Solid oral dosage form:** 150 mg; 300 mg.

6.2.5 *Antituberculosis medicines*

WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

ethambutol	**Tablet:** 100 mg; 400 mg (hydrochloride). **Tablet (dispersible):** 100 mg.
ethionamide	**Tablet:** 250 mg. **Tablet (dispersible):** 125 mg.
isoniazid	**Tablet:** 100 mg; 300 mg. **Tablet (dispersible):** 100 mg.
isoniazid + pyrazinamide + rifampicin	**Tablet (dispersible):** 50 mg + 150 mg + 75 mg.
isoniazid + rifampicin	**Tablet (dispersible):** 50 mg + 75 mg.
isoniazid + rifapentine	**Tablet (scored):** 300 mg + 300 mg.
pyrazinamide	**Tablet:** 400 mg; 500 mg. **Tablet (dispersible):** 150 mg.
rifampicin	**Oral liquid:** 20 mg/mL. **Solid oral dosage form:** 150 mg; 300 mg.
rifapentine	**Tablet:** 150 mg; 300 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

Complementary List

Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.

amikacin	***Injection:*** *250 mg/mL (as sulfate) in 2 mL vial.*
amoxicillin + clavulanic acid*	***Powder for oral liquid:*** *250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5 mL.*
	Tablet: *500 mg (as trihydrate) + 125 mg (as potassium salt).*
	* For use only in combination with meropenem.
bedaquiline	***Tablet:*** *20 mg; 100 mg.*
clofazimine	***Solid oral dosage form:*** *50 mg; 100 mg.*
cycloserine	***Solid oral dosage form:*** *125 mg; 250 mg.*
delamanid	***Tablet (dispersible):*** *25 mg.*
	Tablet: *50 mg.*
☐ ethionamide	***Tablet:*** *250 mg.*
Therapeutic alternatives: *– protionamide*	***Tablet (dispersible):*** *125 mg.*
levofloxacin	***Tablet:*** *250 mg; 500 mg.*
	Tablet (dispersible): *100 mg.*
linezolid	***Tablet:*** *600 mg.*
	Tablet (dispersible): *150 mg.*
meropenem	***Powder for injection:*** *500 mg (as trihydrate); 1 g (as trihydrate) in vial.*
moxifloxacin	***Tablet:*** *400 mg.*
	Tablet (dispersible): *100 mg.*
p-aminosalicylate sodium	***Powder for oral solution:*** *5.52 g in sachet (equivalent to 4 g p aminosalicylic acid.*
streptomycin	***Powder for injection:*** *1 g (as sulfate) in vial.*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.3 Antifungal medicines

amphotericin B*

Powder for injection: 50 mg (liposomal complex) in vial.

Powder for injection: 50 mg (as sodium deoxycholate) in vial.

* Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.

fluconazole

Capsule: 50 mg.

Injection: 2 mg/mL in vial.

Oral liquid: 50 mg/5 mL.

Powder for oral liquid: 50 mg/5 mL.

flucytosine

Capsule: 250 mg.

Infusion: 2.5 g in 250 mL.

griseofulvin

Oral liquid: 125 mg/5 mL.

Solid oral dosage form: 125 mg; 250 mg.

itraconazole*

Capsule: 100 mg.

Oral liquid: 10 mg/mL.

* For treatment of chronic pulmonary aspergillosis, acute invasive aspergillosis, histoplasmosis, sporotrichosis, paracoccidiodomycosis, mycoses caused by *T. marneffei* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffei* in AIDS patients.

nystatin

Lozenge: 100 000 IU.

Oral liquid: 100 000 IU/mL.

Solid oral dosage form: 500 000 IU.

voriconazole*

Tablet: 50 mg; 200 mg.

Powder for injection: 200 mg in vial.

Powder for oral liquid: 40 mg/mL.

* For treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis.

Complementary List

☐ *micafungin*
Therapeutic alternatives:
– *anidulafungin*
– *caspofungin*

Powder for injection: 50 mg (as sodium); 100 mg (as sodium) in vial.

potassium iodide

Saturated solution.

6.   ANTI-INFECTIVE MEDICINES *(continued)*

6.4   Antiviral medicines

6.4.1   *Antiherpes medicines*

aciclovir   **Oral liquid:** 200 mg/5 mL.

Powder for injection: 250 mg (as sodium salt) in vial.

Tablet: 200 mg.

6.4.2   *Antiretrovirals*

Based on current evidence and experience of use, medicines in the following classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post-exposure prophylaxis). WHO emphasizes the importance of using these products in accordance with global and national guidelines. WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.

Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided that adequate quality products are available.

6.4.2.1   *Nucleoside/Nucleotide reverse transcriptase inhibitors*

lamivudine   **Oral liquid:** 50 mg/5 mL.

zidovudine   **Oral liquid:** 50 mg/5 mL.

6.4.2.2   *Non-nucleoside reverse transcriptase inhibitors*

nevirapine [a]   **Oral liquid:** 50 mg/5 mL.

Tablet (dispersible): 50 mg.

[a] > 6 weeks

6.4.2.3   *Protease inhibitors*

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right. All other protease inhibitors should be used in boosted forms (e.g. with ritonavir).

darunavir [a]   **Tablet:** 75 mg.

[a] > 3 years

lopinavir + ritonavir   **Solid oral dosage form:** 40 mg + 10 mg.

Tablet (heat stable): 100 mg + 25 mg.

ritonavir   **Tablet (heat stable):** 25 mg; 100 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.2.4 *Integrase inhibitors*

dolutegravir [a]	**Tablet (dispersible, scored):** 10 mg.
	[a] ≥4 weeks and ≥3 kg
	Tablet: 50 mg.
	[a] ≥ 25 kg
raltegravir*	**Granules for oral suspension:** 100 mg in sachet.
	Tablet (chewable): 25 mg.
	* For use in second-line regimens in accordance with WHO treatment guidelines.

6.4.2.5 *Fixed-dose combinations of antiretroviral medicines*

abacavir + lamivudine	**Tablet (dispersible, scored):** 120 mg (as sulfate) + 60 mg.
lamivudine + zidovudine	**Tablet:** 30 mg + 60 mg.

6.4.2.6 *Medicines for prevention of HIV-related opportunistic infections*

isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	**Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg.

6.4.3 *Other antivirals*

ribavirin*	**Injection for intravenous administration:** 800 mg and 1 g in 10 mL phosphate buffer solution.
	Solid oral dosage form: 200 mg; 400 mg; 600 mg.
	* For the treatment of viral haemorrhagic fevers only.

Complementary List

*oseltamivir**	*Capsule: 30 mg; 45 mg; 75 mg (as phosphate).*
	* *Severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.*
*valganciclovir**	*Powder for oral solution: 50 mg/mL*
	Tablet: 450 mg.
	* *For the treatment of cytomegalovirus retinitis (CMVr).*

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.4.4 *Antihepatitis medicines*

6.4.4.1 *Medicines for hepatitis B*

6.4.4.1.1 *Nucleoside/Nucleotide reverse transcriptase inhibitors*

entecavir	**Oral liquid:** 0.05 mg/mL.
	Tablet: 0.5 mg; 1 mg.

6.4.4.2 *Medicines for hepatitis C*

Pangenotypic direct-acting antivirals should be considered as therapeutically equivalent for the purposes of selection and procurement at national level.

6.4.4.2.1 ☐ *Pangenotypic direct-acting antiviral combinations*

daclatasvir*	**Tablet:** 30 mg; 60 mg (as hydrochloride).
	* Pangenotypic when used in combination with sofosbuvir.
daclatasvir + sofosbuvir	**Tablet:** 60 mg + 400 mg.
glecaprevir + pibrentasvir	**Granules:** 50 mg + 20 mg in sachet.
	Tablet: 100 mg + 40 mg.
sofosbuvir*	**Tablet:** 200 mg; 400 mg.
	* Pangenotypic when used in combination with daclatasvir.
sofosbuvir + velpatasvir	**Tablet:** 200 mg + 50 mg; 400 mg + 100 mg.

~~**6.4.4.2.2 *Non-pangenotypic direct-acting antiviral combinations***~~

~~**6.4.4.2.3 *Other antivirals for hepatitis C***~~

6.5 Antiprotozoal medicines

6.5.1 *Antiamoebic and antigiardiasis medicines*

diloxanide [a]	**Tablet:** 500 mg (furoate).
	[a] > 25 kg.
☐ metronidazole	**Injection:** 500 mg in 100 mL vial.
Therapeutic alternatives:	**Oral liquid:** 200 mg/5 mL (as benzoate).
– tinidazole	**Tablet:** 200 mg; 250 mg; 400 mg; 500 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.2 *Antileishmaniasis medicines*

amphotericin B*	**Powder for injection:** 50 mg (liposomal complex) in vial.
	Powder for injection: 50 mg (as sodium deoxycholate) in vial.
	* Liposomal amphotericin B has a better safety profile than the sodium deoxycholate formulation and should be prioritized for selection and use depending on local availability and cost.
meglumine antimoniate	**Injection:** 1.5 g/5 mL in 5 mL ampoule.
miltefosine	**Solid oral dosage form:** 10 mg; 50 mg.
paromomycin	**Solution for intramuscular injection:** 750 mg of paromomycin base (as sulfate).
sodium stibogluconate	**Injection:** 100 mg/mL in 30 mL vial.

6.5.3 *Antimalarial medicines*

6.5.3.1 *For curative treatment*

Medicines for the treatment of P. falciparum malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. WHO recognizes that not all of the fixed dose combinations (FDCs in the WHO treatment guidelines exist, and encourages their development and rigorous testing. WHO also encourages development and testing of rectal dosage formulations.

amodiaquine*	**Tablet:** 153 mg or 200 mg (as hydrochloride).
	* To be used in combination with artesunate 50 mg.
artemether*	**Oily injection:** 80 mg/mL in 1 mL ampoule.
	* For use in the management of severe malaria.
artemether + lumefantrine*	**Tablet:** 20 mg + 120 mg.
	Tablet (dispersible): 20 mg + 120 mg.
	* Not recommended in the first trimester of pregnancy or in children below 5 kg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

artesunate*	**Injection:** ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. **Rectal dosage form:** 50 mg; 100 mg; 200 mg capsules. For pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care. **Tablet:** 50 mg. * To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.
artesunate + amodiaquine*	**Tablet:** 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg. * Other combinations that deliver the target doses required such as 153 mg or 200 mg (as hydrochloride) with 50 mg artesunate can be alternatives.
artesunate + mefloquine	**Tablet:** 25 mg + 55 mg; 100 mg + 220 mg.
artesunate + pyronaridine tetraphosphate [a]	**Granules:** 20 mg + 60 mg. **Tablet:** 60 mg + 180 mg. [a] > 5 kg
chloroquine*	**Oral liquid:** 50 mg/5 mL (as phosphate or sulfate). **Tablet:** 100 mg; 150 mg (as phosphate or sulfate). * For use only for the treatment of *Plasmodium vivax* infection.
dihydroartemisinin + piperaquine phosphate [a]	**Tablet:** 20 mg + 160 mg; 40 mg + 320 mg. [a] > 5 kg
doxycycline*	**Capsule:** 100 mg (as hydrochloride or hyclate). **Tablet (dispersible):** 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	**Tablet:** 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	**Tablet:** 7.5 mg; 15 mg (as diphosphate). * Only for use to achieve radical cure of *Plasmodium vivax* and *Plasmodium ovale* infections, given for 14 days.
quinine*	**Injection:** 300 mg/mL (hydrochloride) in 2 mL ampoule. **Tablet:** 300 mg (sulfate) or 300 mg (bisulfate). * For use only in the management of severe malaria and should be used in combination with doxycycline.

6. ANTI-INFECTIVE MEDICINES *(continued)*

sulfadoxine + pyrimethamine*	**Tablet:** 500 mg + 25 mg. *Only in combination with artesunate 50 mg.

6.5.3.2 *For chemoprevention*

amodiaquine – sulfadoxine + pyrimethamine	**Co-packaged dispersible tablets:** amodiaquine 76.5 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 250 mg + 12.5 mg [1]; amodiaquine 153 mg (as hydrochloride) [3] and sulfadoxine + pyrimethamine 500 mg + 25 mg [1].
chloroquine*	**Oral liquid:** 50 mg/5 mL (as phosphate or sulfate). **Tablet:** 150 mg (as phosphate or sulfate). * For use only for the treatment of *Plasmodium vivax* infection.
doxycycline [a]	**Solid oral dosage form:** 100 mg (as hydrochloride or hyclate). [a] > 8 years.
mefloquine [a]	**Tablet:** 250 mg (as hydrochloride). [a] > 5 kg or > 3 months.
proguanil*	**Tablet:** 100 mg (as hydrochloride). * For use only in combination with chloroquine.
sulfadoxine + pyrimethamine	**Tablet:** 250 mg + 12.5 mg.

6.5.4 *Antipneumocystosis and antitoxoplasmosis medicines*

pyrimethamine	**Tablet:** 25 mg.
sulfadiazine	**Tablet:** 500 mg.
sulfamethoxazole + trimethoprim	**Injection:** 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. **Oral liquid:** 200 mg + 40 mg/5 mL. **Tablet:** 100 mg + 20 mg; 400 mg + 80 mg. **Tablet (dispersible):** 100 mg + 20 mg.

6. ANTI-INFECTIVE MEDICINES *(continued)*

6.5.5 *Antitrypanosomal medicines*

6.5.5.1 *African trypanosomiasis*

fexinidazole*	**Tablet:** 600 mg
	* For the treatment of 1st and 2nd stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense* infection.

Medicines for the treatment of 1st stage African trypanosomiasis.

pentamidine*	**Powder for injection:** 200 mg (as isetionate) in vial.
	* To be used for the treatment of *Trypanosoma brucei gambiense* infection.
suramin sodium*	**Powder for injection:** 1 g in vial.
	* To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine*	**Injection:** 200 mg/mL (hydrochloride) in 100 mL bottle.
	* To be used for the treatment of *Trypanosoma brucei gambiense* infection.
nifurtimox*	**Tablet (scored):** 30 mg; 120 mg.
	* Only to be used in combination with eflornithine, for the treatment of *Trypanosoma brucei gambiense* infection.

Complementary List

melarsoprol	*Injection: 180 mg/5 mL in 5 mL ampoule (3.6% solution).*

6.5.5.2 *American trypanosomiasis*

benznidazole	**Tablet:** 12.5 mg.
	Tablet (scored): 50 mg; 100 mg.
nifurtimox	**Tablet (scored):** 30 mg; 120 mg.

6.6 Medicines for ectoparasitic infections

ivermectin	**Tablet:** 3 mg

6. ANTI-INFECTIVE MEDICINES *(continued)*	

6.7 Medicines for Ebola virus disease

ansuvimab	**Powder for injection:** 400 mg.
atoltivimab + maftivimab + odesivimab	**Injection:** 241.7 mg + 241.7 mg + 241.7 mg in 14.5 mL vial.

6.8 Medicines for COVID-19

WHO recommends that effective and safe therapeutics for prevention and treatment of COVID-19 should be considered as essential medicines in the context of the public health emergency. WHO recommendations are revised and updated regularly in WHO living guidelines for therapeutics for the treatment and prevention of COVID-19.

Selection of essential therapeutics for COVID-19 at the national level should be informed by recommendations in these guidelines, and consideration of the latest evidence, epidemiology and national priorities.

The latest WHO Therapeutics and COVID-19: living guideline is available online at: https://app.magicapp.org/#/guideline/nBkO1E

The latest WHO Drugs to prevent COVID-19: living guideline is available online at: https://app.magicapp.org/#/guideline/L6RxYL

7. ANTIMIGRAINE MEDICINES	

7.1 For treatment of acute attack

ibuprofen	**Oral liquid:** 100 mg/5 mL.
	Tablet: 200 mg; 400 mg.
paracetamol (acetaminophen)	**Oral liquid:** 120 mg/5 mL or 125 mg/5 mL*; 250 mg/5 mL.
	* The presence of both 120 mg/5 mL and 125 mg/5mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
	Suppository: 250 mg.
	Tablet: 250 mg; 325 mg; 500 mg.
	Tablet (dispersible): 100 mg; 250 mg.

7.2 For prophylaxis

propranolol	**Tablet:** 20 mg; 40 mg (hydrochloride).

8. IMMUNOMODULATORS AND ANTINEOPLASTICS

8.1 Immunomodulators for non-malignant disease

Complementary List

☐ *adalimumab**

Therapeutic alternatives*:
– *etanercept*
– *infliximab*

* *including quality-assured biosimilars*

Injection: *10 mg/0.2 mL; 20 mg/0.4 mL; 40 mg/0.8 mL; 40 mg/0.4 mL.*

azathioprine

Oral liquid: *10 mg/mL.*

Powder for injection: *50 mg; 100 mg (as sodium salt) in vial.*

Tablet: *25 mg.*

Tablet (scored): *50 mg.*

ciclosporin

Capsule: *25 mg.*

Concentrate for injection: *50 mg/mL in 1 mL ampoule.*

Oral liquid: *100 mg/mL.*

tacrolimus

Capsule (immediate-release): *0.5 mg; 0.75 mg; 1 mg; 2 mg; 5 mg.*

Granules for oral supsension: *0.2 mg; 1 mg.*

Injection: *5 mg/mL in 1 mL vial.*

8.2 Antineoplastic and supportive medicines

Medicines listed below should be used according to protocols for treatment of the diseases.

8.2.1 *Cytotoxic medicines*

Complementary List

arsenic trioxide

Concentrate for solution for infusion: *1 mg/mL; 2 mg/mL.*
    – *Acute promyelocytic leukaemia*

asparaginase*

* *including quality-assured biosimilars*

Powder for injection: *10 000 IU in vial.*
    – *Acute lymphoblastic leukaemia*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

bleomycin	***Powder for injection:*** *15 000 IU (as sulfate) in vial.*

> – *Hodgkin lymphoma*
> – *Kaposi sarcoma*
> – *Testicular germ cell tumours*
> – *Ovarian germ cell tumours*

calcium folinate *(leucovorin calcium)*	***Injection:*** *3 mg/mL in 10 mL ampoule; 7.5 mg/mL in 2 mL ampoule; 10 mg/mL in 5 mL ampoule.*
	Tablet: *5 mg; 15 mg; 25 mg.*

> – *Burkitt lymphoma*
> – *Osteosarcoma*

carboplatin	***Injection:*** *50 mg/5 mL; 150 mg/15 mL; 450 mg/45 mL; 600 mg/60 mL.*

> – *Low-grade glioma*
> – *Nephroblastoma (Wilms tumour)*
> – *Osteosarcoma*
> – *Ovarian germ cell tumours*
> – *Retinoblastoma*
> – *Testicular germ cell tumours*

cisplatin	***Injection:*** *10 mg/10 mL; 20 mg/20 mL; 50 mg/50 mL; 100 mg/100mL.*

> – *Low-grade glioma*
> – *Nasopharyngeal cancer*
> – *Osteosarcoma*
> – *Ovarian germ cell tumours*
> – *Testicular germ cell tumours*

cyclophosphamide	***Powder for injection:*** *500 mg; 1 g; 2 g in vial.*
	Solid oral dosage form: *25 mg; 50 mg.*

> – *Acute lymphoblastic leukaemia*
> – *Anaplastic large cell lymphoma*
> – *Burkitt lymphoma*
> – *Diffuse large B-cell lymphoma*
> – *Ewing sarcoma*
> – *Hodgkin lymphoma*
> – *Low-grade glioma*
> – *Nephroblastoma (Wilms tumour)*
> – *Rhabdomyosarcoma*

| 8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)* |

cytarabine	**Injection:** *100 mg/mL in vial.*
	Powder for injection: *100 mg in vial.*
	– Acute lymphoblastic leukaemia
	– Acute myeloid leukaemia
	– Acute promyelocytic leukaemia
	– Anaplastic large cell lymphoma
	– Burkitt lymphoma
	– Langerhans cell histiocytosis
dacarbazine	**Powder for injection:** *100 mg; 200 mg in vial.*
	– Hodgkin lymphoma
dactinomycin	**Powder for injection:** *500 micrograms in vial.*
	– Ewing sarcoma
	– Nephroblastoma (Wilms tumour)
	– Rhabdomyosarcoma
daunorubicin	**Injection:** *2 mg/mL; 5 mg/mL (as hydrochloride) in vial.*
	Powder for injection: *20 mg; 50 mg (as hydrochloride) in vial.*
	– Acute lymphoblastic leukaemia
	– Acute promyelocytic leukaemia.
doxorubicin	**Injection:** *2 mg/mL (hydrochloride) in 5 mL, 25 mL vial.*
	Powder for injection: *10 mg; 50 mg (hydrochloride) in vial.*
	– Acute lymphoblastic leukaemia
	– Anaplastic large cell lymphoma
	– Burkitt lymphoma
	– Diffuse large B-cell lymphoma
	– Ewing sarcoma
	– Hodgkin lymphoma
	– Kaposi sarcoma
	– Nephroblastoma (Wilms tumour)
	– Osteosarcoma
doxorubicin (as pegylated liposomal)	**Injection:** *2 mg/mL (hydrochloride) in 10 mL, 25 mL vial.*
	– Kaposi sarcoma

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

etoposide	**Capsule:** *50 mg; 100 mg.*
	Injection: *20 mg/mL in 5 mL ampoule.*
	Powder for injection: *100 mg (as phosphate) in vial.*

    – *Acute lymphoblastic leukaemia*
    – *Acute myeloid leukaemia*
    – *Anaplastic large cell lymphoma*
    – *Burkitt lymphoma*
    – *Ewing sarcoma*
    – *Hodgkin lymphoma*
    – *Nephroblastoma (Wilms tumour)*
    – *Osteosarcoma*
    – *Ovarian germ cell tumours*
    – *Retinoblastoma*
    – *Testicular germ cell tumours*

fluorouracil **Injection:** *50 mg/mL in vial.*

    – *Early stage colon cancer*
    – *Early stage rectal cancer*
    – *Nasopharyngeal cancer*
    – *Metastatic colorectal cancer*

hydroxycarbamide (hydroxyurea) **Solid oral dosage form:** *100 mg; 200 mg; 300 mg; 400 mg; 500 mg; 1 g.*

    – *Chronic myeloid leukaemia*

ifosfamide **Powder for injection:** *500 mg; 1 g; 2 g in vial.*

    – *Anaplastic large cell lymphoma*
    – *Burkitt lymphoma*
    – *Ewing sarcoma*
    – *Nephroblastoma (Wilms tumour)*
    – *Osteosarcoma*
    – *Ovarian germ cell tumours*
    – *Rhabdomyosarcoma*
    – *Testicular germ cell tumours*

irinotecan **Injection:** *40 mg/2 mL in 2 mL vial; 100 mg/5 mL in 5 mL vial; 500 mg/25 mL in 25 mL vial.*

    – *Metastatic colorectal cancer*
    – *Nephroblastoma (Wilms tumour)*
    – *Rhabdomyosarcoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

mercaptopurine	**Tablet:** *50 mg.*
	Oral liquid: *20 mg/mL.*
	– *Acute lymphoblastic leukaemia*
	– *Acute promyelocytic leukaemia*
	– *Langerhans cell histocytosis*
methotrexate	**Concentrated injection:** *1000 mg/10 mL.*
	Injection: *50 mg/2 mL.*
	Powder for injection: *50 mg (as sodium) in vial.*
	Tablet: *2.5 mg (as sodium).*
	– *Acute lymphoblastic leukaemia*
	– *Acute promyelocytic leukaemia*
	– *Anaplastic large cell lymphoma*
	– *Burkitt lymphoma*
	– *Langerhans cell histocytosis*
	– *Osteosarcoma*
oxaliplatin	**Injection:** *50 mg/10 mL in 10 mL vial; 100 mg/20 mL in 20 mL vial; 200 mg/40 mL in 40 mL vial.*
	Powder for injection: *50 mg; 100 mg in vial.*
	– *Early stage colon cancer*
	– *Metastatic colorectal cancer*
paclitaxel	**Injection:** *6 mg/mL in vial.*
	– *Ovarian germ cell tumours*
pegaspargase*	**Injection:** *3750 units/5 mL in vial*
* *including quality-assured biosimilars*	**Powder for injection:** *3750 units in vial.*
	– *Acute lymphoblastic leukaemia.*
procarbazine	**Capsule:** *50 mg (as hydrochloride).*
	– *Hodgkin lymphoma*
realgar-Indigo naturalis formulation	**Tablet:** *270 mg (containing tetra-arsenic tetra-sulfide 30 mg).*
	– *Acute promyelocytic leukaemia*
tioguanine	**Solid oral dosage form:** *40 mg.*
	– *Acute lymphoblastic leukaemia*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

vinblastine   **Injection:** *10 mg/10 mL (sulfate) in vial.*

Powder for injection: *10 mg (sulfate) in vial.*

– *Anaplastic large cell lymphoma*
– *Hodgkin lymphoma*
– *Langerhans cell histiocytosis*
– *Low-grade glioma*
– *Ovarian germ cell tumours*
– *Testicular germ cell tumours*

vincristine   **Injection:** *1 mg/mL (sulfate); 2 mg/2 mL (sulfate) in vial.*

Powder for injection: *1 mg; 5 mg (sulfate) in vial.*

– *Acute lymphoblastic leukaemia*
– *Burkitt lymphoma.*
– *Diffuse large B-cell lymphoma*
– *Ewing sarcoma*
– *Hodgkin lymphoma*
– *Kaposi sarcoma*
– *Langerhans cell histiocytosis*
– *Low-grade glioma*
– *Nephroblastoma (Wilms tumour)*
– *Retinoblastoma*
– *Rhabdomyosarcoma*

vinorelbine   **Capsule:** *20 mg; 30 mg.*

Injection: *10 mg/mL in 1 mL, 5 mL vial.*

– *Rhabdomyosarcoma*

8.2.2 *Targeted therapies*

Complementary List

all-trans retinoid acid   **Capsule:** *10 mg.*
(ATRA)
– *Acute promyelocytic leukaemia*

dasatinib   **Tablet:** *20 mg; 50 mg; 70 mg; 80 mg.*
– *Imatinib-resistant chronic myeloid leukaemia*

everolimus   **Tablet:** *2.5 mg; 5 mg; 7.5 mg; 10 mg.*

Tablet (dispersible): *2 mg; 3 mg; 5 mg.*

– *Subependymal giant cell astrocytoma*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*	

imatinib
Solid oral dosage form: *100 mg; 400 mg.*
- *Chronic myeloid leukaemia*
- *Gastrointestinal stromal tumour*
- *Philadelphia chromosome positive acute lymphoblastic leukaemia*

nilotinib
Capsule: *150 mg; 200 mg.*
- *Imatinib-resistant chronic myeloid leukaemia*

rituximab*
* including quality-assured biosimilars
Injection (intravenous): *100 mg/10 mL in 10 mL vial; 500 mg/50 mL in 50 mL vial.*
- *Burkitt lymphoma*
- *Diffuse large B-cell lymphoma*

8.2.3 *Immunomodulators*

Complementary List

filgrastim*
* including quality-assured biosimilars
Injection: *120 micrograms/0.2 mL; 300 micrograms/0.5 mL; 480 micrograms/0.8 mL in pre-filled syringe.*

Injection: *300 micrograms/mL in 1 mL vial; 480 micrograms/1.6 mL in 1.6 mL vial.*
- *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy.*
- *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy*
- *To facilitate administration of dose dense chemotherapy regimens*

pegfilgrastim*
* including quality-assured biosimilars
Injection: *6 mg/0.6 mL in pre-filled syringe.*
- *Primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy*
- *Secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy*
- *To facilitate administration of dose dense chemotherapy regimens*

8. IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.4 *Hormones and antihormones*

Complementary List

dexamethasone	**Injection:** *4 mg/mL (as disodium phosphate salt) in 1 mL ampoule.*
	Oral liquid: *2 mg/5 mL.*
	Tablet: *2 mg; 4 mg.*

      – *Acute lymphoblastic leukaemia*
      – *Anaplastic large cell lymphoma*
      – *Burkitt lymphoma*

hydrocortisone	**Powder for injection:** *100 mg (as sodium succinate) in vial.*

      – *Acute lymphoblastic leukaemia*
      – *Burkitt lymphoma*

methylprednisolone	**Injection:** *40 mg/mL (as sodium succinate) in 1 mL single-dose vial and 5 mL multi-dose vials; 80 mg/mL (as sodium succinate) in 1 mL single-dose vial.*

      – *Acute lymphoblastic leukamia*
      – *Burkitt lymphoma*

☐ *prednisolone*	**Oral liquid:** *5 mg/mL.*
Therapeutic alternatives: – *prednisone*	**Tablet:** *5 mg; 25 mg.*

      – *Acute lymphoblastic leukaemia*
      – *Anaplastic large cell lymphoma*
      – *Burkitt lymphoma*
      – *Diffuse large B-cell lymphoma*
      – *Hodgkin lymphoma*
      – *Langerhans cell histiocytosis*

8.   IMMUNOMODULATORS AND ANTINEOPLASTICS *(continued)*

8.2.5   *Supportive medicines*

Complementary List

allopurinol	***Tablet:*** *100 mg; 300 mg.*
	– *Tumour lysis syndrome*
mesna	***Injection:*** *100 mg/mL in 4 mL and 10 mL ampoules.*
	Tablet: *400 mg; 600 mg.*
	– *Burkitt lymphoma*
	– *Ewing sarcoma*
	– *Nephroblastoma (Wilms tumour)*
	– *Osteosarcoma*
	– *Ovarian germ cell tumours*
	– *Rhabdomyosarcoma*
	– *Testicular germ cell tumours*
rasburicase	***Powder and solvent for solution for infusion:*** *1.5 mg; 7.5 mg in vial.*
	– *Tumour lysis syndrome*

9.   THERAPEUTIC FOODS

ready-to-use therapeutic food	**Biscuit or paste***
	* of nutritional composition as determined by the UN joint statement on the community-based management of severe acute malnutrition and Codex alimentarius guidelines.

10. MEDICINES AFFECTING THE BLOOD

10.1 Antianaemia medicines

ferrous salt	**Oral liquid:** equivalent to 25 mg iron (as sulfate)/mL. **Tablet:** equivalent to 60 mg iron.
folic acid	**Tablet:** 1 mg; 5 mg.
hydroxocobalamin	**Injection:** 1 mg (as acetate, as hydrochloride or as sulfate) in 1 mL ampoule.

Complementary List

☐ *erythropoiesis-stimulating agents** *Therapeutic alternatives:* – *epoetin alfa, beta and theta* – *darbepoetin alfa* * *including quality-assured biosimilars*	*Injection: pre-filled syringe* *1000 IU/0.5 mL; 2000 IU/0.5 mL; 3000 IU/0.3 mL; 4000 IU/0.4 mL; 5000 IU/0.5 mL; 6000 IU/0.6 mL; 8000 IU/0.8mL; 10 000 IU/1 mL; 20 000 IU/0.5 mL; 40 000 IU/1 mL.*

10.2 Medicines affecting coagulation

☐ enoxaparin Therapeutic alternatives: – dalteparin – nadroparin * *including quality-assured biosimilars*	**Injection:** ampoule or pre-filled syringe 20 mg/0.2 mL; 40 mg/0.4 mL; 60 mg/0.6 mL; 80 mg/0.8 mL; 100 mg/1 mL; 120 mg/0.8 mL; 150 mg/1 mL.
phytomenadione	**Injection:** 1 mg/mL; 10 mg/mL in ampoule. **Tablet:** 10 mg.

Complementary List

desmopressin	*Injection: 4 micrograms/mL (as acetate) in 1 mL ampoule. Nasal spray: 10 micrograms (as acetate) per dose.*
heparin sodium	*Injection: 1000 IU/mL; 5000 IU/mL in 1 mL ampoule.*
protamine sulfate	*Injection: 10 mg/mL in 5 mL ampoule.*
☐ warfarin *Therapeutic alternatives to be reviewed*	*Tablet: 0.5 mg; 1 mg; 2 mg; 5 mg (sodium).*

| 10. | **MEDICINES AFFECTING THE BLOOD** *(continued)* |

10.3 Other medicines for haemoglobinopathies

☐ deferasirox	**Tablet (dispersible):** 100 mg; 125 mg; 250 mg; 400 mg; 500 mg.
Therapeutic alternatives:	
– deferiprone	**Tablet (film-coated):** 90 mg; 180 mg; 360 mg.

> ***Complementary list***

| *deferoxamine* | ***Powder for injection:*** *500 mg (mesilate) in vial.* |
| *hydroxycarbamide (hydroxyurea)* | ***Solid oral dosage form:*** *100 mg; 200 mg; 500 mg; 1 g.* |

| 11. | **BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES** |

11.1 Blood and blood components

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

☐ cryoprecipitate, pathogen-reduced	**Injection:** frozen liquid in bag or lyophilized powder in vial containing:
Therapeutic alternatives:	– > 50 IU Factor VIII
– cryoprecipitate (not pathogen-reduced)	– > 100 IU vWF
	– > 140 mg clottable fibrinogen per unit

fresh-frozen plasma

platelets

red blood cells

whole blood

11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES *(continued)*

11.2.1 *Human immunoglobulins*

anti-rabies immunoglobulin	**Injection:** 150 IU/mL in vial.
anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.

Complementary List

normal immunoglobulin — ***Intramuscular administration:** 16% protein solution.*

***Subcutaneous administration:** 15%; 16% protein solution.*
    – Primary immune deficiency.

***Intravenous administration:** 5%; 10% protein solution.*
    – Primary immune deficiency
    – Kawasaki disease
    – Langerhans cell histiocytosis

11.2.2 *Blood coagulation factors*

Complementary List

coagulation factor VIII — ***Powder for injection:** 250 IU; 500 IU; 1000 IU in vial.*

☐ coagulation factor IX — ***Powder for injection:** 500 IU; 1000 IU in vial.*
Therapeutic alternatives:
– coagulation factor IX complex

11.3 Plasma substitutes

☐ dextran 70 — **Injectable solution:** 6%.
Therapeutic alternatives:
– Polygeline injectable solution 3.5%

12. CARDIOVASCULAR MEDICINES

12.1 Antianginal medicines

12.2 Antiarrhythmic medicines

12.3 Antihypertensive medicines

☐ enalapril	**Oral liquid:** 1 mg/mL (as hydrogen maleate).

Therapeutic alternatives:
– 4th level ATC chemical
   subgroup (C09AA ACE
   inhibitors, plain)
	Tablet: 2.5 mg; 5 mg; 10 mg (as hydrogen maleate).

12.4 Medicines used in heart failure

furosemide	**Injection:** 10 mg/mL in 2 mL, 5 mL ampoule.
	Oral liquid: 20 mg/5 mL; 50 mg/5 mL.
	Tablet: 20 mg; 40 mg.

Complementary List

digoxin	*Injection: 100 micrograms/mL in 1 mL ampoule; 250 micrograms/mL in 2 mL ampoule.*
	Oral liquid: 50 micrograms/mL.
	Tablet: 62.5 micrograms; 125 micrograms; 250 mg micrograms.
dopamine	*Injection: 40 mg/mL (hydrochloride) in 5 mL vial.*

12.5 Antithrombotic medicines

12.6 Lipid-lowering agents

12.7 Fixed-dose combinations for prevention of atherosclerotic cardiovascular disease

13. DERMATOLOGICAL MEDICINES

13.1 Antifungal medicines

☐ miconazole
Cream or ointment: 2% (nitrate).

Therapeutic alternatives:
– 4th level ATC chemical subgroup (D01AC Imidazole and triazole derivatives) excluding combinations

selenium sulfide
Detergent-based suspension: 2%.

terbinafine
Cream or ointment: 1% (hydrochloride).

13.2 Anti-infective medicines

mupirocin
Cream: 2% (as calcium).
Ointment: 2%.

potassium permanganate
Aqueous solution: 1:10 000.

silver sulfadiazine [a]
Cream: 1%.
[a] > 2 months.

13.3 Anti-inflammatory and antipruritic medicines

☐ betamethasone [a]
Cream or ointment: 0.1% (as valerate).

Therapeutic alternatives:
– 4th level ATC chemical subgroup (D07AC Corticosteroids, potent (group III))
[a] Hydrocortisone preferred in neonates.

calamine
Lotion.

hydrocortisone
Cream or ointment: 1% (acetate).

13.4 Medicines affecting skin differentiation and proliferation

benzoyl peroxide
Cream or lotion: 5%.

☐ calcipotriol
Cream or ointment: 50 micrograms/mL (0.005%).

Therapeutic alternatives:
– calcitriol
– tacalcitol
Lotion: 50 micrograms/mL (0.005%).

coal tar
Solution: 5%.

13. DERMATOLOGICAL MEDICINES *(continued)*

☐ podophyllum resin

Solution: 10% to 25%.

Therapeutic alternatives:
– podophyllotoxin

salicylic acid

Solution: 5%.

urea

Cream or ointment: 5%; 10%.

Complementary List

methotrexate

***Tablet:** 2.5 mg; 10 mg (as sodium).*

13.5 Scabicides and pediculicides

☐ benzyl benzoate a

Lotion: 25%.

Therapeutic alternatives:
– precipitated sulfur topical
  ointment

a > 2 years.

permethrin

Cream: 5%.

Lotion: 1%.

14. DIAGNOSTIC AGENTS

14.1 Ophthalmic medicines

fluorescein

Eye drops: 1% (sodium salt).

☐ tropicamide

Eye drops: 0.5%.

Therapeutic alternatives:
– atropine
– cyclopentolate

14.2 Radiocontrast media

Complementary List

barium sulfate

Aqueous suspension.

15. ANTISEPTICS AND DISINFECTANTS

15.1 Antiseptics

☐ chlorhexidine

Therapeutic alternatives to be reviewed

Solution: 5% (digluconate).

☐ ethanol

Therapeutic alternatives:
– propanol

Solution: 70% (denatured).

☐ povidone iodine

Therapeutic alternatives:
– iodine

Solution: 10% (equivalent to 1% available iodine).

15.2 Disinfectants

alcohol based hand rub

Solution containing ethanol 80% volume/volume.

Solution containing isopropyl alcohol 75% volume/volume.

chlorine base compound

Liquid: (0.1% available chlorine) for solution.

Powder: (0.1% available chlorine) for solution.

Solid: (0.1% available chlorine) for solution.

☐ chloroxylenol

Therapeutic alternatives:
– 4th level ATC chemical subgroup (D08AE Phenol and derivatives)

Solution: 4.8%.

glutaral

Solution: 2%.

16. DIURETICS	
furosemide	**Injection:** 10 mg/mL in 2 mL, 5 mL ampoule.
	Oral liquid: 20 mg/5 mL; 50 mg/5 mL.
	Tablet: 20 mg; 40 mg.

Complementary List

☐ *hydrochlorothiazide*	***Tablet (scored):*** *25 mg.*
Therapeutic alternatives:	
– chlorothiazide	
– chlortalidone	
mannitol	***Injectable solution:*** *10%; 20%.*
spironolactone	***Oral liquid:*** *5 mg/5 mL; 10 mg/5 mL; 25 mg/5 mL.*
	Tablet: *25 mg.*

17. GASTROINTESTINAL MEDICINES	

Complementary List

pancreatic enzymes	*Age-appropriate formulations and doses including lipase, protease and amylase.*

17.1 Antiulcer medicines

☐ omeprazole	**Powder for oral liquid:** 20 mg; 40 mg sachets.
Therapeutic alternatives:	**Solid oral dosage form:** 10 mg; 20 mg; 40 mg.
– 4th level ATC chemical subgroup (A02BC Proton pump inhibitors) excluding combinations	
☐ ranitidine	**Injection:** 25 mg/mL (as hydrochloride) in 2 mL ampoule.
Therapeutic alternatives:	**Oral liquid:** 75 mg/5 mL (as hydrochloride).
– 4th level ATC chemical subgroup (A02BA H$_2$-receptor antagonists) excluding combinations	**Tablet:** 150 mg (as hydrochloride).

17.2 Antiemetic medicines

dexamethasone	**Injection:** 4 mg/mL in 1 mL ampoule (as disodium phosphate salt).
	Oral liquid: 0.5 mg/5 mL; 2 mg/5 mL.
	Solid oral dosage form: 0.5 mg; 0.75 mg; 1.5 mg; 4 mg.

17. GASTROINTESTINAL MEDICINES *(continued)*

metoclopramide [a]	**Injection:** 5 mg/mL (hydrochloride) in 2 mL ampoule.
	Oral liquid: 5 mg/5 mL.
	Tablet: 10 mg (hydrochloride).
	[a] Not in neonates.

□ ondansetron [a]

Therapeutic alternatives:

– dolasetron
– granisetron
– palonosetron
– tropisetron

Injection: 2 mg base/mL in 2 mL ampoule (as hydrochloride).

Oral liquid: 4 mg base/5 mL.

Solid oral dosage form: Eq 4 mg base; Eq 8 mg base.

[a] > 1 month.

Complementary list

aprepitant

Capsule: 80 mg; 125 mg; 165 mg.

Powder for oral suspension: 125 mg in sachet.

17.3 ~~Anti-inflammatory medicines~~

17.4 ~~Laxatives~~

17.5 Medicines used in diarrhoea

oral rehydration salts – zinc sulfate

Co-package containing:

ORS powder for dilution (see Section 17.5.1) – zinc sulfate **solid oral dosage form** 20 mg (see Section 17.5.2)

17.5.1 *Oral rehydration*

oral rehydration salts

Powder for dilution in 200 mL; 500 mL; 1 L.

glucose:	75 mEq
sodium:	75 mEq or mmol/L
chloride:	65 mEq or mmol/L
potassium:	20 mEq or mmol/L
citrate:	10 mmol/L
osmolarity:	245 mOsm/L
glucose:	13.5 g/L
sodium chloride:	2.6 g/L
potassium chloride:	1.5 g/L
trisodium citrate dihydrate*:	2.9 g/L

* trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

17. GASTROINTESTINAL MEDICINES *(continued)*

17.5.2 *Medicines for diarrhoea*

zinc sulfate*	**Solid oral dosage form:** 20 mg.

> * In acute diarrhoea, zinc sulfate should be used as an adjunct to oral rehydration salts.

18. MEDICINES FOR ENDOCRINE DISORDERS

18.1 Adrenal hormones and synthetic substitutes

fludrocortisone	**Tablet:** 100 micrograms (acetate).
hydrocortisone	**Tablet:** 5 mg; 10 mg; 20 mg.

~~18.2 Androgens~~

~~18.3 Estrogens~~

~~18.4 Progestogens~~

18.5 Medicines for diabetes

18.5.1 *Insulins*

insulin injection (soluble)*
* *including quality-assured biosimilars*
Injection: 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.

intermediate-acting insulin*
* *including quality-assured biosimilars*
Injection: 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen (as compound insulin zinc suspension or isophane insulin).

☐ long-acting insulin analogues*
Injection: 100 IU/mL in 3 mL cartridge or pre-filled pen.

Therapeutic alternatives:
– insulin detemir
– insulin degludec
– insulin glargine
* *including quality-assured biosimilars*

18.5.2 *Oral hypoglycaemic agents*

Complementary List

metformin	***Tablet:** 500 mg (hydrochloride).*

18. MEDICINES FOR ENDOCRINE DISORDERS *(continued)*

18.6 Medicines for hypoglycaemia

glucagon | **Injection:** 1 mg/mL.

Complementary List

diazoxide | ***Oral liquid:*** *50 mg/mL*
Tablet: *50 mg*

18.7 Thyroid hormones and antithyroid medicines

levothyroxine | **Tablet:** 25 micrograms; 50 micrograms; 100 micrograms (sodium salt).

Complementary List

Lugol's solution | ***Oral liquid:*** *about 130 mg total iodine/mL.*

☐ *methimazole* | ***Tablet:*** *5 mg; 10 mg; 20 mg.*
Therapeutic alternatives:
– carbimazole (depending on local availability)

potassium iodide | ***Tablet:*** *60 mg.*

propylthiouracil* | ***Tablet:*** *50 mg.*
* For use when alternative first-line treatment is not appropriate or available

~~18.8 Medicines for disorders of the pituitary hormone system~~

19. IMMUNOLOGICALS

19.1 Diagnostic agents

All tuberculins should comply with the WHO requirements for tuberculins.

tuberculin, purified protein derivative (PPD) | **Injection.**

19.2 Sera, immunoglobulins and monoclonal antibodies

All plasma fractions should comply with the WHO requirements.

anti-rabies virus monoclonal antibodies* | **Injection:** 40 IU/mL in 1.25 mL, 2.5 mL vial; 100 IU/mL in 2.5 mL vial (human).
* including quality-assured biosimilars | **Injection:** 300 IU/mL in 10 mL vial; 600 IU/mL in 1 mL, 2.5 mL and 5 mL vial (murine).

19. IMMUNOLOGICALS *(continued)*	
antivenom immunoglobulin*	**Injection.** *Exact type to be defined locally.
diphtheria antitoxin	**Injection:** 10 000 IU; 20 000 IU in vial.
equine rabies immunoglobulin	**Injection:** 150 IU/mL; 200 IU/mL; 300 IU/mL; 400 IU/mL in vial

19.3 Vaccines

WHO immunization policy recommendations are published in vaccine position papers on the basis of recommendations made by the Strategic Advisory Group of Experts on Immunization (SAGE).

WHO vaccine position papers are updated three to four times per year. The list below details the vaccines for which there is a recommendation from SAGE and a corresponding WHO position paper as at March 2023. The most recent versions of the WHO position papers, reflecting the current evidence related to a specific vaccine and the related recommendations, can be accessed at any time on the WHO website at:

https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers

Vaccine recommendations may be universal or conditional (e.g., in certain regions, in some high-risk populations or as part of immunization programmes with certain characteristics). Details are available in the relevant position papers, and in the Summary Tables of WHO Routine Immunization Recommendations available on the WHO website at:

https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization---summary-tables

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities.

All vaccines should comply with the WHO requirements for biological substances.

WHO noted the need for vaccines used in children to be polyvalent.

Recommendations for all

BCG vaccine

diphtheria vaccine

Haemophilus influenzae type b vaccine

hepatitis B vaccine

human papilloma virus (HPV) vaccine

measles vaccine

19. IMMUNOLOGICALS *(continued)*

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

Recommendations for certain regions

Japanese encephalitis vaccine

tick-borne encephalitis vaccine

yellow fever vaccine

Recommendations for some high-risk populations

cholera vaccine

dengue vaccine

hepatitis A vaccine

meningococcal meningitis vaccine

rabies vaccine

typhoid vaccine

Recommendations for immunization programmes with certain characteristics

influenza vaccine (seasonal)

mumps vaccine

varicella vaccine

20. MUSCLE RELAXANTS (PERIPHERALLY-ACTING) AND CHOLINESTERASE INHIBITORS

neostigmine	**Injection:** 500 micrograms/mL (methylsulfate) in 1 mL ampoule; 2.5 mg/mL (methylsulfate) in 1 mL ampoule.
	Tablet: 15 mg (bromide).
suxamethonium	**Injection:** 50 mg/mL (chloride) in 2 mL ampoule.
	Powder for injection: (chloride), in vial.
☐ vecuronium Therapeutic alternatives: – atracurium	**Powder for injection:** 10 mg (bromide) in vial.

Complementary List

pyridostigmine	*Injection: 1 mg in 1 mL ampoule.*
	Tablet: 60 mg (bromide).

21. OPHTHALMOLOGICAL PREPARATIONS

21.1 Anti-infective agents

aciclovir	**Ointment:** 3% w/w.
azithromycin	**Solution (eye drops):** 1.5%. – *Trachoma*
erythromycin	**Ointment:** 0.5%. – *Infections due to Chlamydia trachomatis or Neisseria gonorrhoeae*

☐ gentamicin
Therapeutic alternatives:
– amikacin
– kanamycin
– netilmicin
– tobramycin
	Solution (eye drops): 0.3% (sulfate).
	    – *Bacterial blepharitis*
	    – *Bacterial conjunctivitis*

natamycin	**Suspension (eye drops):** 5%. – *Fungal keratitis*

☐ ofloxacin
Therapeutic alternatives:
– 4th level ATC chemical subgroup (S01AE Fluoroquinolones)
	Solution (eye drops): 0.3%.
	    – *Bacterial conjunctivitis*
	    – *Bacterial keratitis*

21. OPHTHALMOLOGICAL PREPARATIONS *(continued)*

☐ tetracycline

Therapeutic alternatives:
– chlortetracycline
– oxytetracycline

Eye ointment: 1% (hydrochloride).

 – *Bacterial blepharitis*
 – *Bacterial conjunctivitis*
 – *Bacterial keratitis*
 – *Trachoma*

21.2 Anti-inflammatory agents

☐ prednisolone

Therapeutic alternatives to be reviewed

Solution (eye drops): 0.5% (sodium phosphate).

21.3 Local anaesthetics

☐ tetracaine [a]

Therapeutic alternatives:
– 4ᵗʰ level ATC chemical subgroup (S01HA Local anaesthetics) excluding cocaine and combinations

Solution (eye drops): 0.5% (hydrochloride).

[a] Not in preterm neonates.

21.4 ~~Miotics and antiglaucoma medicines~~

21.5 Mydriatics

☐ atropine [a]

Therapeutic alternatives:
– homatropine hydrobromide
– cyclopentolate hydrochloride

Solution (eye drops): 0.1%; 0.5%; 1% (sulfate).

[a] > 3 months.

Complementary List

epinephrine (adrenaline)

Solution (eye drops): *2% (as hydrochloride).*

21.6 ~~Anti-vascular endothelial growth factor (VEGF) preparations~~

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE

22.1 ~~Contraceptives~~

22.2 ~~Ovulation inducers~~

22.3 ~~Uterotonics~~

22.4 ~~Antioxytocics (tocolytics)~~

22.5 ~~Other medicines administered to the mother~~

22. MEDICINES FOR REPRODUCTIVE HEALTH AND PERINATAL CARE *(continued)*	

22.6 Medicines administered to the neonate

caffeine citrate	**Injection:** 20 mg/mL (equivalent to 10 mg caffeine base/mL).
	Oral liquid: 20 mg/mL (equivalent to 10 mg caffeine base/mL).
chlorhexidine	**Solution or gel:** 7.1% (digluconate) delivering 4% chlorhexidine (for umbilical cord care).

Complementary List

☐ *ibuprofen* *Therapeutic alternatives:* *– indometacin*	**Solution for injection:** *5 mg/mL.*
☐ *prostaglandin E1* *Therapeutic alternatives:* *– prostaglandin E2*	**Solution for injection:** 0.5 mg/mL in alcohol.
surfactant	***Suspension for intratracheal instillation:*** *25 mg/mL or 80 mg/mL*

23. PERITONEAL DIALYSIS SOLUTION	

Complementary List

intraperitoneal dialysis solution	**Parenteral solution:** *of appropriate composition.*

24. MEDICINES FOR MENTAL AND BEHAVIOURAL DISORDERS

24.1 ~~Medicines used in psychotic disorders~~

24.2 ~~Medicines used in mood disorders~~

24.2.1 *~~Medicines used in depressive disorders~~*

24.2.2 *~~Medicines used in bipolar disorders~~*

24.3 ~~Medicines for anxiety disorders~~

24.4 ~~Medicines used for obsessive compulsive disorders~~

24.5 ~~Medicines for disorders due to psychoactive substance use~~

24.5.1 *~~Medicines for alcohol use disorders~~*

24.5.2 *~~Medicines for nicotine use disorders~~*

24.5.3 *~~Medicines for opioid use disorders~~*

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic medicines

☐ budesonide

Therapeutic alternatives:
– beclometasone
– ciclesonide
– flunisolide
– fluticasone
– mometasone

Inhalation (aerosol): 100 micrograms per dose; 200 micrograms per dose.

epinephrine (adrenaline)

Injection: 1 mg/mL (as hydrochloride or hydrogen tartrate) in 1 mL ampoule.

☐ salbutamol

Therapeutic alternatives:
– terbutaline

Injection: 50 micrograms/mL (as sulfate) in 5 mL ampoule.
Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose.
Respirator solution for use in nebulizers: 5 mg/mL (as sulfate).

26. SOLUTIONS CORRECTING WATER, ELECTROLYTE AND ACID–BASE DISTURBANCES

26.1 Oral

oral rehydration salts	See section 17.5.1.
potassium chloride	**Powder for solution.**

26.2 Parenteral

glucose	**Injectable solution:** 5% (isotonic); 10% (hypertonic); 50% (hypertonic).
glucose with sodium chloride	**Injectable solution:** 5% glucose, 0.9% sodium chloride (equivalent to Na+ 150 mmol/L and Cl- 150 mmol/L); 5% glucose, 0.45% sodium chloride (equivalent to Na+ 75 mmol/L and Cl- 75 mmol/L).
potassium chloride	**Solution for dilution:** 7.5% (equivalent to K+ 1 mmol/mL and Cl- 1 mmol/mL); 15% (equivalent to K+ 2 mmol/mL and Cl- 2 mmol/mL).
sodium chloride	**Injectable solution:** 0.9% isotonic (equivalent to Na+ 154 mmol/L, Cl- 154 mmol/L).
sodium hydrogen carbonate	**Injectable solution:** 1.4% isotonic (equivalent to Na+167 mmol/L, HCO$_3$- 167 mmol/L). **Solution:** 8.4% in 10 mL ampoule (equivalent to Na+ 1000 mmol/L, HCO$_3$-1000 mmol/L).
sodium lactate, compound solution	**Injectable solution.**

26.3 Miscellaneous

water for injection	2 mL; 5 mL; 10 mL ampoules.

27. VITAMINS AND MINERALS

ascorbic acid	**Tablet:** 50 mg.
☐ colecalciferol Therapeutic alternatives: – ergocalciferol	**Oral liquid:** 400 IU/mL. **Solid oral dosage form:** 400 IU; 1000 IU.
iodine	**Capsule:** 190 mg. **Iodized oil:** 1 mL (480 mg iodine); 0.5 mL (240 mg iodine) in ampoule (oral or injectable); 0.57 mL (308 mg iodine) in dispenser bottle.

27. VITAMINS AND MINERALS *(continued)*

multiple micronutrient powder	**Sachets containing:** – iron (elemental) 12.5 mg (as coated ferrous fumarate) – zinc (elemental) 5 mg – vitamin A 300 micrograms – with or without other micronutrients at recommended daily values
pyridoxine	**Tablet:** 25 mg (hydrochloride).
retinol	**Capsule:** 100 000 IU; 200 000 IU (as palmitate). **Oral oily solution:** 100 000 IU/mL (as palmitate) in multidose dispenser. **Tablet (sugar-coated):** 10 000 IU (as palmitate). **Water-miscible injection:** 100 000 IU (as palmitate) in 2 mL ampoule.
riboflavin	**Tablet:** 5 mg.
thiamine	**Tablet:** 50 mg (hydrochloride).

Complementary List

calcium gluconate	*Injection: 100 mg/mL in 10 mL ampoule.*

28. EAR, NOSE AND THROAT MEDICINES

acetic acid	**Topical:** 2%, in alcohol.
☐ budesonide Therapeutic alternatives to be reviewed	**Nasal spray:** 100 micrograms per dose.
☐ ciprofloxacin Therapeutic alternatives: – ofloxacin	**Solution (ear drops):** 0.3% (as hydrochloride).
☐ xylometazoline a Therapeutic alternatives to be reviewed	**Nasal spray:** 0.05%. a Not in children less than 3 months.

29. MEDICINES FOR DISEASES OF JOINTS

~~29.1 Medicines used to treat gout~~

29.2 Disease-modifying anti-rheumatic drugs (DMARDs)

Complementary List

hydroxychloroquine	***Solid oral dosage form:*** *200 mg (as sulfate).*
methotrexate	***Tablet:*** *2.5 mg (as sodium).*

29.3 Medicines for juvenile joint diseases

Complementary List

acetylsalicylic acid*
(acute or chronic use)

Suppository: *50 mg to 150 mg.*
Tablet: *100 mg to 500 mg.*
* For use for rheumatic fever, juvenile arthritis, Kawasaki disease.

☐ *adalimumab**
Therapeutic alternatives*:
– etanercept
– infliximab
* including quality-assured
  biosimilars

Injection: *10 mg/0.2 mL; 20 mg/0.4 mL; 40 mg/0.8 mL;*
40 mg/0.4 mL.

methotrexate   ***Tablet:*** *2.5 mg (as sodium).*

☐ *triamcinolone*
hexacetonide
Therapeutic alternatives:
– triamcinolone acetonide

Injection: *20 mg/mL in vial.*

30. DENTAL MEDICINES AND PREPARATIONS

fluoride

Gel: containing 2500 to 12 500 ppm fluoride (any type).
Mouthrinse: containing 230 to 900 ppm fluoride (any type).
Toothpaste: cream or gel: containing 1000 to 1500 ppm fluoride (any type).
Varnish: containing 22 500 ppm fluoride (any type).

30. DENTAL MEDICINES AND PREPARATIONS *(continued)*	
glass ionomer cement	**Single-use capsules:** 0.4 g powder + 0.09 mL liquid.
	Multi-use bottle: powder + liquid.
	Powder (fluoro-alumino-silicate glass) contains: 25-50% silicate, 20-40% aluminium oxide, 1-20% fluoride, 15-40% metal oxide, 0-15% phosphate, remainder are polyacrylic acid powder and metals in minimal quantities. Liquid (aqueous) contains: 7-25% polybasic carboxylic acid, 45-60% polyacrylic acid.
resin-based composite (low-viscosity)*	**Single-use applicator or multi-use bottle.**
	* of any type for use as dental sealant.
resin-based composite (high-viscosity)*	**Single-use capsule or multi-use syringe.**
	* of any type for use as dental filling material.
silver diamine fluoride	**Solution:** 38% w/v.

Annex 3

Alphabetical list of essential medicines (with ATC codes & section numbers)

Medicine or item as in EML/EMLc	ATC code	Section
abacavir	J05AF06	6.4.2.1
abacavir + lamivudine	J05AR02	6.4.2.5
abiraterone	L02BX03	8.2.4
acamprosate	N07BB03	24.5.1
acetazolamide	S01EC01	21.4
acetic acid	S02AA10	28
acetylcysteine	V03AB23	4.2
acetylsalicylic acid	B01AC06	12.5.1
acetylsalicylic acid	N02BA01	2.1; 7.1; 29.3
acetylsalicylic acid + atorvastatin + ramipril	C10BX06	12.7
acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide	–	12.7
aciclovir	J05AB01	6.4.1
aciclovir	S01AD03	21.1
adalimumab	L04AB04	8.1
albendazole	P02CA03	6.1.1; 6.1.2; 6.1.4
alcohol based hand rub	D08AX08	15.2
allopurinol	M04AA01	8.2.5; 29.1
all-trans retinoid acid (ATRA)	L01XF01	8.2.2
alteplase	B01AD02	12.5.2
amidotriozate	V08AA01	14.2
amikacin	J01GB06	6.2.1; 6.2.5
amiloride	C03DB01	16
amiodarone	C01BD01	12.2
amitriptyline	N06AA09	2.3; 24.2.1
amlodipine	C08CA01	12.3

Medicine or item as in EML	ATC code	Section
amodiaquine	P01BA06	6.5.3.1
amodiaquine – sulfadoxine + pyrimethamine	P01BA06 P01BD51	6.5.3.2
amoxicillin	J01CA04	6.2.1
amoxicillin + clavulanic acid	J01CR02	6.2.1; 6.2.5
amphotericin B	J02AA01	6.3; 6.5.2
ampicillin	J01CA01	6.2.1
anastrozole	L02BG03	8.2.4
ansuvimab	J06BD04	6.7
anti-D immunoglobulin	J06BB01	11.2.1
anti-rabies immunoglobulin	J06BB05	11.2.1
anti-rabies virus monoclonal antibodies	–	19.2
anti-tetanus immunoglobulin	J06BB02	11.2.1
antivenom immunoglobulin	–	19.2
aprepitant	A04AD12	17.2
arsenic trioxide	L01XX27	8.2.1
artemether	P01BE02	6.5.3.1
artemether + lumefantrine	P01BF01	6.5.3.1
artesunate	P01BE03	6.5.3.1
artesunate + amodiaquine	P01BF03	6.5.3.1
artesunate + mefloquine	P01BF02	6.5.3.1
artesunate + pyronaridine tetraphosphate	P01BF06	6.5.3.1
ascorbic acid	A11GA01	27
asparaginase	L01XX02	8.2.1
atazanavir + ritonavir	J05AR23	6.4.2.3
atoltivimab + maftivimab + odesivimab	–	6.7
atorvastatin + perindopril + amlodipine	C10BX11	12.7
atracurium	M03AC04	20
atropine	A03BA01	1.3; 4.2
atropine	S01FA01	21.5
azathioprine	L04AX01	8.1; 29.2

Medicine or item as in EML	ATC code	Section
azithromycin	J01FA10	6.2.2
azithromycin	S01AA26	21.1
barium sulfate	V08BA01	14.2
BCG vaccine	L03AX03	19.3
bedaquiline	J04AK05	6.2.5
bendamustine	L01AA09	8.2.1
benzathine benzylpenicillin	J01CE08	6.2.1
benznidazole	P01CA02	6.5.5.2
benzoyl peroxide	D10AE01	13.4
benzyl benzoate	P03AX01	13.5
benzylpenicillin	J01CE01	6.2.1
betamethasone	D07AC01	13.3
bevacizumab	S01LA08	21.6
bicalutamide	L02BB03	8.2.4
biperiden	N04AA02	5.3
bisoprolol	C07AB07	12.1; 12.2; 12.3; 12.4
bleomycin	L01DC01	8.2.1
bortezomib	L01XG01	8.2.2
budesonide	R03BA02	25.1
budesonide	R01AD05	28
budesonide + formoterol	R03AK07	25.1
bupivacaine	N01BB01	1.2
bupropion	N06AX12	24.5.2
cabergoline	G02CB03	18.8
caffeine citrate	R07AB	22.6
calamine	D02AB	13.3
calcipotriol	D05AX02	13.4
calcium	A12AA20	27
calcium folinate	V03AF03	8.2.1
calcium gluconate	A12AA03	4.2; 27

Medicine or item as in EML	ATC code	Section
capecitabine	L01BC06	8.2.1
carbamazepine	N03AF01	5.1; 24.2.2
carbetocin	H01BB03	22.3
carboplatin	L01XA02	8.2.1
cefalexin	J01DB01	6.2.1
cefazolin	J01DB04	6.2.1
cefiderocol	J01DI04	6.2.3
cefixime	J01DD08	6.2.2
cefotaxime	J01DD01	6.2.2
ceftazidime	J01DD02	6.2.2
ceftazidime + avibactam	J01DD52	6.2.3
ceftolozane + tazobactam	J01DI54	6.2.3
ceftriaxone	J01DD04	6.2.2
cefuroxime	J01DC02	6.2.2
charcoal, activated	A07BA01	4.1
chlorambucil	L01AA02	8.2.1
chloramphenicol	J01BA01	6.2.1
chlorhexidine	D08AC02	15.1; 22.6
chlorine base compound	–	15.2
chloroquine	P01BA01	6.5.3.1; 6.5.3.2; 29.2
chloroxylenol	D08AE05	15.2
cholera vaccine	J07AE	19.3
ciclosporin	L04AD01	8.1
ciprofloxacin	J01MA02	6.2.2
ciprofloxacin	S02AA15	28
cisplatin	L01XA01	8.2.1
cladribine	L04AA40	5.2
clarithromycin	J01FA09	6.2.2
clindamycin	J01FF01	6.2.1
clofazimine	J04BA01	6.2.4; 6.2.5
clomifene	G03GB02	22.2
clomipramine	N06AA04	24.4

Medicine or item as in EML	ATC code	Section
clopidogrel	B01AC04	12.5.1
clotrimazole	G01AF02	6.3
cloxacillin	J01CF02	6.2.1
clozapine	N05AH02	24.1
coagulation factor IX	B02BD04	11.2.2
coagulation factor VIII	B02BD02	11.2.2
coal tar	D05AA	13.4
codeine	R05DA04	2.2
colecalciferol	A11CC05	27
colistin	J01XB01	6.2.3
condoms	–	22.1.4
copper-containing device	G02BA02	22.1.3
cryoprecipitate, pathogen-reduced	B05AA02	11.1
cyclizine	R06AE03	2.3
cyclophosphamide	L01AA01	8.2.1
cycloserine	J04AB01	6.2.5
cytarabine	L01BC01	8.2.1
dabigatran	B01AE07	10.2
dacarbazine	L01AX04	8.2.1
daclatasvir	J05AP07	6.4.4.2.1
daclatasvir + sofosbuvir	J05AP07 J05AP08	6.4.4.2.1
dactinomycin	L01DA01	8.2.1
dapsone	J04BA02	6.2.4
darbepoetin alfa	B03XA02	10.1
darunavir	J05AE10	6.4.2.3
dasatinib	L01EA02	8.2.2
daunorubicin	L01DB02	8.2.1
deferasirox	V03AC03	10.3
deferoxamine	V03AC01	4.2; 10.3
delamanid	J04AK06	6.2.5

Medicine or item as in EML	ATC code	Section
dengue vaccine	J07BX04	19.3
desmopressin	H01BA02	10.2
dexamethasone	H02AB02	2.3; 3; 8.2.4; 17.2; 22.5
dextran 70	B05AA05	11.3
diaphrams	–	22.1.4
diazepam	N05BA01	2.3; 5.1; 24.3
diazoxide	V03AH01	18.6
diethylcarbamazine	P02CB02	6.1.2
digoxin	C01AA05	12.2; 12.4
dihydroartemisinin + piperaquine phopshate	P01BF05	6.5.3.1
diloxanide	P01AC01	6.5.1
dimercaprol	V03AB09	4.2
diphtheria antitoxin	J06AA01	19.2
diphtheria vaccine	J07AF01	19.3
docetaxel	L01CD02	8.2.1
docusate sodium	A06AA02	2.3
dolutegravir	J05AJ03	6.4.2.4
dolutegravir + lamivudine + tenofovir	J05AR27	6.4.2.5
dopamine	C01CA04	12.4
doxorubicin	L01DB01	8.2.1
doxycycline	J01AA02	6.2.1; 6.5.3.1; 6.5.3.2
efavirenz	J05AG03	6.4.2.2
efavirenz + emtricitabine + tenofovir disoproxil	J05AR06	6.4.2.5
efavirenz + lamivudine + tenofovir disoproxil	J05AR11	6.4.2.5
eflornithine	P01CX03	6.5.5.1
empagliflozin	A10BK03	18.5.2
emtricitabine + tenofovir disoproxil	J05AR03	6.4.2.5
enalapril	C09AA02	12.3; 12.4
enoxaparin	B01AB05	10.2

Medicine or item as in EML	ATC code	Section
entecavir	J05AF10	6.4.4.1.1
ephedrine	C01CA26	1.2
epinephrine	S01EA01	21.5
epinephrine (adrenaline)	C01CA24	3; 12.2; 25.1
equine rabies immunoglobulin	J06BB05	19.2
ergocalciferol	A11CC01	27
ergometrine	G02AB03	22.3
erlotinib	L01EB02	8.2.2
erythromycin	S01AA17	21.1
erythropoiesis-stimulating agents	B03XA01 B03XA02 B03XA03	10.1
estradiol cypionate + medroxyprogesterone acetate	G03AA17	22.1.2
ethambutol	J04AK02	6.2.5
ethambutol + isoniazid + pyrazinamide + rifampicin	J04AM06	6.2.5
ethambutol + isoniazid + rifampicin	J04AM07	6.2.5
ethanol	D08AX08	15.1
ethinylestradiol + etonogestrel	G02BB01	22.1.6
ethinylestradiol + levonorgestrel	G03AA07	22.1.1
ethinylestradiol + norethisterone	G03AA05	22.1.1
ethionamide	J04AD03	6.2.5
ethosuximide	N03AD01	5.1
etonogestrel-releasing implant	G03AC08	22.1.5
etoposide	L01CB01	8.2.1
everolimus	L01EG02	8.2.2
fentanyl	N02AB03	2.2
ferrous salt	B03AA02 B03AA07	10.1
ferrous salt + folic acid	B03AD02 B03AD03	10.1
fexinidazole	P01CA03	6.5.5.1

Medicine or item as in EML	ATC code	Section
filgrastim	L03AA02	8.2.3
fluconazole	J02AC01	6.3
flucytosine	J02AX01	6.3
fludarabine	L01BB05	8.2.1
fludrocortisone	H02AA02	18.1
fluorescein	S01JA01	14.1
fluoride	A01AA	30
fluorouracil	L01BC02	8.2.1; 13.4
fluoxetine	N06AB03	2.3; 24.2.1
fluphenazine	N05AB02	24.1
folic acid	B03BB01	10.1
fomepizole	V03AB34	4.2
fosfomycin	J01XX01	6.2.3
fresh frozen plasma	B05AX03	11.1
furosemide	C03CA01	12.4; 16
gemcitabine	L01BC05	8.2.1
gentamicin	J01GB03	6.2.1
gentamicin	S01AA11	21.1
glass ionomer cement	–	30
glatiramer acetate	L03AX13	5.2
glecaprevir + pibrentasvir	J05AP57	6.4.4.2.1
gliclazide	A10BB09	18.5.2
glucagon	H04AA01	18.6
glucose	B05CX01	26.2
glucose with sodium chloride	B05BA03	26.2
glutaral	–	15.2
glyceryl trinitrate	C01DA02	12.1
griseofulvin	D01BA01	6.3
Haemophilus influenzae type b vaccine	J07AG01	19.3
haloperidol	N05AD01	2.3; 24.1

Medicine or item as in EML	ATC code	Section
halothane	N01AB01	1.1.1
heparin sodium	B01AB01	10.2
hepatitis A vaccine	J07BC02	19.3
hepatitis B vaccine	J07BC01	19.3
hydralazine	C02DB02	12.3
hydrochlorothiazide	C03AA03	12.3; 12.4; 16
hydrocortisone	A07EA02	17.3
hydrocortisone	D07AA02	13.3
hydrocortisone	H02AB09	3; 8.2.4; 18.1
hydroxocobalamin	B03BA03	10.1
hydroxycarbamide	L01XX05	8.2.1; 10.3
hydroxychloroquine	P01BA02	29.2
hyoscine butylbromide	A03BB01	2.3
hyoscine hydrobromide	A04AD01	2.3
ibrutinib	L01EL01	8.2.2
ibuprofen	C01EB16	22.6
ibuprofen	M01AE01	2.1; 7.1
ifosfamide	L01AA06	8.2.1
imatinib	L01EA01	8.2.2
influenza vaccine	J07BB	19.3
insulin injection (soluble) (human)	A10AB01	18.5.1
Intermediate-acting insulin (human)	A10AC01	18.5.1
intraperitoneal dialysis solution	–	23
iodine	H03CA	18.7; 27
iodine	D08AG03	6.3
iohexol	V08AB02	14.2
ipratropium bromide	R03BB01	25.1
irinotecan	L01CE02	8.2.1
isoflurane	N01AB06	1.1.1
isoniazid	J04AC01	6.2.5
isoniazid + pyrazinamide + rifampicin	J04AM05	6.2.5

Medicine or item as in EML	ATC code	Section
isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	J04AM08	6.4.2.6
isoniazid + rifampicin	J04AM02	6.2.5
isoniazid + rifapentine	J04AC51	6.2.5
isosorbide dinitrate	C01DA08	12.1
itraconazole	J02AC02	6.3
ivermectin	P02CF01	6.1.1; 6.1.2; 6.6
Japanese encephalitis vaccine	J07BA02 J07BA03	19.3
ketamine	N01AX03	1.1.2
lactulose	A06AD11	2.3
lamivudine	J05AF05	6.4.2.1
lamivudine + zidovudine	J05AR01	6.4.2.5
lamotrigine	N03AX09	5.1
latanoprost	S01EE01	21.4
ledipasvir + sofosbuvir	J05AP51	6.4.4.2.2
lenalidomide	L04AX04	8.2.3
letrozole	L02BG04	22.2
leuprorelin	L02AE02	8.2.4
levamisole	P02CE01	6.1.1
levetiracetam	N03AX14	5.1
levodopa + carbidopa	N04BA02	5.3
levofloxacin	J01MA12	6.2.5
levonorgestrel	G03AC03	22.2.1
levonorgestrel	G03AD01	22.2.1
levonorgestrel-releasing implant	G03AC03	22.1.5
levonorgestrel-releasing intrauterine system	G02BA03	22.1.3
levothyroxine	H03AA01	18.7
lidocaine	C01BB01	12.2

Medicine or item as in EML	ATC code	Section
lidocaine	N01BB02	1.2
lidocaine + epinephrine	N01BB52	1.2
linezolid	J01XX08	6.2.3; 6.2.5
lisinopril + amlodipine	C09BB03	12.3
lisinopril + hydrochlorothiazide	C09BA03	12.3
lithium carbonate	N05AN01	24.2.2
long-acting insulin analogues	A10AE04 A10AE05 A10AE06	18.5.1
loperamide	A07DA03	2.3
lopinavir + ritonavir	J05AR10	6.4.2.3
loratadine	R06AX13	3
lorazepam	N05BA06	5.1
losartan	C09CA01	12.3; 12.4
Lugol's solution	H03CA	18.7
magnesium sulfate	B05XA05	5.1
mannitol	B05BC01	16
measles vaccine	J07BD01	19.3
mebendazole	P02CA01	6.1.1; 6.1.4
medroxyprogesterone acetate	G03AC06	22.1.2
medroxyprogesterone acetate	G03DA02	18.4
mefloquine	P01BC02	6.5.3.1; 6.5.3.2
meglumine antimoniate	P01CB01	6.5.2
meglumine iotroxate	V08AC02	14.2
melarsoprol	P01CD01	6.5.5.1
melphalan	L01AA03	8.2.1
meningococcal meningitis vaccine	J07AH	19.3
mercaptopurine	L01BB02	8.2.1
meropenem	J01DH02	6.2.2; 6.2.5
meropenem + vaborbactam	J01DH52	6.2.3
mesna	V03AF01	8.2.5

Medicine or item as in EML	ATC code	Section
metformin	A10BA02	18.5.2
methadone	N07BC02	2.2; 24.5
methimazole	H03BB02	18.7
methotrexate	L01BA01	8.2.1
methotrexate	L04AX03	29.2
methyldopa	C02AB01	12.3
methylprednisolone	H02AB04	8.2.4
methylthioninium chloride (methylene blue)	V03AB17	4.2
metoclopramide	A03FA01	2.3; 17.2
metronidazole	J01XD01	6.2.1
metronidazole	P01AB01	6.5.1
micafungin	J02AX05	6.3
miconazole	D01AC02	13.1
midazolam	N05CD08	1.3; 2.3; 5.1
mifepristone – misoprostol	G03XB51	22.3
miltefosine	P01CX04	6.5.2
misoprostol	G02AD06	22.3
morphine	N02AA01	1.3; 2.2
moxifloxacin	J01MA14	6.2.5
multiple micronutrient powder	A11AA01	27
multiple micronutrient supplement	A11AA01	22.5
mumps vaccine	J07BE01	19.3
mupirocin	D06AX09	13.2
naloxone	V03AB15	4.2
naltrexone	N07BB04	24.5.1
natamycin	S01AA10	21.1
neostigmine	N07AA01	20
nevirapine	J05AG01	6.4.2.2
niclosamide	P02DA01	6.1.1
nicotinamide	A11HA01	27

Medicine or item as in EML	ATC code	Section
nicotine replacement therapy	N07BA01	24.5
nifedipine	C08CA05	22.4
nifurtimox	P01CC01	6.5.5.1; 6.5.5.2
nilotinib	L01EA03	8.2.2
nitrofurantoin	J01XE01	6.2.1
nitrous oxide	N01AX13	1.1.1
nivolumab	L01FF01	8.2.3
norethisterone enantate	G03AC01	22.1.2
normal immunoglobulin	J06BA	11.2.1
nystatin	A07AA02	6.3
nystatin	G01AA01	6.3
octreotide	H01CB02	18.8
ofloxacin	S01AE01	21.1
olanzapine	N05AH03	24.1
omeprazole	A02BC01	17.1
ondansetron	A04AA01	2.3; 17.2
oral rehydration salts	A07CA	17.5.1; 26.1
oral rehydration salts – zinc sulfate	A07CA A12CB01	17.5
oseltamivir	J05AH02	6.4.3
oxaliplatin	L01XA03	8.2.1
oxamniquine	P02BA02	6.1.3
oxygen	V03AN01	1.1.1; 1.4
oxytocin	H01BB02	22.3
paclitaxel	L01CD01	8.2.1
p-aminosalicylate sodium	J04AA01	6.2.5
pancreatic enzymes	A09AA02	17
paracetamol	N02BE01	2.1; 7.1
paromomycin	A07AA06	6.5.2
pegaspargase	L01XX24	8.2.1

Medicine or item as in EML	ATC code	Section
pegfilgrastim	L03AA13	8.2.3
penicillamine	M01CC01	4.2; 29.2
pentamidine	P01CX01	6.5.4; 6.5.5.1
permethrin	P03AC04	13.5
pertussis vaccine	J07AJ01	19.3
phenobarbital	N03AA02	5.1
phenoxymethylpenicillin	J01CE02	6.2.1
phenytoin	N03AB02	5.1
phytomenadione	B02BA01	10.2
pilocarpine	S01EB01	21.4
piperacillin + tazobactam	J01CR05	6.2.2
platelets	B05AX02	11.1
plazomicin	J01GB14	6.2.3
pneumococcal vaccine	J07AL01	19.3
podophyllum resin	D06BB04	13.4
poliomyelitis vaccine	J07BF	19.3
polymyxin B	J01XB02	6.2.3
potassium chloride	B05XA01	26.1; 26.2
potassium ferric hexacyanoferrate (II) ·$2H_2O$	V03AB31	4.2
potassium iodide	D08AG03	6.3
potassium iodide	V03AB21	18.7
potassium permanganate	D08AX06	13.2
povidone iodine	D08AG02	15.1
praziquantel	P02BA01	6.1.1; 6.1.3; 6.1.4
prednisolone	H02AB06	3; 8.2.4
prednisolone	S01BA04	21.2
pretomanid	J04AK08	6.2.5
primaquine	P01BA03	6.5.3.1
procaine benzylpenicillin	J01CE09	6.2.1
procarbazine	L01XB01	8.2.1
progesterone vaginal ring	G02BB02	22.1.6

Medicine or item as in EML	ATC code	Section
proguanil	P01BB01	6.5.3.2
propofol	N01AX10	1.1.2
propranolol	C07AA05	7.2
propylthiouracil	H03BA02	18.7
prostaglandin E1	C01EA	22.6
protamine sulfate	V03AB14	10.2
pyrantel	P02CC01	6.1.1
pyrazinamide	J04AK01	6.2.5
pyridostigmine	N07AA02	20
pyridoxine	A11HA02	27
pyrimethamine	P01BD01	6.5.4
quetiapine	N05AH04	24.2.2
quinine	P01BC01	6.5.3.1
rabies vaccine	J07BG	19.3
raltegravir	J05AJ01	6.4.2.4
ranitidine	A02BA02	17.1
rasburicase	V03AF07	8.2.5
ravidasvir	–	6.4.4.2.1
ready-to-use therapeutic food	–	9
realgar-Indigo naturalis formula	–	8.2.1
red blood cells	B05AX01	11.1
resin-based composites	–	30
retinol	A11CA01	27
ribavirin	J05AP01	6.4.3; 6.4.4.2.3
riboflavin	A11HA04	27
rifabutin	J04AB04	6.2.5
rifampicin	J04AB02	6.2.4; 6.2.5
rifapentine	J04AB05	6.2.5
risperidone	N05AX08	24.1
ritonavir	J05AE03	6.4.2.3

Medicine or item as in EML	ATC code	Section
rituximab	L01FA01	5.2; 8.2.2
rotavirus vaccines	J07BH	19.3
rubella vaccines	J07BJ	19.3
salbutamol	R03AC02	25.1
salicylic acid	D01AE12	13.4
selenium sulfide	D01AE13	13.1
senna	A06AB06	2.3; 17.4
sevoflurane	N01AB08	1.1.1
silver diamine fluoride	–	30
silver sulfadiazine	D06BA01	13.2
simvastatin	C10AA01	12.6
sodium calcium edetate	V03AB03	4.2
sodium chloride	B05XA03	26.2
sodium hydrogen carbonate	B05XA02	26.2
sodium lactate compound solution	–	26.2
sodium nitrite	V03AB08	4.2
sodium nitroprusside	C02DD01	12.3
sodium stibogluconate	P01CB02	6.5.2
sodium thiosulfate	V03AB06	4.2; 13.1
sofosbuvir	J05AP08	6.4.4.2.1
sofosbuvir + velpatasvir	J05AP55	6.4.4.2.1
spectinomycin	J01XX04	6.2.1
spironolactone	C03DA01	12.4; 16
streptokinase	B01AD01	12.5.2
streptomycin	J01GA01	6.2.5
succimer	–	4.2
sulfadiazine	J01EC02	6.5.4
sulfadoxine + pyrimethamine	P01BD51	6.5.3.1
sulfamethoxazole + trimethoprim	J01EE01	6.2.1; 6.5.4
sulfasalazine	A07EC01	17.3; 29.2
sumatriptan	N02CC01	7.1

Medicine or item as in EML	ATC code	Section
suramin sodium	P01CX02	6.5.5.1
suxamethonium	M03AB01	20
tacrolimus	L04AD02	8.1
tamoxifen	L02BA01	8.2.4
telmisartan + amlodipine	C09DB04	12.3
telmisartan + hydrochlorothiazide	C09DA07	12.3
tenofovir disoproxil fumarate	J05AF07	6.4.2.1; 6.4.4.1.1
terbinafine	D01AE15	13.1
testosterone	G03BA03	18.2
tetanus vaccine	J07AM01	19.3
tetracaine	S01HA03	21.3
tetracycline	S01AA09	21.1
thalidomide	L04AX02	8.2.3
thiamine	A11DA01	27
tick-borne encephalitis vaccine	J07BA01	19.3
timolol	S01ED01	21.4
tioguanine	L01BB03	8.2.1
tiotropium	R03BB04	25.1
tranexamic acid	B02AA02	10.2; 22.5
trastuzumab	L01FD01	8.2.2
triamcinolone hexacetonide	H02AB08	29.3
triclabendazole	P02BX04	6.1.3
trimethoprim	J01EA01	6.2.1
tropicamide	S01FA06	14.1
tuberculin, purified protein derivative (PPD)	V04CF01	19.1
typhoid vaccine	J07AP	19.3
ulipristal	G03AD02	22.1.1
urea	D02AE01	13.4

Medicine or item as in EML	ATC code	Section
valganciclovir	J05AB14	6.4.3
valproic acid (sodium valproate)	N03AG01	5.1; 24.2.2
vancomycin	A07AA09	6.2.2
vancomycin	J01XA01	6.2.2
varenicline	N07BA03	24.5
varicella vaccines	J07BK	19.3
vecuronium	M03AC03	20
verapamil	C08DA01	12.1; 12.2
vinblastine	L01CA01	8.2.1
vincristine	L01CA02	8.2.1
vinorelbine	L01CA04	8.2.1
voriconazole	J02AC03	6.3
warfarin	B01AA03	10.2
water for Injection	V07AB	26.3
whole blood	B05A	11.1
xylometazoline	R01AA07	28
yellow fever vaccine	J07BL01	19.3
zidovudine	J05AF01	6.4.2.1
zinc sulfate	A12CB01	17.5.2
zoledronic acid	M05BA08	8.2.5

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

WHO electronic Essential Medicines List (eEML) World Health Organization (2023)
https://list.essentialmeds.org/

AWaRe classification of antibiotics for evaluation and monitoring of use (2023)
https://iris.who.int/handle/10665/371093

The WHO AWaRe (access, watch, reserve) antibiotic book (2022)
https://iris.who.int/handle/10665/365237

The WHO AWaRe (Access, Watch, Reserve) antibiotic book – Infographics (2022)
https://iris.who.int/handle/10665/365135

Selection of essential medicines at country level. Using the WHO Model List of Essential Medicines to update a national essential medicines list (2019)
https://iris.who.int/handle/10665/330898

The selection and use of essential in vitro diagnostics: report of the fourth meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics, 2022 (including the fourth WHO model list of essential in vitro diagnostics)
https://iris.who.int/handle/10665/373322

Technical report: pricing of cancer medicines and its impacts: a comprehensive technical report for the World Health Assembly Resolution 700.12: operative paragraph 2.9 on pricing approaches and their impacts on availability of medicines for the prevention and treatment of cancer (2018)
https://iris.who.int/handle/10665/277190

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Third edition (2023)
https://iris.who.int/handle/10665/374250

Abortion care guideline (2022)
https://iris.who.int/handle/10665/349316

Therapeutics and COVID-19: living guideline (13 January 2023)
https://app.magicapp.org/#/guideline/nBkO1E

Therapeutics for Ebola virus disease (2022)
https://iris.who.int/handle/10665/361697

This report presents the recommendations of the WHO Expert Committee responsible for updating the WHO Model List of Essential Medicines and WHO Model List of Essential Medicines for Children. It contains a summary of the evidence presented and the Committee's consideration, justifications and recommendations for additions, deletions and changes to medicines on the Model Lists.