SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MabThera® SC 1400 mg

Strength: Each mL contains 120 mg of rituximab.

Pharmaceutical form: Solution for subcutaneous injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: rituximab.

Single dose vials contain 1400 mg/11,7 mL for subcutaneous injection. Each mL contains 120 mg of rituximab.

MabThera SC contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered medicines when administered subcutaneously.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences.

The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

This medicinal product contains less than 1mmol sodium per dose, i.e. essentially sodium free.

Sugar Free

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

MabThera SC 1400 mg is a clear to opalescent, colourless to yellowish liquid provided in sterile,

preservative-free, non-pyrogenic, 15 mL single dose vials at 120 mg/mL, with an extractable volume of 11,7 mL (1400 mg/11,7 mL).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MabThera SC 1400 mg is indicated for the treatment of Non-Hodgkin's lymphoma (NHL):

- patients with relapsed or chemo-resistant low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma
- previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy
- patients with follicular lymphoma as maintenance treatment, after response to induction therapy
- patients with high grade CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (Cyclophosphamide - C, Doxorubicin - H, Vincristine - O, Prednisone - P) chemotherapy.

4.2 Posology and method of administration

General

Subcutaneous Formulations

Substitution by any other biological medicinal product requires the consent of the prescribing healthcare professional.

It is important to check the product labels to ensure that the appropriate formulation (IV or SC) is being given to the patient, as prescribed. MabThera SC 1400 mg should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced healthcare professional (see section 4.4).

The safety and efficacy of alternating or switching between MabThera SC 1400 mg and products that are biosimilar but not deemed interchangeable has not been established. Therefore, the

benefit-risk of alternating or switching needs to be carefully considered.

Premedication and Prophylactic Medications

Premedication consisting of an analgesic/anti-pyretic and an antihistaminic, e.g. paracetamol/acetaminophen and diphenhydramine, should always be given before each administration of MabThera.

Premedication with glucocorticoids should also be considered, particularly if MabThera is not given in combination with steroid-containing chemotherapy (see section 4.4).

Method of administration

MabThera SC 1400 mg is NOT intended for intravenous administration (see Section 6.6).

MabThera SC 1400 mg is intended for subcutaneous administration in non-Hodgkin's lymphoma (NHL) only, and in patients who tolerated a first IV administration.

MabThera SC 1400 mg should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, or hard areas where there are moles or scars. No data are available on performing the injection in other sites of the body, therefore injections should be restricted to the abdominal wall.

During the treatment course with MabThera SC 1400 mg, other medications for subcutaneous administration should preferably be administered at different sites.

MabThera SC 1400 mg injection should be administered over approximately 5 minutes. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging.

If an injection is interrupted it can be resumed or another location may be used, if appropriate.

Posology

The recommended dose of MabThera SC formulation used for adult patients is a subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's body surface area.

Dosage adjustments during treatment: No dose reductions of MabThera are recommended. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutics medicines should be applied.

Low-grade/CD20 positive or Follicular B-cell Non-Hodgkin's lymphoma

All patients must always receive their first dose of MabThera by intravenous administration.

During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with MabThera IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (see section 4.4).

The subcutaneous formulation must only be given at the second or subsequent cycles (see "*First administration: Intravenous formulation*" and "*Subsequent administrations: Subcutaneous formulation*" sub-sections, below).

First administration: MabThera IV:

The first administration of MabThera must always be given by intravenous infusion at a dose of 375 mg/m^2 body surface area (BSA).

Subsequent administrations:

Patients unable to receive the full MabThera intravenous infusion dose should continue to receive subsequent cycles with MabThera IV until a full IV dose is successfully administered.

For patients who tolerate the full MabThera IV infusion dose well, the second or subsequent MabThera dose can be given subcutaneously using the MabThera SC 1400 mg (see section 4.4).

Initial treatment: ***Follicular B-cell Non-Hodgkin's lymphoma:***

- *Subcutaneous monotherapy:* The recommended dosage of MabThera SC 1400 mg used as monotherapy for adult patients is subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's body surface area, once weekly for 3 weeks following MabThera IV at week 1 (1st week R-IV then 3 weeks R-SC; 4 weeks in total).

- *Subcutaneous combination therapy:* The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/refractory patients with follicular lymphoma is: first cycle with MabThera intravenous formulation 375 mg/m^2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle for up to 8 cycles.

MabThera SC 1400 mg should be administered on day 0 or day 1 of each chemotherapy cycle after administration of the glucocorticoid component of the chemotherapy, if applicable.

The recommended dosage in combination with any chemotherapy is MabThera IV (R-IV) 375 mg/m^2 BSA intravenously for the first cycle followed by subcutaneous injection of MabThera SC (R-SC) at a fixed dose of 1400 mg irrespective of the patient's body surface area.

- 1st cycle R-IV with CVP + 7 cycles R-SC with CVP (21 days/cycle)
- 1st cycle R-IV with MCP + 7 cycles R-SC with MCP (28 days/cycle)
- 1st cycle R-IV with CHOP + 7 cycles R-SC with CHOP (21 days/cycle); or a total of 6 cycles (1st cycle R-IV then 5 cycles R-SC) if complete remission is achieved after 4 cycles
- 1st cycle R-IV with CHVP-Interferon + 5 cycles R-SC with CHVP-Interferon (21 days/cycle).

Re-treatment following relapse:

Patients who have responded to MabThera IV or SC initially may be treated again with MabThera SC at a fixed dose of 1400 mg, administered as a subcutaneous injection once weekly, following a first administration of MabThera given by intravenous infusion at a dose of 375 mg/m^2 BSA (1st week R-IV then 3 weeks R-SC; 4 weeks in total).

Maintenance treatment:

- Previously untreated patients after response to induction treatment may receive maintenance therapy with MabThera SC 1400 mg given at a fixed dose of 1400 mg once every 2 months until disease progression or for a maximum period of two years (12 administrations in total).

- Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with MabThera SC given at a fixed dose of 1400 mg once every 3 months until disease progression or for a maximum period of two years (8 administrations in total).

High grade/CD 20 positive or Diffuse Large B-cell/Non-Hodgkin's Lymphoma: Intravenous Formulation

In patients with diffuse large B cell non-Hodgkin's lymphoma, MabThera IV should be used in combination with CHOP chemotherapy (R-CHOP). The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after *IV* administration of the glucocorticoid component of CHOP. The other components of CHOP should be given after the administration of MabThera IV. Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

All patients must always receive their first dose of MabThera SC 1400 mg by intravenous administration. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with MabThera SC 1400 mg IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (see section 4.4). The subcutaneous formulation must only be given at the second or subsequent cycles (see "*First administration: Intravenous formulation"* and "*Subsequent administrations: Subcutaneous formulation*" sub-sections, below).

In patients with diffuse large B cell non-Hodgkin's lymphoma MabThera SC 1400 mg SC 1400 mg should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy.

First administration: Intravenous formulation

The first administration of MabThera SC 1400 mg must always be given by intravenous infusion at a dose of 375 mg/m² BSA.

Subsequent administrations: Subcutaneous formulation

Patients unable to receive the full MabThera SC 1400 mg intravenous infusion dose should continue to receive subsequent cycles with MabThera SC 1400 mg IV until a full IV dose is successfully administered.

For patients who are able to receive the full MabThera SC 1400 mg IV infusion dose, the second or subsequent MabThera SC 1400 mg doses can be given subcutaneously using the MabThera SC 1400 mg SC formulation (see section 4.4)

The recommended dosage of MabThera SC 1400 mg SC is a fixed dose of 1400 mg, irrespective of the patient's BSA, administered on day 1 of each chemotherapy cycle for 8 cycles (1st cycle R-IV with CHOP + 7 cycles R-SC with CHOP; 8 cycles in total) after IV administration of the glucocorticoid component of CHOP.

Paediatric population

Children and adolescents: The safety and efficacy of MabThera in children and adolescents (≤ 18 years) have not been established.

Special populations

Elderly: No dose adjustment is required in elderly patients (aged > 65 years).

4.3 Contraindications

- Hypersensitivity to rituximab or to any of the excipients or to murine proteins.
- Active, severe infections.
- Patients in a severely immunocompromised state.
- Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease (see section 4.4 and section 4.8).
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

WARNING

Infusion-related reactions: Infusion-related deaths (death within 24 hours of infusion) have

been reported. These events appear as manifestations of an infusion-related complex and include hypoxia, lung infiltration, adult respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Most fatal infusion-related events occurred in association with the first Infusion.

Tumour Lysis Syndrome (TLS): Acute renal failure requiring dialysis and with instances of fatal outcome has been reported. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g. patients with a high tumour burden or with a high number (>25 x 10^9/L) of circulating malignant cells such as patients with CLL or mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. See section 4.4.

General: In order to improve the traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded (or stated) in the patient file. The information provided in this section pertains to the use of MabThera SC 1400 mg. For information related to the other indications, please refer to the professional information of MabThera intravenous formulation.

The use of MabThera SC 1400 mg as monotherapy in patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy cannot be recommended as the safety of the once weekly subcutaneous administration has not been established.

Progressive Multifocal Leukoencephalopathy (PML)

Use of MabThera SC 1400 mg may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML) (see section 4.8).

The majority of patients had received MabThera SC1400 mg IV in combination with chemotherapy or as part of a haematopoietic stem cell transplant.

Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended

until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated.

If any doubt exists, further evaluation, including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered.

The medical practitioner should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. If a patient develops PML, the dosing of MabThera must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of MabThera therapy may lead to similar stabilisation or improved outcome.

Non-Hodgkin's Lymphoma Patients

Infusion/Administration-related reactions:

MabThera is associated with infusion-related reactions (IRRs) in most patients, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions. This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of MabThera and can be observed with both formulations. Severe infusion-related reactions with fatal outcome have been reported during post-marketing use of the MabThera intravenous formulation, with an onset ranging within 30 minutes to 2 hours after starting the first MabThera intravenous infusion. They were characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome, in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see section 4.8).Patients

with a high number (> 25 x 10^9/L) of circulating malignant cells or high tumour burden who may be at higher risk of especially severe IRRs should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still > 25 x 10^9/L (see section 4.8). Infusion related adverse reactions of all kinds have been observed in 77 % of patients treated with MabThera intravenous formulation (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % of patients) (see section 4.8). These symptoms are usually reversible with interruption of MabThera infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.

Administration related reactions have been observed in up to 50 % of patients treated with MabThera subcutaneous formulation in clinical trials. The reactions occurring within 24 hours of the subcutaneous injection consisted primarily of erythema pruritus, rash and injections site reactions such as pain, swelling and redness and were generally of mild or moderate (grade 1 or 2) and transient nature (see section 4.8).

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema.

Fatal outcomes have been reported for patients who developed severe cytokine release syndrome, occasionally associated with signs and symptoms of tumour lysis syndrome leading to multi-organ failure, respiratory failure and renal failure.

This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome frequently manifests

itself within one or two hours of initiating the first infusion.

Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.

Hypersensitivity reactions / Anaphylaxis:

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medications for the treatment of hypersensitivity reactions, e.g. epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MabThera. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome. Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Administration-related reactions:

Local cutaneous reactions, including injection site reactions, have been reported in patients receiving MabThera SC 1400 mg. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash (see section 4.8). Some local cutaneous reactions occurred more than 24 hours after the SC administration. The majority of local cutaneous reactions seen following administration of the SC formulation were mild or moderate and resolved without any specific treatment.

***All patients must always receive their first dose of MabThera by intravenous administration in order to avoid an irreversible administration of the full MabThera SC dose during Cycle 1*.** During this cycle the patient would have the highest risk of experiencing an IRR that can be treated effectively by slowing or stopping the infusion. The subcutaneous formulation must only be given at the second or subsequent cycles. Patients, unable to tolerate the full MabThera IV infusion dose should continue to receive subsequent cycles with MabThera IV until the full IV dose is successfully administered. For patients who are able to receive the full MabThera IV infusion dose, the second or subsequent MabThera dose can be given subcutaneously using MabThera SC 1400 mg formulation (see section 4.2).

Therefore, the switch to MabThera SC 1400 mg can only occur at the second or subsequent cycles of treatment. As with the intravenous formulation, MabThera SC 1400 mg should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of a healthcare professional. Premedication consisting of an analgesic/antipyretic and an antihistamine should always be administered before each dose of MabThera SC. Premedication with glucocorticoids should also be considered.

Patients should be observed for at least 15 minutes following MabThera SC 1400 mg administration. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

Patients should be instructed to contact their treating medical practitioner immediately if symptoms that are suggestive of severe hypersensitivity reactions or cytokine release syndrome occur at any time after administration.

Pulmonary events

Pulmonary events have included hypoxia, lung infiltration, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs.

Rapid tumour lysis:

MabThera IV/SC mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g., hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur within 30 minutes to 2 hours after the first MabThera IV infusion in patients with high numbers of circulating malignant lymphocytes. If these signs and symptoms develop, treatment should be stopped immediately. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g. patients with a high tumour burden or with a high number [> 25 x 10^9/L] of circulating malignant cells such as patients with CLL or mantle cell lymphoma). Patients at risk of developing rapid tumour lysis should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent MabThera IV therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Cardiovascular:

Since hypotension may occur during MabThera IV/SC administration, consideration should be given to withholding antihypertensive medicines 12 hours prior to and throughout MabThera IV/SC administration. Angina pectoris or cardiac dysrhythmia, such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with MabThera IV/SC. Less frequently, patients experienced an exacerbation of pre-existing cardiac conditions such as angina pectoris or congestive heart failure. Therefore, in patients with a known cardiac history, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with MabThera and patients should be closely monitored.

Monitoring of blood counts (haematological toxicities):

Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts of < 1,5 x 10^9 /L and/or platelet counts of

< 75 x 10^9/L, as clinical experience with such patients is limited. MabThera IV has been used in patients who underwent autologous bone marrow transplantation and in other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity. Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MabThera IV/SC. When MabThera IV/SC is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections:

MabThera treatment should not be initiated in patients with severe active infections. Based on the mechanism of action of MabThera and the knowledge that B-cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following MabThera IV therapy. It is recommended that immunoglobulin levels are determined prior to initiating treatment with MabThera.

Serious infections, including fatalities, can occur during therapy with MabThera. MabThera treatment should not be administered to patients with active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3), or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Medical practitioners should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8).

Patients treated with MabThera should avoid exposure to patients with tuberculosis and should avoid contact with children and adults recently vaccinated with attenuated live vaccines. Patients who develop infection following MabThera IV therapy should be promptly evaluated and treated appropriately.

Tuberculosis

All patients should be screened for active or latent tuberculosis (TB) infection prior to starting MabThera therapy. Patients with active or latent TB should be treated with standard anti-

mycobacterial therapy before initiating MabThera.

Risks of tuberculosis disease

- Cases of tuberculosis (and tuberculosis reactivation) have been observed in patients treated with TNF-alpha inhibitors and similar immune-modulatory medicines, including MabThera.
- Tuberculosis in these patients may be due to reactivation of latent tuberculosis infection or due to new infections.
- Prophylactic treatment of a latent tuberculosis infection should be initiated prior to starting treatment with MabThera.
- Patients may become infected with tuberculosis during the course of therapy with MabThera and medical practitioners should continue to monitor the patient for signs and symptoms of tuberculosis, including patients who have tested negative for latent tuberculosis at the start of therapy.
- Treatment of tuberculosis should follow current national guidelines.

Hepatitis B Infections:

In patients with non-Hodgkin's Lymphoma, and CLL, receiving MabThera in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported, including reports of fulminant hepatitis, some of which were fatal. The reports were confounded by both the underlying disease state and the cytotoxic chemotherapy.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At a minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Very rare cases of PML have been reported during post-marketing use of the MabThera intravenous formulation in NHL (see section 4.8). The majority of patients had received

rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Skin reactions:

Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome, some with fatal outcome, have been reported (see Post-Marketing). In case of such an event, with a suspected relationship to MabThera, treatment should be permanently discontinued.

Immunisation:

The safety of immunisation with live viral vaccines, following MabThera IV/SC therapy has not been studied and vaccination with live virus vaccines is not recommended whilst on MabThera or whilst peripherally B-cell depleted (see section 4.3).

Patients treated with MabThera IV/SC may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a non-randomised study, patients with relapsed low-grade NHL who received MabThera IV monotherapy when compared to healthy untreated controls, had a lower rate of response to vaccination with tetanus recall antigen (16 % vs. 81 %) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4 % vs. 76 % when assessed for > 2-fold increase in antibody titre).

Mean pre-therapeutic antibody titres against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with MabThera IV.

4.5 Interaction with other medicines and other forms of interaction

Currently, limited data are available on possible medicine interactions with MabThera SC 1400 mg.

Co-administration with MabThera did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition, there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of rituximab.

Co-administration with methotrexate had no effect on the pharmacokinetics of MabThera IV in rheumatoid arthritis (RA) patients.

Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Due to the long retention time of rituximab in B-cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and up to 12 months following MabThera therapy.

Pregnancy

MabThera is contraindicated in pregnancy and lactation. Pregnant women should not be treated with MabThera SC. IgG immunoglobulins are known to cross the placental barrier.

B-cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy.

Breastfeeding

Women who are breastfeeding their babies, should not be treated with MabThera SC.

Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, MabThera should not be given to women who are breastfeeding.

Fertility

Animal studies did not reveal deleterious effects of rituximab or recombinant human hyaluronidase (rHuPH20) on reproductive organs.

4.7 Effects on ability to drive and use machines

No studies on the effects of MabThera on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest

that MabThera would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The information provided in this section pertains to the use of MabThera SC 1400 mg in oncology. For information related to the autoimmune indications, please refer to the professional information for MabThera intravenous formulation.

Summary of the safety profile:

During the developmental programme, the safety profile of MabThera SC 1400mg was comparable to that of the IV formulation with the exception of local cutaneous reactions.

Local cutaneous reactions, including injection site reactions, were very common (≥ 1/10) in patients receiving MabThera SC 1400 mg. In the phase 3 SABRINA (BO22334) study, local cutaneous reactions were reported in up to 23 % of patients receiving MabThera SC 1400 mg. The most common local cutaneous reactions in the MabThera SC 1400 mg arm were: injection site erythema (13 %), injection site pain (8 %), and injection site oedema (4 %).

Similar events were observed in the SAWYER (BO25341) study and were reported in up to 42 % of patients in the MabThera SC arm. The most common local cutaneous reactions were: injection site erythema (26 %), injection site pain (16 %), and injection site swelling (5 %).

Events seen following subcutaneous administration were mild to moderate, apart from the one patient who reported a local cutaneous reaction Grade 3 intensity (injection site rash) following the first MabThera SC administration (Cycle 2). Local cutaneous reactions of any Grade in the MabThera SC 1400 mg arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections.

No cases of anaphylaxis or severe hypersensitivity reactions, cytokine release syndrome or tumour lysis syndrome were observed following subcutaneous administration during the MabThera SC 1400 mg development program.

Adverse reactions reported in MabThera SC 1400 mg usage

The risk of acute administration-related reactions associated with the subcutaneous formulation

of MabThera was assessed in three clinical studies.

In the SparkThera (BP22333) study no severe administration-related reactions were reported.

In the SABRINA (BO22334) study severe administration-related reactions (Grade ≥3) were reported in two patients (1 %) following MabThera SC administration. These events were Grade 3 injection site rash and dry mouth.

In the SAWYER (BO25341) study severe administration-related reactions (Grade ≥3) were reported in four patients (5 %) following MabThera SC administration. These events were Grade 4 thrombocytopenia and Grade 3 anxiety, injection-site erythema and urticaria.

Adverse reactions reported in MabThera intravenous formulation usage

Experience from Non-Hodgkin's Lymphoma and Chronic Lymphocytic

Leukaemia.

The overall safety profile of MabThera in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera IV monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.

The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera IV were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of MabThera IV.

Infectious events (predominantly bacterial and viral) occurred in approximately 30 - 55 % of patients during clinical trials in patients with NHL and in 30 - 50 % of patients during clinical trials in patients with CLL.

The most frequent reported or observed serious adverse drug reactions were infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), infections and cardiovascular events. Other serious ADRs reported include hepatitis B reactivation and PML (See section 4.4).

The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised in the tables below. Within each frequency grouping, side effects are presented in order of decreasing seriousness.

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1 000 to < 1/100) and rare (≥ 1/10 000 to < 1/1 000).

The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under “not known”.

Table 1: ADRs reported in clinical trials or during post-marketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/maintenance or in combination with chemotherapy.

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Infections and infestations	bacterial infections, viral infections, [+]bronchitis	sepsis, [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown aetiology,		Serious viral infection[2]		

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
		+acute bronchitis, +sinusitis, hepatitis B[1]				
Blood and lymphatic system disorders	neutropenia, leucopenia, +febrile neutropenia, +thrombocytopenia	anaemia, +pancytopenia, +granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels[3]	late neutropenia[3]
Immune system disorders	infusion related reactions[4] angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombocytopenia[4]

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Metabolism and nutrition disorders		hyperglycaemia, decreased weight, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation,	dysgeusia		peripheral neuropathy, facial nerve palsy[5]	cranial neuropathy, loss of other senses[5]

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
		dizziness, anxiety				
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]
Cardiac disorders		[+]myocardial infacrction[4 & 6], dysrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]left ventricular failure, [+]supra-ventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial	severe cardiac events [4 & 6]	heart failure[4 & 6]	

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
			ischaemia, bradycardia			
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocyte elastic vasculitis	
Respiratory, thoracic and mediastinal disorders		bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4]	lung infiltration
Gastrointestinal disorders	nausea	vomiting, diarrhoea, abdominal	abdominal enlargement		gastrointestinal perforati	

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
		pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation			on[7]	
Skin and subcutaneous tissue disorders	pruritus, rash, [+]alopecia	urticaria, sweating, night sweats, [+]skin disorder			severe bullous skin reactions, Stevens-Johnson Syndrome, toxic epidermal necrolysis[7] (Lyell's Syndrome)[7]	

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure[4]	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, [+]fatigue, [+]shivering, [+]multi-organ failure[4]	infusion site pain			
Investigations	decreased IgG levels					

For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported:

[1] includes reactivation and primary infections; frequency based on R-FC regimen in elapsed/refractory CLL.

[2] see also section infection below.

[3] see also section haematologic adverse reactions below.

[4] see also section infusion-related reactions below. Rarely fatal cases reported

[5] signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera therapy.

[6] observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions.

[7] includes fatal cases

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the MabThera-arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia, septic shock, superinfection lung, implant infection, septicaemia staphylococcal, lung infection, rhinorrheoa, pulmonary oedema, cardiac failure, venous thrombosis, mucosal inflammation nos, influenza-like illness, lower limb oedema, abnormal ejection fraction, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, positive blood culture, diabetes mellitus inadequate control.

Further information on selected, serious adverse drug reactions

Infusion-related reactions:

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50 % of patients in clinical trials, and occurred predominantly during the first infusion, usually in the first one to two hours. Hypotension, fever, chills, rigors, bronchospasm, sensation of tongue or throat swelling (angioedema), dyspnoea, nausea, urticaria/rash, fatigue, headache, rhinitis, pruritus, vomiting, flushing, and pain at disease sites have occurred in association with MabThera infusion as part of an infusion-related symptom complex. Some features of tumour lysis syndrome have also been observed.

Severe infusion-related reactions occurred in up to 12 % of all patients at the time of the first

treatment cycle with MabThera in combination with chemotherapy. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is < 1 % of patients by the eighth cycle of MabThera (containing) treatment. Additional reactions reported were dyspepsia, rash, hypertension, tachycardia, features of tumour lysis syndrome. Isolated cases of myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia were also reported.

Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies.

The incidence of infusion-related symptoms decreased substantially with subsequent intravenous infusions and is <1 % of patients by the eighth cycle of MabThera (containing) treatment.

Description of selected adverse reactions

Infections:

MabThera induced B-cell depletion in 70 % to 80 % of patients but was associated with decreased serum immunoglobulins only in a minority of patients. Bacterial, viral, fungal and unknown etiology infections irrespective of causal assessment, occurred in 30,3 % of 356 patients.

Severe infectious events (grade 3 or 4), including sepsis occurred in 3,9 % of patients.

Higher frequencies of infections overall, including grade 3-4 infections, were observed during MabThera treatment. There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part of a haematopoietic stem cell transplant.

Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (PML) and hepatitis C virus.

Data from clinical trials included cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see section 4.4).

Cases of hepatitis B reactivation, have been reported, the majority of which were in patients receiving MabThera in combination with cytotoxic chemotherapy. Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Haematologic adverse reactions:

Haematologic abnormalities occurred in a minority of patients and are usually mild and reversible. Severe (grade 3 and 4) thrombocytopenia and neutropenia were reported in 1,7 % and 4,2 % of patients respectively, and severe anaemia was reported in 1,1 % of patients.

During MabThera maintenance treatment (NHL) for up to 2 years, there was a higher incidence of grade 3-4 leucopenia (observation 2 %, MabThera 5 %) and neutropenia (observation 4 %, MabThera 10 %) in the MabThera arm compared to the observation arm. The incidence of grade 3 to 4 thrombocytopenia was low (observation 1 %, MabThera < 1 %). In approximately half of the patients with available data on B-cell recovery after the end of MabThera induction treatment, it took 12 months or more for their B-cell levels to return to normal values.

During treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88 % vs CHOP 79 %, R-FC 23 % vs FC 12 %), neutropenia (R-CVP 24 % vs CVP 14 %; R-CHOP 97 % vs CHOP 88 %, R-FC 30 % vs FC 19 % in previously untreated CLL), were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. There were no differences reported for

the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of MabThera were reported.

Studies in previously untreated and relapsed/refractory CLL have established that in some cases neutropenia was prolonged or with a late onset following treatment in the MabThera SC 1400 mg IV plus FC group.

In studies of MabThera in patients with Waldenstrom's macroglobulinemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

No relevant difference between the treatment arms was observed with respect to Grade 3 and 4 anaemia or thrombocytopenia. In the CLL first-line study Grade 3 and 4 anaemia was reported by 4 % of patients treated with R-FC compared to 7 % of patients receiving FC, and Grade 3 and 4 thrombocytopenia was reported by 7 % of patients in the R-FC group compared to 10 % of patients in the FC group. In the relapsed/refractory CLL study, adverse events of Grade 3 and 4 anaemia were reported in 12 % of patients treated with R FC compared to 13 % of patients receiving FC and Grade 3 and 4 thrombocytopenia was reported by 11 % of patients in the R-FC group compared to 9 % of patients in the FC group.

Cardiovascular events:

Cardiovascular events were reported in 18,8 % of patients during the treatment period. The most frequently reported events were hypotension and hypertension. Cases of grade 3 or 4 dysrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during a MabThera infusion were reported.

During maintenance treatment, the incidence of grade 3 to 4 cardiac disorders was comparable between the two treatment groups. Cardiac events were reported as serious adverse event in < 1 % of patients on observation and in 3 % of patients on MabThera: atrial fibrillation (1 %), myocardial infarction (1 %), left ventricular failure (< 1 %), myocardial ischaemia (< 1 %).

MabThera in combination with chemotherapy i.e. in the R-CHOP study the incidence of grade 3

and 4 cardiac dysrhythmias, predominantly supraventricular dysrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (6,9 % of patients) as compared to the CHOP group (1,5 % of patients). All of these dysrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease (see section 4.4).

No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4 % R-FC, 3 % FC) and in the relapsed/refractory study (4 % R-FC, 4 % FC).

Respiratory system:

Cases of interstitial lung disease, some with fatal outcome have been reported.

Neurologic disorders:

During the treatment period (induction treatment phase comprising of R-CHOP for at most eight cycles), 2 % of patients treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, 1,5 % of patients had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study (4 % R-FC, 4 % FC) and in the relapsed/refractory study (3 % R-FC, 3 % FC).

Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients underlying disease,

hypertension, immunosuppressive therapy and/or chemotherapy.

Gastrointestinal system:

Gastrointestinal perforation, in some cases leading to death, has been observed in patients receiving MabThera in combination with chemotherapy for Non-Hodgkin's lymphoma.

IgG levels:

Maintenance Treatment (NHL) up to 2 years:

After induction treatment, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant during MabThera treatment. The proportion of patients with IgG levels below the LLN was about 60 % in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36 % after 2 years).

Skin and subcutaneous tissue disorders:

Toxic Epidermal Necrolysis (Lyell's Syndrome) and Stevens-Johnson Syndrome, some with fatal outcome, have been reported very rarely.

Subpopulations – MabThera Monotherapy – 4 weeks treatment:

Elderly patients (≥ 65 years): The incidence of any adverse event and of grade 3 and 4 adverse events was similar in elderly and younger patients.

Bulky disease:

Patients with bulky disease had a higher incidence of grade 3 and 4 adverse events than patients without bulky disease (25,6 % vs 15,4 %).

The incidence of any adverse event was similar in these two groups.

Re-treatment:

The percentage of patients reporting any adverse event and grade 3 and 4 adverse events upon re-treatment with further courses of MabThera was similar to the percentage of patients reporting any adverse event and grade 3 and 4 adverse events upon initial exposure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Patients who experience overdose should have immediate interruption or reduction of their infusion and be closely monitored. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

Three patients in the MabThera SC SABRINA (BO22334) study were inadvertently administered the SC formulation through the IV route up to a maximum rituximab dose of 2 780 mg, with no untoward effect.

Patients who experience overdose or medication error with MabThera SC should be closely monitored.

In the post-marketing setting five cases of MabThera overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1,8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A30.1 Biologicals – Monoclonal Antibodies; Antineoplastic agent: ATC Code: L01XC02

MabThera subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered substances when

administered subcutaneously.

Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20. This antigen is located on pre-B and mature B lymphocytes. The antigen is expressed on >95 % of all B cell non-Hodgkin's lymphomas. CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. Following antibody binding, CD20 is not internalised or shed from the cell membrane into the environment. CD20 does not circulate in the plasma as a free antigen and thus does not compete for antibody binding.

Rituximab binds to the CD20 antigen on B lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanism of cell lysis, include complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC).

Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis. Finally, in-vitro studies have demonstrated that rituximab sensitises drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.

Peripheral B-cell counts declined to levels below normal following the first dose of rituximab. In patients treated for haematological malignancies B-cell recovery began within 6 months of treatment and generally returning to normal levels within 12 months after completion of therapy, although in some patients this did take longer. In patients with rheumatoid arthritis, the duration of peripheral B-cell depletion was variable. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether MabThera was administered as monotherapy or in combination with methotrexate. The majority of patients received further treatment prior to B cell repletion. Some patients experienced prolonged B cell depletion.

Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were noted. Of 356 patients evaluated for human anti-chimeric antibodies (HACA), 1,1 % (4 patients) were positive.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with MabThera SC 1400 mg.

Data from the development programme of MabThera subcutaneous formulation indicate that the formation of antirituximab antibodies after subcutaneous administration is comparable with that observed after intravenous administration. In the SABRINA trial (BO22334) the incidence of treatment-induced/enhanced anti-rituximab antibodies was low and similar in the intravenous and subcutaneous groups (1,9 % vs. 2 %, respectively). The incidence of treatment-induced/enhanced anti-rHuPH20 antibodies was 8 % in the intravenous group compared with 15 % in the subcutaneous group, and none of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

The overall proportion of patients found to have anti-rHuPH20 antibodies remained generally constant over the follow-up period in both cohorts.

In the SAWYER study (BO25341) the incidence of treatment-induced/enhanced anti-rituximab antibodies was similar in the two treatment arms; 15 % IV vs. 12 % SC. The incidence of treatment-induced/enhanced anti-rHuPH20 antibodies, only measured in patients in the SC arm was 12 %. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.The clinical relevance of the development of anti-rituximab antibodies or anti-rHuPH20 antibodies after treatment with MabThera subcutaneous formulation is not known.

There was no apparent impact of the presence of anti-rituximab or anti-rHuPH20 antibodies on safety or efficacy.

Clinical experience of MabThera concentrate for solution for infusion in Non-Hodgkin's lymphoma

Follicular lymphoma

Initial treatment in combination with chemotherapy:

In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m2, vincristine 1,4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for 8 cycles or MabThera 375 mg/m^2 in combination with CVP (R-CVP). MabThera was administered on the first day of each treatment cycle. A total of 321 patients (162 RCVP, 159 CVP) received therapy and were analysed for efficacy. The median follow up of patients was 53 months. RCVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6,6 months, p < 0,0001, log-rank test). The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher (p< 0,0001 Chi-Square test) in the R-CVP group (80,9 %) than the CVP group (57,2 %). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33,6 months and 14,7 months, respectively (p < 0,0001, log-rank test). The median duration of response was 37,7 months in the R-CVP group and was 13,5 months in the CVP group (p < 0,0001, log-rank test).The difference between the treatment groups with respect to overall survival showed a significant clinical difference (p=0,029, log-rank test stratified by center): survival rates at 53 months were 80,9 % for patients in the R-CVP group compared to 71,1 % for patients in the CVP group. Results from three other randomised trials using MabThera in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four trials are summarised in table 3.

Table 3 Summary of key results from four phase III randomized trials evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

Trial	**Treatment, N**	**Median FU, months**	**ORR, %**	**CR, %**	**Median TTF/PFS/ EFS**	**OS rates, %**

					mo	
M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14,7 33,6 P<0,0001	53-months 71,1 80,9 p=0,029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2,6 years Not reached p < 0,001	18-months 90 95 p = 0,016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28,8 Not reached p < 0,0001	48-months 74 87 p = 0,0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p < 0 ,0001	42-months 84 91 p = 0,029

EFS – Event Free Survival

TTP – Time to progression or death

PFS – Progression-Free Survival

TTF – Time to Treatment Failure

OS rates – survival rates at the time of the analyses

Maintenance therapy

Previously untreated follicular lymphoma

In a prospective, open label, international, multi-center, phase III trial 1193 patients with

previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1 078 patients responded to induction therapy, of which 1 018 were randomised to MabThera maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. MabThera maintenance treatment consisted of a single infusion of MabThera at 375 mg/m^2 body surface area given every 2 months until disease progression or for a maximum period of two years.

The pre-specified primary analysis was conducted at a median observation time of 25 months from randomisation, maintenance therapy with MabThera resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma (Table 4).

Significant benefit from maintenance treatment with MabThera was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) in the primary analysis (Table 4).

Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of MabThera maintenance therapy in terms of PFS, EFS, TNLT and TNCT (Table 5).

Table 5 Overview of efficacy results for MabThera maintenance vs. observation at the protocol-defined primary analysis and after 9 years median follow-up (final analysis)

	Primary analysis (median FU: 25 months)		**Final analysis** (median FU: 9.0 years)	
	Observation N=513	**MabThera** N=505	**Observation** N=513	**MabThera** N=505
Primary efficacy				

Progression-free survival (median)	NR	NR	4,06 years	10,49 years
log-rank p value	<0,0001		<0,0001	
hazard ratio (95% CI)	0,50 (0,39,0,64)		0,61 (0,52, 0,73)	
risk reduction	50 %		39 %	
Secondary efficacy				
Overall survival (median)	NR	NR	NR	NR
log-rank p value	0,7246		0,7948	
hazard ratio (95% CI)	0,89 (0,45, 1,74)		1,04 (0,77, 1,40)	
Risk reduction	11 %		-6 %	
Event-free survival (median)	38 months	NR	4,04 years	9,25 years
log-rank p value	<0,0001		<0,0001	
hazard ratio (95% CI)	0,54 (0,43, 0,69)		0,64 (0,54, 0,76)	
risk reduction	46 %		36 %	
TNLT (median)	NR	NR	6,11 years	NR
log-rank p value	0,0003		<0,0001	
hazard ratio (95% CI)	0,61 (0,46, 0,80)		0,66 (0,55, 0,78)	
risk reduction	39 %		34 %	
TNCT (median)	NR	NR	9.32 years	NR
log-rank p value	0,0011		0,0004	
hazard ratio (95% CI)	0,60 (0,44, 0,82)		0,71 (0,59, 0,86)	
risk reduction	40 %		39 %	
Overall response	55 %	74 %	61 %	79 %

rate*				
chi-squared test p value	<0,0001		<0,0001	
odds ratio (95%CI)	2,33 (1,73, 3,15)		2,43 (1,84, 3,22)	
Complete response (CR/CRu) rate*	48 %	67 %	53 %	67 %
chi-squared test p value	<0,0001		<0,0001	
odds ratio (95 % CI)	2,21 (1,65, 2,94)		2,34 (1,80, 3,03)	

* at end of maintenance/observation; final analysis results based on median follow-up of 73 months.

FU: follow-up; NR: not reached at time of clinical cut off, TNCT: time to next chemotherapy treatment; TNLT: time to next anti lymphoma treatment.

MabThera maintenance treatment provided consistent benefit in all predefined subgroups tested: gender (male, female), age (< 60 years, >= 60 years), FLIPI score (<=1, 2 or >= 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR/CRu or PR). Exploratory analyses of the benefit of maintenance treatment showed a less pronounced effect in elderly patients (> 70 years of age), however sample sizes were small.

Relapsed/Refractory follicular lymphoma

In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular lymphoma were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MabThera plus CHOP (R-CHOP, n=234).

The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to MabThera maintenance therapy (n=167) or observation (n=167). MabThera maintenance treatment consisted of a single infusion of

MabThera at 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period of two years.

The final efficacy analysis included all patients randomised to both parts of the trial. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular lymphoma when compared to CHOP (see Table 6).

Table 6 Induction phase: overview of efficacy results for CHOP vs. R-CHOP (31 months median observation time)

	CHOP	**R-CHOP**	**p-value**	**Risk Reduction[1)]**
Primary efficacy				
ORR[2)]	74 %	87 %	0,0003	Na
CR[2)]	16 %	29 %	0,0005	Na
PR[2)]	58 %	58 %	0,9449	Na

1) Estimates were calculated by hazard ratios

2) Last tumour response as assessed by the investigator. The “primary” statistical test for “response” was the trend test of CR versus PR versus non-response (p < 0,0001).

Abbreviations: NA, not available; ORR: overall response rate; CR: complete response; PR: partial response.

For patients randomised to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomisation.

Maintenance treatment with MabThera led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomisation to relapse, disease progression or death) when compared to observation alone (p< 0,0001 log-rank test). The median PFS was 42,2 months in the MabThera maintenance arm compared to 14.3 months in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61 % with MabThera maintenance treatment when compared to observation (95 % CI; 45 %-72 %). Kaplan-Meier estimated progression-free

rates at 12 months were 78 % in the MabThera maintenance group vs. 57 % in the observation group.

An analysis of overall survival confirmed the significant benefit of MabThera maintenance over observation (p=0,0039 log-rank test). MabThera maintenance treatment reduced the risk of death by 56 % (95 % CI; 22 %- 75 %).

Table 7 Maintenance phase: overview of efficacy results MabThera vs. observation (28 months median observation time)

Efficacy Parameter	**Kaplan-Meier Estimate of Median Time to Event (Months)**			**Risk Reduction**
	Observation (N = 167)	**MabThera (N=167)**	**Log-Rank p value**	
Progression-free survival (PFS)	*14,3*	*42,2*	*<0,0001*	*61 %*
Overall survival	*NR*	*NR*	*0,0039*	*56 %*
Time to new lymphoma treatment	*20,1*	*38,8*	*< 0,0001*	*50 %*
Disease-free survival[a]	*16,5*	*53,7*	*0,0003*	*67 %*
Subgroup analysis				
PFS				
CHOP	*11,6*	*37,5*	*< 0,0001*	*71 %*
R-CHOP	*22,1*	*51,9*	*0,0071*	*46 %*
CR	*14,3*	*52,8*	*0,0008*	*64 %*
PR	*14,3*	*37,8*	*< 0,0001*	*54 %*
OS				
CHOP	*NR*	*NR*	*0,0348*	*55 %*
R-CHOP	*NR*	*NR*	*0,0482*	*56 %*

NR: not reached; a: only applicable to patients achieving a CR.

The benefit of MabThera maintenance treatment was confirmed in all subgroups analysed,

regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (table 7). MabThera maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37,5 months vs. 11,6 months, p< 0,0001) as well as in those responding to R-CHOP induction (median PFS 51,9 months vs. 22,1 months, p=0,0071). Although subgroups were small, MabThera maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

Diffuse large B cell non-Hodgkin's lymphoma

In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1,4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for eight cycles, or MabThera 375 mg/m^2 plus CHOP (R-CHOP). MabThera was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months.

The two treatment groups were well balanced in baseline disease characteristics and disease status. The final analysis confirmed that R-CHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration of event-free survival (the primary efficacy parameter; where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p = 0,0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41 %. At 24 months, estimates for overall survival were 68,2 % in the R-CHOP arm compared to 57,4 % in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0,0071),

representing a risk reduction of 32 %.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76,2 % in the R-CHOP group and 62,4 % in the CHOP group (p=0,0028). The risk of disease progression was reduced by 46 % and the risk of relapse by 51 %. In all patient subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0,83 and 0,95 respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI.

5.2 Pharmacokinetic properties

Absorption

Rituximab pharmacokinetics following single dose administration of MabThera subcutaneous 375 mg/m^2, 625 mg/m^2 and 800 mg/m^2 were compared with MabThera intravenous 375 mg/m^2 in FL patients.

Following subcutaneous administration, the absorption of rituximab is slow, reaching maximal concentrations about 3 days after administration. Based on popPK analysis an absolute bioavailability of 71 % was estimated. Rituximab exposure increased dose proportional over the 375 mg/m^2 to 800 mg/m^2 subcutaneous dose range.

Pharmacokinetic parameters such as clearance, distribution volume, and elimination half-life were comparable for both formulations.

Trial BP22333 (SparkThera)

A two-stage phase Ib trial to investigate the pharmacokinetics, safety and tolerability of MabThera subcutaneous formulation in patients with follicular lymphoma (FL) as part of maintenance treatment.

In stage 2, MabThera subcutaneous formulation at a fixed dose of 1400 mg was administered as

subcutaneous injection during maintenance treatment, after at least one cycle of MabThera intravenous formulation to FL patients who had previously responded to MabThera intravenous formulation in induction.

The comparison of predicted median C_{max} data for MabThera subcutaneous formulation and intravenous formulation are summarised in Table 8.

Table 8: Trial BP22333 (SparkThera): Absorption - Pharmacokinetic parameters of MabThera SC compared to MabThera IV

	MabThera subcutaneous	MabThera intravenous
Predicted median C_{max} (q2m) µg/mL	201	209
Predicted median C_{max} (q3m) µg/mL	189	184

The median T_{max} in the MabThera subcutaneous formulation was approximately 3 days as compared to the T_{max} occuring at or close to the end of the infusion for the intravenous formulation.

Trial BO22334 (SABRINA)

MabThera subcutaneous formulation at a fixed dose of 1400 mg was administered for 6 cycles subcutaneously during induction at 3-weekly intervals, following the first cycle of MabThera intravenous formulation, in previously untreated FL patients in combination with chemotherapy. The serum rituximab C_{max} at cycle 7 was similar between the two treatment arms, with geometric mean (CV %) values of 250,63 (19,01) µg/mL and 236,82 (29,41) µg/mL for the intravenous and the subcutaneous formulations respectively, with the resulting geometric mean ratio (C_{max}, SC/C_{max}, IV) of 0,941 (90 % CI: 0,872, 1,015).

Distribution/Elimination

Geometric mean C_{trough} and geometric mean AUC from the BP22333 and BO22334 trials are summarised in Table 9.

Table 9: Distribution/Elimination - Pharmacokinetic parameters of MabThera subcutaneous

compared to MabThera intravenous

Trial BP22333 (SparkThera)				
	Geometric mean C_{trough} (q2m) µg/mL	Geometric mean C_{trough} (q3m) µg/mL	Geometric mean AUC cycle 2 (q2m) µg.day/mL	Geometric mean AUC cycle 2 (q3m) µg.day/mL
MabThera subcutaneous formulation	32,2	12,1	5430	5 320
MabThera intravenous formulation	25,9	10,9	4012	3 947
Trial BO22334 (SABRINA)				
	Geometric mean C_{trough} values at pre-dose cycle 8: µg/mL		Geometric mean AUC values at cycle 7: µg.day/mL	
MabThera subcutaneous formulation	134,6		3 778	
MabThera intravenous formulation	83,1		2 734	

In a population pharmacokinetic analysis in 403 follicular lymphoma patients who received subcutaneous and/or intravenous MabThera, single or multiple infusions of MabThera as a single agent or in combination with chemotherapy, the population estimates of nonspecific clearance (CL1), initial specific clearance (CL2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V1) were 0,194 L/day, 0,535 L/day, and 4,37 L/day, respectively. The estimated median terminal elimination half-life of MabThera subcutaneous formulation was 29,7 days (range, 9,9 to 91,2 days). The analysis data set

contained 6 003 quantifiable samples from 403 patients administered SC and/or IV rituximab in trials BP22333 (3736 samples from 277 patients) and BO22334 (2267 samples from 126 patients). Twenty nine (0,48 %) post-dose observations (all from trial BP22333) were below the quantification limit. There were no missing covariate values except baseline B-cell count. Baseline tumour load was available only in trial BO22334

Special populations

In clinical trial BO22334, an effect was observed between body size and exposure ratios reported in cycle 7, between rituximab subcutaneous formulation 1400 mg q3w and rituximab intravenous formulation 375 mg/m^2 q3w with C_{trough} ratios of 2,29;1,31 and 1,41 in patients with low, medium and high BSA, respectively (low BSA ≤ 1,70 m^2; 1,70 m^2 < medium BSA < 1,90 m^2; high BSA ≥ 1,90 m^2). The corresponding AUC ratios were 1,66, 1,17 and 1,32. There was no evidence of clinically relevant dependencies of rituximab pharmacokinetics on age and sex.

Anti-rituximab antibodies were detected in only 13 patients and did not result in any clinically relevant increase in steady-state clearance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: α, α-trehalose dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, N_2 medical gas, polysorbate 80,recombinant human hyaluronidase (rHuPH20), water for injections.

This medicinal product contains less than 1mmol sodium per dose, i.e. essentially sodium free.

6.2 Incompatibilities

No incompatibilities between MabThera SC 1400 mg and polypropylene or polycarbonate syringe material or stainless-steel transfer and injection needles have been observed.

6.3 Shelf life

Unopened vial: 30 months

After first opening: Once transferred from the vial into the syringe, the solution of MabThera subcutaneous formulation is physically and chemically stable for 48 hours at 2 °C - 8 °C and subsequently for 8 hours at 30 °C in diffuse daylight. From a microbiological point of view, the product should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions.

In-use storage times and conditions prior to use are the responsibility of the user. (see section 6.6)

6.4 Special precautions for storage

Store vials in a refrigerator between 2 - 8 °C. Do not freeze. Keep the container in the outer carton in order to protect from light. MabThera SC 1400 mg solution (once transferred from the vial into the syringe) is physically and chemically stable for 48 hours at 2 °C - 8 °C and subsequent 8 hours at 30 °C in diffused daylight.

From a microbiological point of view, the product should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 48 hours at 2 °C - 8 °C and subsequent 8 hours at 30 °C in diffused daylight.

6.5 Nature and contents of container

MabThera SC 1400 mg: Pack of 1 vial. Colourless 15 mL type 1 glass vial with a grey butyl rubber stopper with aluminium over seal and a pink plastic flip-off disc.

6.6 Special precautions for disposal and other handling

MabThera SC 1400 mg SC solution (once transferred from the vial into the syringe) is physically and chemically stable for 48 hours at 2 °C - 8 °C and subsequent 8 hours at 30 °C in diffused daylight.

MabThera SC 1400 mg SC is provided in sterile, preservative-free, non- pyrogenic, single use vials.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

24 Fricker Road

Illovo, Gauteng,

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

MabThera SC 1400 mg: 49/30.1/0466

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 26 June 2019

10. DATE OF REVISION OF THE TEXT

19 November 2020

Namibia	NS2 18/26/0023
Zimbabwe	PP 2017/9.7/5511