EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2021[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 3-6 May 2021 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 3-6 May 2021 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (17-20 May 2021) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available guidance. Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] The relevant EPITT reference number should be used in any communication related to a signal.

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The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the Questions and Answers on signal management.

1. Recommendations for update of the product information[3]

1.1. Alemtuzumab – Sarcoidosis

Authorisation procedure	Centralised
EPITT No	19638
PRAC rapporteur(s)	Anette Kirstine Stark (DK)
Date of adoption	6 May 2021

Recommendation

The PRAC has considered available evidence ascertained from EudraVigilance, the literature, nonclinical and clinical data and additional data submitted by Sanofi Belgium. Based on review of the weighted cumulative evidence, PRAC considers that a causal relation between Sarcoidosis and Alemtuzumab cannot be excluded. The PRAC recommends that the MAH for Lemtrada, Sanofi Belgium, should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below (new text underlined):

The proposal to update the SmPC and PIL is as follows (new text underlined, text to be removed struck-through).

Summary of product characteristics

4.4. Special warnings and precautions for use

Autoimmunity

Treatment may result in the formation of autoantibodies and increase the risk of autoimmune mediated conditions which may be serious and life threatening. Reported autoimmune conditions, include thyroid disorders, immune thrombocytopenic purpura (ITP), nephropathies (e.g. anti-glomerular basement membrane disease), autoimmune hepatitis (AIH), ~~and~~ acquired haemophilia A, and sarcoidosis. In the post-marketing setting, patients developing multiple autoimmune disorders after LEMTRADA treatment have been observed.

Patients who develop autoimmunity should be assessed for other autoimmune mediated conditions (see section 4.3). Patients and physicians should be made aware of the potential later onset of autoimmune disorders after the 48 months monitoring period.

[…]

4.8. Undesirable effects

SOC: Immune system disorders

Frequency uncommon: Sarcoidosis

Package leaflet

2. What you need to know before you are administered LEMTRADA

[…]

- **Autoimmune conditions**

[3] Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

[…]

More helpful information about these autoimmune conditions (and the testing for them) can be found in the LEMTRADA Patient Guide.

[…]

o Liver inflammation

Some patients have developed liver inflammation after receiving LEMTRADA. Liver inflammation can be diagnosed from the blood tests that you will be having regularly after LEMTRADA treatment. If you develop one or more of the following symptoms report this to your doctor: nausea, vomiting, abdominal pain, fatigue, loss of appetite, yellow skin or eyes, dark urine, or bleeding or bruising more easily than normal.

o Sarcoidosis
There have been reports of an immune system disorder (sarcoidosis) in patients treated with LEMTRADA. Symptoms can include persistent dry cough, shortness of breath, chest pain, fever, lymph node swelling, weight loss, skin rashes, and blurred vision.

o Other autoimmune conditions

Uncommonly, patients have experienced autoimmune conditions involving red blood cells or white blood cells. These can be diagnosed from the blood tests that you will be having regularly after LEMTRADA treatment. If you develop one of these conditions your doctor will tell you, and take appropriate measures to treat it.

[…]

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most important side effects are the autoimmune conditions described in section 2 which include:

[…]

- Thyroid disorders (very common – may affect more than 1 in 10 people): may show as excessive sweating; unexplained weight-loss or gain; eye swelling; nervousness; fast heartbeat; feeling cold; worsening tiredness; or newly occurring constipation.
- Red and white blood cells disorders (uncommon – may affect up to 1 in 100 people): diagnosed from your blood tests.
- Sarcoidosis (uncommon – may affect up to 1 in 100 people): Symptoms can include persistent dry cough, shortness of breath, chest pain, fever, lymph node swelling, weight loss, skin rashes, and blurred vision.

All of these serious side effects can start many years after you have received LEMTRADA. **If you notice any of these signs or symptoms, call your doctor right away to report them.** You will also have regular blood and urine tests to ensure that if you develop any of these conditions, they

[…]

These are the **side effects** that you may experience:

Uncommon (may affect up to 1 in 100 people)

- Sarcoidosis
- […]

1.2. Clindamycin – Acute renal failure

Authorisation procedure	Non-centralised
EPITT No	19647
PRAC rapporteur(s)	Sonja Hrabcik (AT)
Date of adoption	6 May 2021

Recommendation

Having considered the available evidence in EudraVigilance, the literature, and the data submitted by Pfizer the PRAC has agreed that the MAH(s) of clindamycin-containing medicinal products for systemic use should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

If therapy is prolonged, liver functions tests should be performed.

Acute kidney injury

Acute kidney injury, including acute renal failure, has been reported infrequently. Therefore, monitoring of renal function should be considered in patients receiving prolonged therapy, suffering from pre-existing renal dysfunction or taking concomitant nephrotoxic drugs (see section 4.8).

4.8. Undesirable effects

Renal and urinary disorders

Frequency 'not known': Acute kidney injury#

See section 4.4

Package leaflet

2. What you need to know before you take <product name>

Warnings and precautions

Acute kidney disorders may occur. Please inform your doctor about any medication you currently take and if you have any existing problems with your kidneys. If you experience decreased urine output, fluid retention causing swelling in your legs, ankles or feet, shortness of breath, or nausea you should contact your doctor immediately.

4. Possible side effects

Tell your doctor immediately if you develop:

- fluid retention causing swelling in your legs, ankles or feet, shortness of breath or nausea

1.3. COVID-19 mRNA[4] vaccine (nucleoside-modified) – Comirnaty – Localised swelling in persons with history of dermal filler injections

Authorisation procedure	Centralised
EPITT No	19674
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of adoption	6 May 2021

Recommendation

Having considered the available evidence from the cumulative review submitted by the Marketing Authorisation Holder (MAH), as well as from case reports in EudraVigiance, the PRAC has agreed that the MAH of the COVID-19 mRNA vaccine (nucleoside-modified) COMIRNATY (BioNTech Manufacturing GmbH) should submit a variation within 2 weeks from the publication of the PRAC recommendation, to amend the product information as described below (new text underlined):

Summary of the product characteristics

4.8. Undesirable effects

[The following text should be inserted in Table 1: Adverse reactions from Comirnaty clinical trials and post-authorisation experience]

General disorders and administration site conditions

Not known: Facial swelling*

[The following text should be inserted as footnote to Table 1]

*Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been reported in the post-marketing phase.

Package leaflet

Section 4 – Possible side effects

Not known (cannot be estimated from the available data)

Swelling of the face (swelling of the face may occur in patients who have had facial dermatological fillers)

1.4. Secukinumab – Henoch-Schonlein purpura

Authorisation procedure	Centralised
EPITT No	19640
PRAC rapporteur(s)	Eva A. Segovia (ES)
Date of adoption	6 May 2021

Recommendation

The PRAC has considered the available evidence in EudraVigilance, the literature, and the data submitted by Novartis regarding the risk of vasculitis associated with secukinumab. The PRAC agrees

[4] Messenger ribonucleic acid

that the available information is considered sufficient to support a causal association. Therefore, the PRAC recommends that the marketing authorisation holder for secukinumab (Novartis) should submit a variation within 2 months from the publication of the adopted recommendation to amend the product information as described below (new text **underlined and in bold**).

Summary of product characteristics

4.8 Undesirable effects

Tabulated list of adverse reactions

Table 2 List of adverse reactions in clinical studies[1)] and post-marketing experience

System Organ Class	Frequency	Adverse reaction
Skin and Subcutaneous Tissue Disorders	Uncommon	Urticaria
	Rare	Exfoliative dermatitis [2)]
		Hypersensitivity vasculitis

Package leaflet

4. Possible side effects

Other side effects

Rare (may affect up to 1 in 1,000 people)

Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps (vasculitis)

1.5. Sulfamethoxazole, trimethoprim (co-trimoxazole) – Acute respiratory distress syndrome (ARDS)

Authorisation procedure	Non-centralised
EPITT No	19625
PRAC rapporteur(s)	Nikica Mirošević Skvrce (HR)
Date of adoption	6 May 2021

Recommendation

Having considered the available evidence, including the data submitted by the relevant MAHs, the PRAC has agreed that the MAHs of co-trimoxazole containing medicinal products should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below (new text underlined).

The wording applies to all co-trimoxazole containing medicinal products. If there is a reference to lung infiltration or respiratory toxicity already included in section 4.4, the proposed recommendation on ARDS should supersede current wording in place. The same applies for the PIL.

Summary of product characteristics

4.4. Special warnings and precautions for use

Respiratory toxicity

Very rare, severe cases of respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS), have been reported during co-trimoxazole treatment. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function may be preliminary signs of ARDS. In such circumstances, co-trimoxazole should be discontinued and appropriate treatment given.

Package leaflet

2. What you need to know before you take <product name>

Warnings and precautions

If you develop an unexpected worsening of cough and shortness of breath, inform your doctor immediately.

1.6. Sulfamethoxazole, trimethoprim (co-trimoxazole) – Haemophagocytic lymphohistiocytosis

Authorisation procedure	Non-centralised
EPITT No	19655
PRAC rapporteur(s)	Nikica Mirošević Skvrce (HR)
Date of adoption	6 May 2021

Recommendation *[see also section 3]*

The PRAC has considered the available evidence in EudraVigilance, the literature, and the data submitted by Roche/ Eumedica, Aspen Pharma and Teva regarding the risk of Haemophagocytic lymphohistiocytosis (HLH) with sulfamethoxazole/trimethoprim in combination. The PRAC agrees that the available information is considered sufficient to support a warning statement in the product information. Therefore, the PRAC recommends that the marketing authorisation holders for medicinal products containing sulfamethoxazole/trimethoprim in combination should submit a variation within 2 months from the publication of the adopted recommendation to amend the product information as described below (new text **underlined and in bold**).

Haemophagocytic lymphohistiocytosis should also be added as important safety concern and should be monitored and analysed by marketing authorisation holders in PSURs.

Summary of product characteristics

4.4. Special warnings and precautions for use

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported very rarely in patients treated with co-trimoxazole. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and

haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, co-trimoxazole treatment should be discontinued.

Package leaflet

2. What you need to know before you take <product name>

Warnings and precautions

Haemophagocytic lymphohistiocytosis

There have been very rare reports about excessive immune reactions due to a dysregulated activation of white blood cells resulting in inflammations (haemophagocytic lymphohistiocytosis), which can be life-threatening if not diagnosed and treated early. If you experience multiple symptoms such as fever, swollen glands, feeling weak, lightheaded, shortness of breath, bruising, or skin rash simultaneously or with a slight delay, contact your doctor immediately.

1.7. Tramadol; tramadol, dexketoprofen; tramadol, paracetamol – Serotonin syndrome

Authorisation procedure	Non-centralised
EPITT No	19635
PRAC rapporteur(s)	Tiphaine Vaillant (FR)
Date of adoption	6 May 2021

Recommendation

Having considered the available evidence and following the assessment of the data submitted by the concerned Marketing Authorisation Holders (MAHs), the PRAC has agreed that the product information for tramadol should be updated to reflect the risk of serotonin syndrome.

All the MAHs of products containing tramadol, including the fixed combinations of tramadol-paracetamol and tramadol-dexketoprofen, should submit a variation within two months from the publication of the PRAC recommendation, to amend the product information as described here (new text underlined)*:

Summary of product characteristics

4.4. Special warnings and precautions for use

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin ~~toxicity~~ syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8). ~~Serotonin syndrome is likely when one of the following is observed:~~

~~• Spontaneous clonus~~

~~• Inducible or ocular clonus with agitation or diaphoresis~~

~~• Tremor and hyperreflexia~~

~~• Hypertonia and body temperature > 38 ºC and inducible or ocular clonus~~

~~Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.~~

4.8. Undesirable effects

Nervous system disorders

Not known: Serotonin syndrome

4.9. Overdose

Serotonin syndrome has also been reported.

Package leaflet

2. What you need to know before you take <product name>

Warnings and precautions

Talk to your doctor before taking <product name> if you:

Suffer from depression and you are taking antidepressants as some of them may interact with tramadol (see 'Other medicines and <product name>').

[…]

There is a small risk that you may experience a so-called serotonin syndrome that can occur after having taken tramadol in combination with certain antidepressants or tramadol alone. Seek medical advice immediately if you have any of the symptoms related to this serious syndrome (see section 4 'Possible side effects').

Other medicines and <product name>

[…]

The risk of side effects increases,

[..]

- if you are taking certain antidepressants, <product name> may interact with these medicines and you may experience serotonin syndrome (see section 4 'Possible side effects'). ~~symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C.~~

4. Possible side effects

Not known: frequency cannot be estimated from the available data

Serotonin syndrome, that can manifest as mental status changes (e.g. agitation, hallucinations, coma), and other effects, such as fever, increase in heart rate, unstable blood pressure, involuntary twitching, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) (see section 2 'What you need to know before you take <product name>').

** Due to differences in the national SmPCs and Package Leaflets, it is acknowledged that further text already included in the product information will have to be modified/adjusted in order to accommodate the new text stated in this PRAC recommendation.*

1.8. COVID-19 vaccine (Ad26.COV2-S [recombinant]) - COVID-19 Vaccine Janssen - Embolic and thrombotic events[5]

Authorisation procedure	Centralised
EPITT No	19689
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	6 May 2021

Recommendation *[see also section 3]*

The PRAC has reviewed additional evidence concerning thromboembolic events in association with Covid-19 Janssen vaccine, with particular focus on cases with combination of thrombosis and thrombocytopenia. Recently, this condition has been named 'thrombosis with thrombocytopenia syndrome (TTS)'. The updated review has included data ascertained from newly identified spontaneously reported cases both in EudraVigilance and other sources, clinical, pre-clinical and literature data and data from the marketing authorisation holder (MAH).

Based on review of the available evidence the PRAC considers that further updates to the product information are required including information to outline that patients who are diagnosed with

[5] Translations in all EU languages have already been included in the COVID-19 Vaccine Janssen product information.

thrombocytopenia within three weeks of vaccination should be actively investigated for signs of thrombosis. Similarly, updates have been included in order to reflect that patients who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia. Furthermore, the condition should be renamed 'thrombosis with thrombocytopenia syndrome'.

The PIL should be updated to include information at the start of section 4, concerning the signs and symptoms of thrombosis with thrombocytopenia.

The PRAC has also reviewed preclinical and literature data concerning possible pathophysiological mechanisms. A plan concerning additional pharmacovigilance activities, aimed to further elucidate potential pathophysiological mechanism(s) for TTS, and for quantification of the magnitude of the risk, should be submitted.

Following further consideration, the text regarding TTS which was added to section 6 of the package leaflet following the extraordinary PRAC meeting on 20 April 2021, should be removed. The reason is that it is not considered to fulfil the purpose of the information to be added to that section of the package leaflet, as per the requirements specified in QRD template 10.2.

The PRAC recommends that the MAH for Covid-19 Vaccine Janssen (Janssen-Cilag International NV) should submit a variation by 7th May 2021 (8am) to amend the product information as described below (new text underlined/text to be removed with strikethrough):

Section 4.4

~~Thrombocytopenia and coagulation disorders~~ **Thrombosis with thrombocytopenia syndrome**

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis as well as arterial thrombosis concomitant with thrombocytopenia. Fatal outcome has been reported. These cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain, leg swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, seizures, mental status change or blurred vision after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Individuals diagnosed with thrombocytopenia within 3 weeks after vaccination with COVID-19 Vaccine Janssen should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 3 weeks of vaccination should be evaluated for thrombocytopenia.

Package leaflet

Section 2

[…]

Blood disorders

A combination of blood clots and low levels of 'platelets' (cells that help blood to clot) in the blood has been observed very rarely following vaccination with COVID-19 Vaccine Janssen. This includes severe cases with blood clots, including in unusual locations such as the brain, liver, bowel and spleen, in some cases in combination with bleeding. These cases occurred within the first three weeks following vaccination and occurred mostly in women below 60 years of age. Fatal outcome has been reported.

Seek immediate medical attention if you experience severe or persistent headaches, seizures (fits), mental status change or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, pinpoint round spots beyond the site of vaccination, develop shortness of breath, chest pain, leg pain, leg swelling, or persistent abdominal pain. Inform your health care provider that you have recently received COVID-19 Vaccine Janssen.

Section 4

Like all vaccines, COVID-19 Vaccine Janssen can cause side effects, although not everybody gets them. Most of the side effects occur in the 1 or 2 days of getting the vaccination.

Get medical attention immediately if within 3 weeks of vaccination you get any of the following symptoms:

- experience a severe or persistent headache, blurred vision, mental status changes or seizures (fits)
- develop shortness of breath, chest pain, leg swelling, leg pain or persistent abdominal pain
- notice unusual skin bruising or pinpoint round spots beyond the site of vaccination

Get urgent medical attention if you get symptoms of a severe allergic reaction. …. **…//**

Section 6

The following information is intended for healthcare professionals only:

[…]

- ~~Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain, leg swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, seizures, mental status change or blurred vision after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention. Thrombosis in combination with thrombocytopenia requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.~~

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
COVID-19 mRNA[6] vaccine (nucleoside-modified) - COVID-19 Vaccine Moderna	Immune thrombocytopenia (19679)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 4 June 2021)	Moderna Biotech Spain, S.L.
COVID-19 vaccine (ChAdOx1-S [recombinant]) - Vaxzevria	Immune thrombocytopenia (19678)	Jean-Michel Dogné (BE)	Supplementary information requested (submission by 4 June 2021)	AstraZeneca AB
COVID-19 vaccine (ChAdOx1-S [recombinant]) - Vaxzevria	Acute macular outer retinopathy (19703)[7]	Jean-Michel Dogné (BE)	Supplementary information requested (submission by 15 June 2021)	AstraZeneca AB
Ipilimumab	Transverse myelitis (19677)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 2 June 2021)	Bristol-Myers Squibb Pharma EEIG
Labetalol	Nipple pain and suppressed lactation (19639)	Pernille Harg (NO)	Supplementary information requested (submission by 1 July 2021)	Aspen Pharma
Methotrexate	Progressive multifocal leukoencephalopathy (PML) (18473)	Martin Huber (DE)	Supplementary information requested (submission by 1 July 2021)	Pfizer; Nordic; all MAHs who previously submitted data
Ponatinib	Panniculitis (19681)	Annika Folin (SE)	Supplementary information requested (submission by 1 July 2021)	Incyte Biosciences
Warfarin	Anticoagulant-related nephropathy (19652)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 28 July 2021)	Bristol-Myers Squibb, Teofarma S.r.l.

[6] Messenger ribonucleic acid
[7] Signal discussed at the PRAC ORGAM teleconference of 20 May 2021

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
COVID-19 vaccine (Ad26.COV2-S [recombinant]) - COVID-19 Vaccine Janssen	Embolic and thrombotic events (19689)	Ulla Wändel Liminga (SE)	· See section 1.8 · Update the risk management plan (RMP)	Janssen-Cilag International NV
Eliglustat	Erectile dysfunction (19644)	Eva A. Segovia (ES)	Routine pharmacovigilance	Genzyme Europe BV
Immune checkpoint inhibitors: atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; pembrolizumab; nivolumab	Immune-mediated cystitis (19610)	Menno van der Elst (NL)	Submit a proposed wording to amend the product information (submission by 4 June 2021)	Merck Sharp & Dohme B.V.; Bristol-Myers Squibb Pharma EEIG; AstraZeneca AB; Merck Europe B.V.; Regeneron Ireland U.C.; Roche Registration GmbH
Romosozumab	Cardiac arrhythmia (19629)	Tiphaine Vaillant (FR)	· Update the risk management plan (RMP) · Update the list of safety concerns within the PSUR	UCB Pharma S.A.
Sulfamethoxazole, trimethoprim (co-trimoxazole)	Haemophagocytic lymphohistiocytosis (HLH) (19655)	Nikica Mirošević Skvrce (HR)	· See section 1.6 · Add HLH as important safety concern and monitor in PSURs	MAHs of medicinal products containing sulfamethoxazole/trimethoprim in combination