2 August 2021 [1]
EMA/PRAC/380226/2021 Corr[2]
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 5-8 July 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 5-8 July 2021 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][3] 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 (19-22 July 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.

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] An introductory paragraph in the PRAC recommendation for donepezil was added on 3 August 2021 (see page 3).
[3] The relevant EPITT reference number should be used in any communication related to a signal.

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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.

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[4]

1.1. Donepezil – Cardiac conduction disorders including QT prolongation and Torsade de Pointes

Authorisation procedure	Non-centralised
EPITT No	19667
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	8 July 2021

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC considers that the causal relationship between donepezil and QT interval prolongation and Torsade de Pointes is at least a reasonable possibility and has agreed that the MAH of donepezil -containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined)[5]:

Summary of product characteristics

4.4. Special warnings and precautions for use

Cardiovascular conditions

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block.

There have been reports of syncope and seizures. In investigating such patients, the possibility of heart block or long sinusal pauses should be considered.

<u>There have been post-marketing reports of QTc interval prolongation and Torsade de Pointes (see sections 4.5 and 4.8). Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.</u>

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

<u>Cases of QTc interval prolongation and Torsade de Pointes have been reported for donepezil. Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring (ECG) may be required. Examples include:</u>

<u>Class IA antiarrhythmics (e.g. quinidine)</u>

<u>Class III antiarrhythmics (e.g. amiodarone, sotalol)</u>

<u>Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline)</u>

[4] Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.
[5] Paragraph added on 3 August 2021 (missing in the initial version published on 2 August 2021).

Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone)

Certain antibiotics (e.g. clarithromycin, erythromycin, levofloxacin, moxifloxacin)

4.8. Undesirable effects

Tabulated list of adverse reactions

SOC Cardiac disorders:

uncommon: Bradycardia

rare: Sino-atrial Block; Atrioventricular Block

Frequency not known: Polymorphic ventricular tachycardia including Torsade de Pointes; Electrocardiogram QT interval prolonged

SOC Injury and poisoning:

common: Accidents including falls

Package leaflet

2. What you need to know before you take [product name]

Warnings and precautions

Talk to your doctor or pharmacist before taking [product name] if you have or have had:

a heart condition (such as irregular or very slow heart beat, heart failure, myocardial infarction)

a heart condition called 'prolonged QT interval' or a history of certain abnormal heart rhythms called Torsade de Pointes or if anyone in your family have 'prolonged QT interval'

low levels of magnesium or potassium in your blood

Other medicines and [product name]

In particular it is important to tell your doctor if you are taking any of the following types of medicines:

medicines for heart rhythm problems (e.g. amiodarone, sotalol, and quinidine)

depression (e.g. citalopram, escitalopram, amitriptyline), medicines for psychoses (e.g. pimozide, sertindole, ziprasidone), medicines for bacterial infections (such as clarithromycin, erythromycin, levofloxacin, moxifloxacin)

4. Possible side effects

Frequency not known:

Changes in the heart activity which can be seen on an electro-cardiogram (ECG) called 'prolonged QT interval'

Fast, irregular heart beat, fainting which could be symptoms of a life-threatening condition known as Torsade de Pointes

Common side effects:

accidents (patients may be more prone to falls and accidental injury)

1.2. Immune checkpoint inhibitors: atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; pembrolizumab; nivolumab – Immune-mediated cystitis

Authorisation procedure	Centralised
EPITT No	19610
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of adoption	8 July 2021

Recommendation

Considering the available evidence (e.g. EudraVigilance, literature), as well as a plausible mechanism of action a potential class effect of immune-mediated non-infectious cystitis induced by treatment with check point inhibitors is considered sufficient.

Therefore, the PRAC concluded that the Marketing Authorisation Holders (MAHs) of Keytruda (Merck Sharp & Dohme B.V.), Opdivo and Yervoy (Bristol-Myers Squibb Pharma EEIG), Tecentriq (Roche Registration GmbH), Bavencio (Merck Europe B.V.), Imfinzi (AstraZeneca AB) and Libtayo (Regeneron Ireland U.C.) should submit should submit a variation within 2 months, to amend the product information as described below (new text to be added underlined, text to be removed ~~strike-through~~):

For Keytruda (pembrolizumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'rare' in the column for monotherapy within table 2 'adverse reactions in patients treated with pembrolizumab'.

Package leaflet

4. Possible side effects

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the list of adverse reactions with a frequency 'rare'.

For Opdivo (nivolumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'rare' for nivolumab monotherapy in table 6 'Adverse reactions with nivolumab monotherapy'.

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'uncommon' for nivolumab in combination with ipilimumab in table 7 'Adverse reactions with nivolumab in combination with ipilimumab' and in table 8 'Adverse reactions with nivolumab in combination with ipilimumab and chemotherapy'.

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'rare' in table 9 'Adverse reactions with nivolumab in combination with cabozantinib'.

Package leaflet

4. Possible side effects

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the list of adverse reactions with a frequency 'rare' for treatment with Opdivo alone.

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the list of adverse reactions with a frequency 'uncommon' for treatment with Opdivo in combination with other anti-cancer medicines.

For Yervoy (ipilimumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'uncommon' in table 4 'Adverse reactions in patients with advanced melanoma treated with ipilimumab 3 mg/kg'.

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'uncommon' for nivolumab in combination with ipilimumab in table 5 'Adverse reactions with ipilimumab in combination with nivolumab' and in table 6 'Adverse reactions with ipilimumab in combination with nivolumab and chemotherapy'.

Package leaflet

4. Possible side effects

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the lists of adverse reactions with a frequency 'uncommon' for treatment with ipilimumab monotherapy respectively ipilimumab combination therapy.

For Tecentriq (atezolizumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Other immune-related adverse reactions

Given the mechanism of action of atezolizumab, other potential immune-related adverse reactions may occur, including noninfective cystitis.

Evaluate all suspected immune-related adverse reactions to exclude other causes. Patients should be monitored for signs and symptoms of immune-related adverse reactions and, based on the severity of the reaction, managed with treatment modifications and corticosteroids as clinically indicated (see section 4.2 and section 4.8).

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'not known' in the column for monotherapy within table 2 'Summary of adverse reactions occurring in patients treated with atezolizumab'

Package leaflet

4. Possible side effects

The following side effects have been reported in clinical trials with Tecentriq used alone:
Very common: may affect more than 1 in 10 people
[…] […]
• urinary tract infection
[…]
Other side effects that have been reported (frequency not known):

Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.

For Bavencio (avelumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'rare' in table 2 'Adverse reactions in patients treated with avelumab as monotherapy'.

Package leaflet

4. Possible side effects

Bavencio acts on your immune system and may cause inflammation in parts of your body (see section 2). Inflammation may cause serious damage to your body and some inflammatory conditions may lead to death and need treatment or withdrawal of Bavencio.

Seek urgent medical attention if you experience inflammation in any part of your body or if you have any of the following signs or symptoms, or if they get worse.

[…]

Do not try to treat yourself with other medicines.

Other side effects

Some side effects may not have symptoms and may only be discovered through blood tests.

The following side effects have been reported in clinical trials with avelumab alone:

Very common (may affect more than 1 in 10 people)

[…] […]

Rare (may affect up to 1 in 1000 people)

- Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

For Imfinzi (durvalumab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'rare' in the column for Imfinzi monotherapy within table 3 'Adverse drug reactions in patients treated with Imfinzi monotherapy and Imfinzi in combination with chemotherapy'

Package leaflet

4. Possible side effects

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the list of adverse reactions with a frequency 'rare'.

For Libtayo (cemiplimab)

Summary of product characteristics

4.4. Special warnings and precautions for use

Addition of 'cystitis noninfective' in the paragraph on other immune-related reactions with a cross-reference to sections 4.2 and 4.8.

4.8. Undesirable effects

Addition of 'cystitis noninfective' as ADR in the SOC Renal and urinary disorders with a frequency 'not known' in table 2 'Tabulated list of adverse reactions in patients treated with cemiplimab'.

Package leaflet

4. Possible side effects

Addition of 'Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.' among the list of adverse reactions with a frequency 'not known'.

1.3. Octreotide – Pancreatic exocrine insufficiency

Authorisation procedure	Non-centralised
EPITT No	19661
PRAC rapporteur(s)	Ronan Grimes (IE)
Date of adoption	8 July 2021

Recommendation *[see also section 3]*

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that:

1) In order to minimise the risk of underdiagnosis and delayed treatment of concomitant Pancreatic exocrine insufficiency (PEI) which occurs frequently in patients receiving octreotide for neuroendocrine tumours, the MAH(s) of octreotide-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):

Summary of product characteristics

4.4. Special warnings and precautions for use

Pancreatic function:

Pancreatic exocrine insufficiency (PEI) has been observed in some patients receiving octreotide therapy for gastroenteropancreatic neuroendocrine tumours. Symptoms of PEI can include steatorrhea, loose stools, abdominal bloating and weight loss. Screening and appropriate treatment for PEI according to clinical guidelines should be considered in symptomatic patients.

Package leaflet

2. What you need to know before you take [product name]

Test and checks

Your doctor may wish to check your pancreatic enzyme function.

1.4. COVID-19 mRNA[6] vaccine (nucleoside-modified) – Comirnaty – Myocarditis and pericarditis[7]

Authorisation procedure	Centralised
EPITT No	19712
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of adoption	8 July 2021

Recommendation *[see also section 3]*

Having considered the available evidence from the data provided by the Marketing Authorisation Holder (MAH) and from the EudraVigilance database, including data from clinical trials, post-marketing experience, the literature and from observed to expected analyses, the PRAC has agreed that based on the evidence assessed, a causal association between Comirnaty and myocarditis/pericarditis is considered of at least a reasonable possibility. The PRAC has agreed that the MAH for Comirnaty (BioNTech Manufacturing GmbH) should address the below recommendation:

The MAH should submit by 12 July 2021, 9 a.m. CEST a variation to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

4.8. Undesirable effects

"Myocarditis" and "Pericarditis" in SOC: "Cardiac disorders" with frequency "unknown"

Package leaflet

2. What you need to know before you are given Comirnaty

Warnings and precautions

[6] Messenger ribonucleic acid
[7] Translations in all EU languages have already been included in the Comirnaty product information.

Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have been reported after vaccination with Comirnaty. The cases have primarily occurred within two weeks following vaccination, more often after the second vaccination, and more often occurred in younger men. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

4. Possible side effects

Frequency "unknown": Inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain.

1.5. COVID-19 mRNA[8] vaccine (nucleoside-modified) – Spikevax (previously COVID-19 Vaccine Moderna) – Myocarditis and pericarditis[9]

Authorisation procedure	Centralised
EPITT No	19713
PRAC rapporteur(s)	Hans Christian Siersted (DK)
Date of adoption	8 July 2021

Recommendation *[see also section 3]*

Having considered the available evidence from the data provided by the Marketing Authorisation Holder (MAH) and from the EudraVigilance database, including data from clinical trials, post-marketing experience, the literature and from observed to expected analyses, the PRAC has agreed that based on the evidence assessed, a causal association between Spikevax and myocarditis/pericarditis is considered of at least a reasonable possibility. The PRAC has agreed that the MAH for Spikevax (Moderna Biotech Spain, S.L.) should address the below recommendation:

The MAH should submit by 12 July 2021, 9 a.m. CEST a variation to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Spikevax. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms

[8] Messenger ribonucleic acid
[9] Translations in all EU languages have already been included in the Spikevax product information.

indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

4.8. Undesirable effects

"Myocarditis" and "Pericarditis" in SOC: "Cardiac disorders" with frequency "unknown"

Package leaflet

2. What you need to know before you are given Spikevax

Warnings and precautions

Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have been reported after vaccination with Spikevax. The cases have primarily occurred within two weeks following vaccination, more often after the second vaccination, and more often occurred in younger men. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

4. Possible side effects

Frequency "unknown": Inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Atezolizumab	Cholangitis sclerosing (19708)	Márcia Sofia Sanches de Castro Lopes Silva (PT)	Assess in the next PSUR (submission by 26 July 2021)	Roche Registration GmbH
COVID-19 mRNA[10] vaccine (nucleoside-modified) - Comirnaty	Erythema multiforme (19721)[11]	Menno van der Elst (NL)	Supplementary information requested (submission by 27 August 2021)	BioNTech Manufacturing GmbH
COVID-19 mRNA[8] vaccine (nucleoside-modified) - Comirnaty	Glomerulonephritis and nephrotic syndrome (19722) [9]	Menno van der Elst (NL)	Supplementary information requested (submission by 27 August 2021)	BioNTech Manufacturing GmbH
COVID-19 mRNA[8] vaccine (nucleoside-modified) - Spikevax (previously COVID-19 Vaccine Moderna)	Erythema multiforme (19720)[9]	Hans Christian Siersted (DK)	Supplementary information requested (submission by 27 August 2021)	Moderna Biotech Spain, S.L.
COVID-19 mRNA[8] vaccine (nucleoside-modified) - Spikevax (previously COVID-19 Vaccine Moderna)	Glomerulonephritis and nephrotic syndrome (19724) [9]	Hans Christian Siersted (DK)	Supplementary information requested (submission by 27 August 2021)	Moderna Biotech Spain, S.L.
COVID-19 mRNA[8] vaccine (nucleoside-modified) - Spikevax (previously COVID-19 Vaccine Moderna)	Immune thrombocytopenia (19679)	Hans Christian Siersted (DK)	Assess in the next PSUR (submission by 26 August 2021)	Moderna Biotech Spain, S.L.

[10] Messenger ribonucleic acid
[11] Signal discussed at the PRAC ORGAM meeting of 22 July 2021

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ertapenem	Toxic encephalopathy in patients with renal impairment (19498)	Ana Sofia Diniz Martins (PT)	Supplementary information requested (submission by 25 August 2021)	Merck Sharp & Dohme B.V.
Propylthiouracil	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19692)	Maia Uusküla (EE)	Supplementary information requested (submission by 25 August 2021)	MAHs of propylethiluracil containing products

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
COVID-19 mRNA[12] vaccine (nucleoside-modified) – Comirnaty	Myocarditis and pericarditis (19712)	Menno van der Elst (NL)	· See section 1.4 · Distribute a direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the CHMP · Provide responses to list of questions (submission by 2 August 2021) · Update the risk management plan (RMP)	BioNTech Manufacturing GmbH
COVID-19 mRNA[10] vaccine (nucleoside-modified) - Spikevax (previously COVID-19 Vaccine Moderna)	Myocarditis and pericarditis (19713)	Hans Christian Siersted (DK)	· See section 1.5 · Distribute a direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the CHMP · Provide supplementary information (submission by 2 August 2021)	Moderna Biotech Spain, S.L.

[12] Messenger ribonucleic acid

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
			· Update the risk management plan (RMP)	
COVID-19 vaccine (ChAdOx1-S [recombinant]) - Vaxzevria	Immune thrombocytopenia (19678)	Jean-Michel Dogné (BE)	· Update the risk management plan (RMP) · Provide responses to list of questions (submission by 27 August 2021) · Provide anti-PF4 antibody test results in MSSRs	AstraZeneca AB
COVID-19 vaccine (ChAdOx1-S [recombinant]) - Vaxzevria	Acute macular outer retinopathy (19703)	Jean-Michel Dogné (BE)	· Update the risk management plan (RMP) · Review in MSSR (no later than the submission due in October 2021)	AstraZeneca AB
Octreotide	Pancreatic exocrine insufficiency (19661)	Ronan Grimes (IE)	· See section 1.3 · Assess in the next PSUR (submission by 28 September 2023)	MAH of octreotide-containing medicinal products
Olaparib	Pneumocystis jirovecii pneumonia (19651)	Ilaria Baldelli (IT)	Monitor in PSUR	AstraZeneca AB