25 October 2021[1]
EMA/PRAC/540066/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 27-30 September 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 27-30 September 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 (11-14 October 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. COVID-19 mRNA[4] vaccine (nucleoside-modified) – Comirnaty – Erythema multiforme

Authorisation procedure	Centralised
EPITT No	19721
PRAC rapporteur	Menno van der Elst (NL)
Date of adoption	30 September 2021

Recommendation

Having considered the available evidence from the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of the COVID-19 mRNA vaccine (nucleoside-modified) COMIRNATY (BioNTech Manufacturing GmbH) should submit a variation by 1 November 2021, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects
SOC: "Skin and subcutaneous tissue disorders"

"Erythema multiforme" with frequency "Not Known"

Package leaflet

4. Possible side effects

Frequency "Not known": a skin reaction that causes red spots or patches on the skin, that may look like a target or "bulls-eye" with a dark red centre surrounded by paler red rings (erythema multiforme).

1.2. COVID-19 mRNA[4] vaccine (nucleoside-modified) – Spikevax – Erythema multiforme

Authorisation procedure	Centralised
EPITT No	19720
PRAC rapporteur	Hans Christian Siersted (DK)
Date of adoption	30 September 2021

Recommendation

Having considered the available evidence from the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of the COVID-19 mRNA vaccine (nucleoside-modified) Spikevax (Moderna Biotech Spain, S.L) should submit a variation by 1 November 2021, to amend the product information as described below (new text underlined):

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

Summary of product characteristics

4.8. Undesirable effects

SOC: "Skin and subcutaneous tissue disorders"

"Erythema multiforme" with frequency "Not Known"

Package leaflet

4. Possible side effects

Frequency "Not known": a skin reaction that causes red spots or patches on the skin, that may look like a target or "bulls-eye" with a dark red centre surrounded by paler red rings (erythema multiforme).

1.3. COVID-19 vaccine (ChAdOx1-S [recombinant]) – Vaxzevria – Immune thrombocytopenia

Authorisation procedure	Centralised
EPITT No	19678
PRAC rapporteur	Jean-Michel Dogné (BE)
Date of adoption	30 September 2021

Recommendation *[see also section 3]*

Having considered the available evidence, including the responses submitted by the MAH for Vaxzevria (AstraZeneca AB), the PRAC has agreed that there is at least a reasonable possibility that vaccination with Vaxzevria may be associated with cases of thrombocytopenia including immune thrombocytopenia and that healthcare professionals should be aware of this risk, in particular in patients with a history of a thrombocytopenic disorder.

Update of the product information

The MAH for Vaxzevria (AstraZeneca AB) should submit a variation by 13 October 2021, to amend the product information as described below (new text underlined, text to be removed with ~~strikethrough~~).

Summary of product characteristics

4.4. Special warnings and precautions for use

Coagulation disorders

Thrombosis with thrombocytopenia syndrome~~ and coagulation disorders~~

Thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first three weeks following vaccination.

Thrombocytopenia

Cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been reported after receiving Vaxzevria, typically within the first four weeks after vaccination. Very rarely, these presented with very low platelet levels (<20,000 per µL) and/or were associated with bleeding. Some of these cases occurred in individuals with a history of immune thrombocytopenia. Cases with fatal outcome have been reported. If an individual has a history of a thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination.

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 swelling, leg pain, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, blurred vision, confusion or seizures after vaccination, or who experiences spontaneous bleeding, skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

Individuals diagnosed with thrombocytopenia within three weeks after vaccination with Vaxzevria, should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within three weeks of vaccination should be evaluated for thrombocytopenia.

TTS 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.

4.8. Undesirable effects

Table 1 Adverse drug reactions

MedDRA SOC	Frequency	Adverse Reactions
Blood and lymphatic system disorders	Common	Thrombocytopenia[a]
	Uncommon	Lymphadenopathy
	Not known	Immune thrombocytopenia[b]
(…)		
General disorders and administration site conditions	Very common	Injection site tenderness Injection site pain Injection site warmth Injection site pruritus Injection site bruising[bc] Fatigue Malaise Feverishness Chills
	Common	Injection site swelling Injection site erythema Fever[cd] Influenza-like illness Asthenia

[a] In clinical trials, transient mild thrombocytopenia was commonly reported (see section 4.4).
[b] Cases have been reported post-marketing (see also section 4.4).
[bc] Injection site bruising includes injection site haematoma (uncommon)
[cd] Measured fever ≥38°C
*Severe and very rare cases of thrombosis with thrombocytopenia syndrome have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis (see section 4.4).

Package leaflet

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

Blood disorders

Very rare blood clots in combination with low level of blood platelets, in some cases together with bleeding, has been observed following vaccination with Vaxzevria. This included some severe cases with blood clots in different or unusual locations (e.g. brain, bowel, liver, spleen) and excessive clotting or bleeding throughout the body. The majority of these cases occurred within the first three weeks following vaccination. Some cases had a fatal outcome.

Very low levels of blood platelets (immune thrombocytopenia), that can be associated with bleeding, have been reported very rarely, usually within the first four weeks following vaccination with Vaxzevria.

Seek immediate medical attention if you develop shortness of breath, chest pain, leg swelling, leg pain or persistent abdominal pain following vaccination (see section 4).

Also, seek immediate medical attention if you experience after a few days following vaccination severe or persistent headaches, blurred vision, confusion or seizures (fits) after vaccination, or experience unexplained bleeding or skin bruising or pinpoint round spots beyond the site of vaccination which appears after a few days (see section 4).

4. Possible side effects

Common (may affect up to 1 in 10 people)
- swelling or redness where the injection is given
- fever (≥38°C)
- being sick (vomiting) or diarrhoea
- mild and transient decreased ~~low~~ level of blood platelets (laboratory findings)
- pain in legs or arms
- flu-like symptoms, such as high temperature, sore throat, runny nose, cough and chills
- physical weakness or lack of energy

Not known (cannot be estimated from the available data)
- severe allergic reaction (anaphylaxis)
- hypersensitivity
- rapid swelling under the skin in areas such as the face, lips, mouth and throat (which may cause difficulty in swallowing or breathing)
- capillary leak syndrome (a condition causing fluid leakage from small blood vessels)
- very low levels of blood platelets (immune thrombocytopenia) that can be associated with bleeding (see section 2, Blood Disorders)

1.4. Piperacillin; piperacillin, tazobactam – Haemophagocytic lymphohistiocytosis

Authorisation procedure	Non-centralised
EPITT No	19676
PRAC rapporteur	Marek Juračka (SK)
Date of adoption	30 September 2021

Recommendation *[see also section 3]*

PRAC has agreed that the MAHs of medicinal products containing piperacillin/tazobactam and monocomponent piperacillin 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

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported in patients treated with <piperacillin/tazobactam><piperacillin>, often following treatment longer than 10 days. 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, <piperacillin/tazobactam><piperacillin> 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 reports about a disease in which the immune system makes too many of otherwise normal white blood cells called histiocytes and lymphocytes, resulting in inflammation (haemophagocytic lymphohistiocytosis). This condition may be life-threatening if not diagnosed and treated early. If you experience multiple symptoms such as fever, swollen glands, feeling weak, feeling lightheaded, shortness of breath, bruising, or skin rash, contact your doctor immediately.

1.5. Warfarin – Anticoagulant-related nephropathy

Authorisation procedure	Non-centralised
EPITT No	19652
PRAC rapporteur	Anette Kirstine Stark (DK)
Date of adoption	30 September 2021

Recommendation *[see also section 3]*

PRAC has reviewed the cumulative data from spontaneous case reports, clinical trials and the literature regarding the risk of anticoagulant related nephropathy in patients treated with warfarin.

PRAC has agreed that the MAHs of warfarin-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, text to be removed ~~strikethrough~~). Where applicable, the proposed wording should be adapted to existing text regarding anticoagulant-related nephropathy.

The concerned MAHs should also provide in the next PSUR a literature review of anticoagulant-related nephropathy with warfarin, with specific focus on the potential increased mortality and on the decreased renal function as a consequence of anticoagulant-related nephropathy. The review should address any new published information regarding possible risk factors of developing anticoagulant-related nephropathy from warfarin treatment; The strength and limitations of the publications should also be discussed.

Summary of product characteristics

4.4. Special warnings and precautions for use

~~Use in patients with altered glomerular function~~ Anticoagulant-related nephropathy

In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and hematuria. A few cases have been reported in patients with no pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with a supratherapeutic INR and hematuria (including microscopic).

4.8. Undesirable effects

SOC: Renal and urinary disorders

Frequency 'not known': Anticoagulant-related nephropathy (see section 4.4)

Package leaflet

4. Possible side effects

Adverse effects with no known frequency: Impairment of renal function occurring with excessive anticoagulation and presence of blood in urine (anticoagulant-related nephropathy).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Enzalutamide	Erythema multiforme (19734)	Eva A. Segovia (ES)	Supplementary information requested (submission by 8 December 2021)	Astellas Pharma Europe B.V.
Sorafenib	Tumour lysis syndrome (TLS) (19733)	Annika Folin (SE)	Supplementary information requested (submission by 8 December 2021)	Bayer AG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
COVID-19 mRNA[5] vaccine (nucleoside-modified) - Comirnaty	Glomerulonephritis and nephrotic syndrome (19722)	Menno van der Elst (NL)	Monitor in PSUR	BioNTech Manufacturing
COVID-19 mRNA[6] vaccine (nucleoside-modified) - Spikevax	Glomerulonephritis and nephrotic syndrome (19724)	Hans Christian Siersted (DK)	Monitor in PSUR	Moderna Biotech Spain, S.L.
COVID-19 vaccine (ChAdOx1-S [recombinant]) - Vaxzevria	Immune thrombocytopenia (19678)	Jean-Michel Dogné (BE)	· See section 1.3 · Distribute a direct healthcare professional communication (DHPC) according to the text and communication plan agreed with the CHMP · Monitor in future Monthly Safety Summary Reports (MSSRs)	AstraZeneca AB

[5] Messenger ribonucleic acid
[6] Messenger ribonucleic acid

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
			· Continue to evaluate cases of bleeding with/without thrombocytopenia	
Piperacillin; piperacillin, tazobactam	Haemophagocytic lymphohistiocytosis (19676)	Marek Juračka (CZ)	· See section 1.4 · Add haemophagocytic lymphohistiocytosis as important potential risk in the PSUR · Monitor in PSUR	MAHs of piperacillin and piperacillin/tazobactam containing medicinal products
Warfarin	Anticoagulant-related nephropathy (19652)	Anette Kirstine Stark (DK)	· See section 1.5 · Provide a literature review in the next PSUR	MAHs of warfarin-containing medicinal products