



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3 May 2021¹
EMA/PRAC/199751/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 6-9 April 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 6-9 April 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 (19-22 April 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.



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

1.1. Azathioprine – Erythema nodosum³

Authorisation procedure	Non-centralised
EPITT No	19623
PRAC rapporteur(s)	Hans Christian Siersted (DK)
Date of adoption	9 April 2021

Recommendation [see also section 2 for mercaptopurine-containing products]

The PRAC has considered the available evidence in EudraVigilance, the literature, and the data submitted by the Novartis, Aspen and Teva. The PRAC agrees that a causal association between azathioprine and erythema nodosum cannot be excluded as a new aspect of azathioprine hypersensitivity reaction. The PRAC recommends that the MAHs of azathioprine-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

4.8. Undesirable effects

Immune system disorders

Several different clinical syndromes, which appear to be idiosyncratic manifestations of hypersensitivity, have been described occasionally following administration of azathioprine tablets and injection. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, erythema nodosum, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis (section 4.8 - Hepatobiliary disorders).

[...]

Package leaflet

4. Possible side effects

[...]

- allergic reactions, (these are uncommon side effects which may affect up to 1 in 100 people) the signs may include:

[...]

- swelling of the eyelids, face or lips
- redness of the skin, skin nodules or a skin rash (including blisters, itching or peeling skin)

[...]

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

1.2. COVID-19 vaccine (ChAdOx1-S [recombinant]) - Vaxzevria (previously COVID-19 Vaccine AstraZeneca) – Embolic and thrombotic events⁴

Authorisation procedure	Centralised
EPITT No	19683
PRAC rapporteur(s)	Jean-Michel Dogné (BE)
Date of adoption	7 April 2021

Recommendation [see also section 3]

The review of additional data analysis from EudraVigilance with individual case review (conclusions and recommendations are based on the EV search with cut-off date: 22 March 2021) and O/E analysis, input from the AHEG and available literature pointed to signals of Embolic and thromboembolic events, Cerebral venous sinus thrombosis, Splanchnic vein thrombosis and Arterial thrombosis, with or without thrombocytopenia, mainly occurring in women below 60 years and with a time-to-onset within 2 weeks following vaccination.

Following input from experts, it is considered that an atypical heparin induced thrombocytopenia (aHIT) like disorder is the most plausible hypothesis for the events of thrombosis in combination with thrombocytopenia, given the similarities observed in both the serological profile and clinical presentation of affected patients. It is considered likely that the syndrome, which resembles aHIT, concerns a severe autoantibody against PF4 which exhibits a high binding affinity. It was hypothesised that the antibody itself may change the structure of PF4, similar to what has been shown for aHIT. It was noted that high titres of anti-PF4 antibodies were observed in all patients whose biomaterial was analysed, which contributes to this hypothesis.

PRAC is of the view that a causal relationship between the vaccination with Vaxzevria and the adverse events is at least a reasonable possibility.

So far, the reported cases occurred after administration of the first dose of Vaxzevria. Experience of exposure to the second dose is still limited.

Furthermore, a number of studies will be put in place to identify the exact pathophysiological mechanism for the occurrence of these thrombotic events and define the precise magnitude of the risk.

The PRAC recommends that the MAH for Vaxzevria (AstraZeneca AB) should submit a variation by 07 April 2021 EOB to amend the product information as described below (new text underlined/text to be removed with ~~striketrough~~):

Summary of Product Characteristics:

Section 4.4 Special warnings and precautions for use

Thrombocytopenia and coagulation disorders

A combination of thrombosis and thrombocytopenia, 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 ~~mesenteric 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 ~~seven to~~ fourteen days following vaccination and occurred mostly in women under ~~55~~ 60 years of age, ~~however this may reflect the increased use of the vaccine in this population. Some cases had a fatal outcome.~~

⁴ Translations in all EU languages have already been included in the [Vaxzevria product information](#).

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, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches 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.

Section 4.8 Undesirable effects

Table 1 - Adverse drug reactions

MedDRA SOC	Frequency	Adverse Reactions
<u>Blood and lymphatic system disorders</u>	<u>Common</u>	<u>Thrombocytopenia</u>
<u>Vascular disorders</u>	<u>Very rare</u>	<u>Thrombosis in combination with thrombocytopenia*</u>

And at the end of the table the following statement should be added:

*Severe and very rare cases of thrombosis in combination with thrombocytopenia 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

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

Talk to your doctor, pharmacist or nurse before you are vaccinated:

...

...

Blood disorders

Very rare blood clots, often in unusual locations (e.g. brain, bowel, liver, spleen), in combination with low level of blood platelets ~~A combination of blood clots and low level of platelets,~~ in some cases together with bleeding, has been observed ~~very rarely~~ following vaccination with Vaxzevria. This included some severe cases with blood clots in different or unusual locations and excessive clotting or bleeding throughout the body. The majority of these cases occurred within the first ~~seven to~~ fourteen days following vaccination and occurred mostly in women under ~~55~~ 60 years of age, ~~however more women under 55 received the vaccine than other people.~~ Some cases had a fatal outcome.

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

Also, seek immediate medical attention if you experience after a few days severe or persistent headaches or blurred vision after vaccination, or experience skin bruising or pinpoint round spots beyond the site of vaccination which appears after a few days.

Section 4 Possible side effects

Common

- low level of blood platelets

Very rare

- blood clots often in unusual locations (e.g. brain, bowel, liver, spleen) in combination with low level of blood platelets

1.3. COVID-19 vaccine (Ad26.COV2-S [recombinant]) - COVID-19 Vaccine Janssen - Embolic and thrombotic events⁵

Authorisation procedure	Centralised
EPITT No	19689
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	20 April 2021

Recommendation [see also section 3]

The PRAC has reviewed the available evidence on the occurrence of thromboembolic events following the administration of COVID-19 Vaccine Janssen, including data ascertained from spontaneous case reports identified in EudraVigilance, clinical trials and additional data from the MAH. The evaluation of the data revealed eight reports of interest, which included 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.

PRAC is of the view that there is sufficient evidence to conclude, with a reasonable possibility, that *thrombosis in combination with thrombocytopenia* can be considered as a very rare adverse drug reaction of the Covid-19 Vaccine Janssen.

Regarding additional risk minimisation measures, a DHPC is warranted to inform health care professionals.

The PRAC recommends that the MAH for Covid-19 Vaccine Janssen (Janssen-Cilag International NV) should submit a variation by 21st April 2021 (8am CET) to amend the product information as described below (new text underlined/text to be removed with strikethrough):

Summary of Product Characteristics (SmPC)

Section 4.4

Thrombocytopenia and coagulation disorders

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 swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches 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.

⁵ Signal discussed at the Extraordinary PRAC meeting of 20 April 2021. Translations in all EU languages have already been included in the [COVID-19 Vaccine Janssen product information](#).

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.

Risk of bleeding with intramuscular administration

Section 4.8

In the Table

SOC: Vascular disorders: Thrombosis in combination with thrombocytopenia*

* *Severe and very rare cases of thrombosis in combination with thrombocytopenia 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).

Frequency: Very rare

Package leaflet

Section 2

[...]

As with any vaccine, vaccination with COVID-19 Vaccine Janssen may not fully protect all those who receive it. It is not known how long you will be protected.

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 or blurred vision, unexplained skin bruising beyond the site of vaccination which appear a few days after vaccination, develop shortness of breath, chest pain, leg swelling, or persistent abdominal pain. Inform your health care provider that you have recently received COVID-19 Vaccine Janssen.

Section 4

Very Rare (may affect up to 1 in 10,000 people) - blood clots often in unusual locations (e.g. brain, liver, bowel, spleen) in combination with low level of blood platelets

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 swelling, or persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches 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 vaccine (Ad26.COVS2-S [recombinant]) - COVID-19 Vaccine Janssen	Embolic and thrombotic events (19689)	Ulla Wändel Liminga (SE)	Provide responses to list of questions (submission by 15 April 2021)	Janssen-Cilag International NV
COVID-19 vaccine (ChAdOx1-S [recombinant]) - Vaxzevria (previously COVID-19 Vaccine AstraZeneca)	Capillary leak syndrome (19672)	Jean-Michel Dogné (BE)	Supplementary information requested (submission by 7 May 2021)	AstraZeneca AB
Mercaptopurine	Erythema nodosum (19623)	Annika Folin (SE)	Provide cumulative review in the next PSUR (submission by 30 November 2021)	MAHs for mercaptopurine-containing products (eligible to submit PSURs)
Pembrolizumab	Paraneoplastic neurological syndrome (19671)	Menno van der Elst (NL)	Provide cumulative review in the next PSUR (submission by 12 November 2021)	Merck Sharp & Dohme B.V.
Piperacillin; piperacillin, tazobactam	Hemophagocytic lymphohistiocytosis (HLH) (19676)	Marek Juračka (SK)	Supplementary information requested (submission by 1 July 2021)	Novartis, Pfizer, Fresenius Kabi, Mylan, Teva

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ciprofloxacin; delafloxacin; norfloxacin; levofloxacin; lomefloxacin; moxifloxacin; pefloxacin; ofloxacin; rufloxacin	Acquired thrombotic thrombocytopenia purpura (19669)	Pernille Harg (NO)	No action at this stage	Not applicable
COVID-19 vaccine (ChAdOx1-S [recombinant]) - Vaxzevria (previously COVID-19 Vaccine AstraZeneca)	Embolic and thrombotic events (19683)	Jean-Michel Dogné (BE)	<ul style="list-style-type: none"> · See section 1.2 · Update the risk management plan (RMP) · Address list of issues (submission in the Monthly Summary Safety Reports) 	AstraZeneca AB
COVID-19 vaccine (Ad26.COVS2-S [recombinant]) - COVID-19 Vaccine Janssen	Embolic and thrombotic events (19689) ⁶	Ulla Wändel Liminga (SE)	<ul style="list-style-type: none"> · See section 1.3 · 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 22 April 2021) 	Janssen-Cilag International NV

⁶ Signal discussed at the Extraordinary PRAC meeting of 20 April 2021.