6 April 2021[1]
EMA/PRAC/146285/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

# PRAC recommendations on signals

## Adopted at the 8-11 March 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 8-11 March 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 (22-25 March 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.

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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. Anakinra; canakinumab – Drug reaction with eosinophilia and systemic symptoms (DRESS)*

| | |
|---|---|
| **Authorisation procedure** | Centralised |
| **EPITT No** | 19566 |
| **PRAC rapporteur(s)** | Anette Kirstine Stark (DK) |
| **Date of adoption** | 11 March 2021 |

### Recommendation *[see also section 3]*

Having considered the available evidence from EudraVigilance, literature and from the cumulative reviews provided by the MAHs concerned by the signal, indicating a potential association between use of IL-1 inhibitors and drug reaction with eosinophilia and systemic symptoms (DRESS), as well as the uncertainties, rarity and severity of DRESS including potentially fatal outcomes, particularly in the pediatric population with systemic juvenile idiopathic arthritis (sJIA), the PRAC has agreed that the MAH(s) of anakinra and canakinumab-containing medicinal products should submit a variation within 3 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

- Anakinra

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has rarely been reported in patients treated with Kineret, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Patients with DRESS may require hospitalization, as this condition may be fatal. If signs and symptoms of DRESS are present and an alternative aetiology cannot be established, Kineret should be discontinued and a different treatment considered.

- Canakinumab

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has rarely been reported in patients treated with Ilaris, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Patients with DRESS may require hospitalization, as this condition may be fatal. If signs and symptoms of DRESS are present and an alternative aetiology cannot be established, Ilaris should not be re-administered and a different treatment considered.

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

**Package leaflet**

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

- Anakinra

**Contact your doctor immediately**

- if you have ever developed an atypical, widespread rash or skin peeling after taking Kineret.

The serious skin reaction, DRESS (drug reaction with eosinophilia and systemic symptoms), has rarely been reported in association with Kineret treatment, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Seek medical attention immediately if you notice an atypical, widespread rash, which may occur in conjunction with high body temperature and enlarged lymph nodes.

- Canakinumab

**Contact your doctor immediately**

- if you have ever developed an atypical, widespread rash or skin peeling after taking Ilaris.

The serious skin reaction, DRESS (drug reaction with eosinophilia and systemic symptoms), has rarely been reported in association with Ilaris treatment, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Seek medical attention immediately if you notice an atypical, widespread rash, which may occur in conjunction with high body temperature and enlarged lymph nodes.

## *1.2. COVID-19 vaccine (ChAdOx1-S [recombinant]) (COVID-19 Vaccine AstraZeneca) – Anaphylactic reaction*

| | |
|---|---|
| **Authorisation procedure** | Centralised |
| **EPITT No** | 19668 |
| **PRAC rapporteur(s)** | Jean-Michel Dogné (BE) |
| **Date of adoption** | 11 March 2021 |

## **Recommendation** *[see also section 3]*

Having considered the case reports in EudraVigilance, the PRAC has agreed that there is enough evidence that anaphylaxis and other types of hypersensitivity reactions may occur following administration of COVID-19 Vaccine AstraZeneca. Therefore, the MAH for COVID-19 Vaccine AstraZeneca (AstraZeneca AB) should submit by 20 April 2021 a variation to update the product information as described below (new text underlined):

**Summary of product characteristics**

4.4. Special warnings and precautions for use

Hypersensitivity and anaphylaxis

Events of anaphylaxis have been reported.

Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 Vaccine AstraZeneca.

4.8. Undesirable effects

Immune system disorders

Frequency 'Not known': Anaphylaxis; Hypersensitivity

**Package leaflet**

4. Possible side effects

Frequency unknown

- severe allergic reactions (anaphylaxis)

- hypersensitivity

## *1.3. Trastuzumab emtansine – Extravasation and epidermal necrosis*

| | |
|---|---|
| **Authorisation procedure** | Centralised |
| **EPITT No** | 19611 |
| **PRAC rapporteur(s)** | Anette Kirstine Stark (DK) |
| **Date of adoption** | 11 March 2021 |

## Recommendation

Having considered the available evidence, including the data submitted by the MAH (Roche), the PRAC has agreed that the MAH 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 and in bold):

**Summary of product characteristics**

4.2. Posology and method of administration

Posology

[…]

The initial dose should be administered as a 90 minute intravenous infusion. Patients should be observed during the infusion and for at least 90 minutes following the initial infusion for fever, chills, or other infusion-related reactions. The infusion site should be closely monitored for possible subcutaneous infiltration during administration. **Cases of delayed epidermal injury or necrosis following extravasation have been observed in post-marketing setting** (see section**s 4.4 and** 4.8).

4.4. Special warnings and precautions for use

[…]

*Infusion-related reactions*

Trastuzumab emtansine treatment has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR); treatment is not recommended for these patients. Patients should be observed closely for infusion-related reactions, especially during the first infusion.

Infusion-related reactions (due to cytokine release), characterized by one or more of the following symptoms have been reported: flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm, and tachycardia. In general, these symptoms were not severe (see section 4.8). In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Treatment should be interrupted in patients with a severe IRR until signs and symptoms resolve. Consideration for re-treatment should be based on clinical assessment of the severity of the reaction. Treatment must be permanently discontinued in the event of a life threatening infusion-related reaction (see section 4.2).

**Injection site reactions:**
**Extravasation of trastuzumab emtansine during intravenous injection may produce local pain, severe tissue lesions (erythema, vesiculation) and epidermal necrosis. If extravasation occurs, the infusion should be terminated immediately and the patient should be examined regularly as necrosis may occur within days or weeks after the infusion.**

4.8. Undesirable effects

Description of selected adverse reactions

[…]

Extravasation

Reactions secondary to extravasation have been observed in clinical studies with trastuzumab emtansine. These reactions were usually mild or moderate and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. These reactions have been observed more frequently within 24 hours of infusion. **In the post-marketing setting, cases of epidermal injury or necrosis following extravasation have been observed within days to weeks after infusion**. Specific treatment for trastuzumab emtansine extravasation is unknown at this time **(see section 4.4).**

**Package leaflet**

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

Tell your doctor or nurse straight away if you notice any of the following serious side effects while you are given Kadcyla:

Infusion-related reactions or allergic reactions: Kadcyla can cause flushing, shivering fits, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of your face, tongue, or trouble swallowing during the infusion or after the infusion on the first day of treatment. Your doctor or nurse will check to see whether you are having any of these side effects. If you develop a reaction, they will slow down or stop the infusion and may give you treatment to counteract the side effects. The infusion may be continued after the symptoms improve.

**Injection site reactions: If you get a burning sensation, feel pain or tenderness at the infusion site, this could indicate that Kadcyla leaks outside the blood vessel. Tell your doctor or nurse immediately. If Kadcyla has leaked outside the blood vessel increased pain, discoloration, blistering and sloughing of your skin (skin necrosis) can occur within days or**

**weeks after the infusion.**

4. Possible side effects

Tell your doctor or nurse straight away if you notice any of following serious side effects.

[…]

**Frequency not known:**
**If the Kadcyla infusion solution leaks into the area around the infusion site you may develop pain, discoloration, blistering and sloughing of your skin (skin necrosis) at the infusion site. Contact your doctor or nurse immediately.**

## *1.4. COVID-19 vaccine (ChAdOx1-S [recombinant]) (COVID-19 Vaccine AstraZeneca) – Embolic and thrombotic events*[4]

| | |
|---|---|
| **Authorisation procedure** | Centralised |
| **EPITT No** | 19683 |
| **PRAC rapporteur(s)** | Jean-Michel Dogné (BE) |
| **Date of adoption** | 18 March 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 AstraZeneca, using a wide range of sources including spontaneous case reports in EudraVigilance, quality, clinical, pre-clinical and literature data and additional data from the MAH. The review of EudraVigilance data included observed-to-expected analyses that pointed to possible signals of cerebral venous sinus thrombosis and disseminated intravascular coagulation, as well as an individual case review that suggested a possible pattern in women below 55 years with a time-to-onset within 1-2 weeks following vaccination. The PRAC has also explored possible pathophysiological explanations for the observed cases.

The PRAC has concluded that there may be a risk of rare thrombotic events accompanied by thrombocytopenia following receipt of COVID-19 Vaccine AstraZeneca that needs to be reflected in the product information, while further evidence is being collected.

The PRAC recommends by a majority of 31 out of 32 votes that the MAH for COVID-19 Vaccine AstraZeneca (AstraZeneca AB) should submit a variation by 19 March 2021 to amend the product information as described below (new text underlined/text to be removed with ~~strikethrough~~):

**Summary of Product Characteristics**

**Section 4.4 Special warnings and precautions for use**

Thrombocytopenia and coagulation disorders

[4] Signal discussed at the Extraordinary PRAC meeting of 18 March 2021. Translations in all EU languages have already been included in the COVID-19 Vaccine AstraZeneca product information.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine AstraZeneca. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, mesenteric vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of these cases occurred within the first seven to fourteen days following vaccination and occurred in women under 55 years of age, however this may reflect the increased use of the vaccine in this population. Some cases had a fatal outcome.

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.

Risk of bleeding with intramuscular administration

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

**Package leaflet**

**Section 2 Warnings and Precautions**

Talk to your doctor, pharmacist or nurse before you are ~~given COVID-19 Vaccine AstraZeneca~~ vaccinated:

…

…

Blood disorders

A combination of blood clots and low level of platelets, in some cases together with bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine AstraZeneca. 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 mostly occurred in women under 55 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.

## 2. Recommendations for submission of supplementary information

| INN | Signal (EPITT No) | PRAC Rapporteur | Action for MAH | MAH |
|---|---|---|---|---|
| COVID-19 mRNA[4] vaccine (nucleoside-modified) (Comirnaty) | Immune thrombocytopenia (19680) | Menno van der Elst (NL) | Supplementary information requested:<br>· in the 2nd Monthly Safety Summary Report (submission by 15 March 2021)<br>· in the 3rd Monthly Safety Summary Report submission by 15 April 2021) | BioNTech Manufacturing GmbH |
| COVID-19 mRNA[5] vaccine (nucleoside-modified) (Comirnaty) | Localised swelling in persons with history of dermal filler injections (19674) | Menno van der Elst (NL) | Supplementary information requested (submission by 30 March 2021) | BioNTech Manufacturing GmbH |
| COVID-19 vaccine (ChAdOx1-S [recombinant]) (COVID-19 Vaccine AstraZeneca) | Immune thrombocytopenia (19678) | Jean-Michel Dogné (BE) | Supplementary information requested (submission by 30 March 2021) | AstraZeneca AB |
| COVID-19 mRNA[4] vaccine (nucleoside-modified) (COVID-19 Vaccine Moderna) | Immune thrombocytopenia (19679) | Hans Christian Siersted (DK) | Supplementary information requested (submission by 30 March 2021) | Moderna Biotech Spain, S.L. |
| Donepezil | Cardiac conduction disorders including QT prolongation and torsades de pointes (19667) | Martin Huber (DE) | Supplementary information requested (submission by 5 May 2021) | Eisai |
| Octreotide | Pancreatic exocrine insufficiency (19661) | Ronan Grimes (IE) | Supplementary information requested (submission by 5 May 2021) | Novartis |

[5] Messenger ribonucleic acid

## 3. Other recommendations

| INN | Signal (EPITT No) | PRAC Rapporteur | Action for MAH | MAH |
|---|---|---|---|---|
| Anakinra; canakinumab | Drug reaction with eosinophilia and systemic symptoms (DRESS) (19566) | Anette Kirstine Stark (DK) | · See section 1.1<br>· Add DRESS as Important Potential Risk for the purpose of PSURs preparation | Swedish Orphan Biovitrum; Novartis Europharm Limited |
| COVID-19 vaccine (ChAdOx1-S [recombinant]) (COVID-19 Vaccine AstraZeneca) | Anaphylactic reaction (19668) | Jean-Michel Dogné (BE) | · See section 1.2<br>· Provide a thorough analysis of cases of hypersensitivity (submission by 23 March 2021)<br>· Risk management plan update to include anaphylaxis as an important identified risk | AstraZeneca AB |
| COVID-19 vaccine (ChAdOx1-S [recombinant]) (COVID-19 Vaccine AstraZeneca) | Embolic and thrombotic events (19683)[6] | Jean-Michel Dogné (BE) | · See section 1.4<br>· Distribute a direct healthcare professional communication (DHPC) in line with the agreed communication plan | AstraZeneca AB |
| Efavirenz | Microcephaly (19595) | Ana Sofia Martins (PT) | Routine pharmacovigilance | Bristol-Myers Squibb Pharma EEIG; Merck Sharp & Dohme B.V. |
| Tofacitinib | Major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancer (NMSC) from a clinical trial (19382) | Liana Gross-Martirosyan (NL) | · Respond to a list of questions (submission by 7 April 2021)<br>· Distribute a direct healthcare professional communication (DHPC) in line with the agreed communication plan | Pfizer Europe MA EEIG |

[6] Signal discussed at the Extraordinary PRAC meeting of 18 March 2021.