



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 January 2024¹
EMA/PRAC/539397/2023 Corr²
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 27-30 November 2023 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 November 2023 (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 (11-14 December 2023) 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 The scope of the signal for pirfenidone and drug reaction with eosinophilia and systemic symptoms (DRESS) was extended to all pirfenidone-containing products on 17 January 2024 (see pages 5-6).

³ The relevant EPITT reference number should be used in any communication related to a signal.



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 information⁴

1.1. *Axicabtagene ciloleucel – Progressive multifocal leukoencephalopathy (PML)*

Authorisation procedure	Centralised
EPITT No	19940
PRAC Rapporteur	Karin Erneholm (DK)
Date of adoption	30 November 2023

Recommendation [see also section 3]

Having considered the available evidence, including the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH for Yescarta, (Kite Pharma EU B.V.), 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 deleted ~~strike-through~~):

Summary of product characteristics

4.4. Special warnings and precautions for use

~~HBV~~ Viral reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B-cells. Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Yescarta.

Reactivation of JC virus, leading to progressive multifocal leukoencephalopathy (PML), has been reported in patients treated with Yescarta who have also received prior treatment with other immunosuppressive medications. Cases with fatal outcome have been reported. The possibility of PML should be considered in immunosuppressed patients with new onset or worsening neurological symptoms and appropriate diagnostic evaluations should be performed.

Package leaflet

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

After you have been given Yescarta

Tell your doctor or nurse immediately if you have any of the following:

[...]

- Bleeding or bruising more easily, which may be symptoms of low levels of cells in the blood known as platelets.
- Blurred vision, loss of vision or double vision, difficulty speaking, weakness or clumsiness of an arm or a leg, a change in the way you walk or problems with your balance, personality changes, changes in thinking, memory and orientation leading to confusion. These may all be symptoms of a serious and potentially fatal brain condition known as progressive multifocal leukoencephalopathy (PML). These symptoms may start several months after treatment has ended and they usually develop slowly and gradually over weeks or months. It is important that your relatives or caregivers are also aware of these symptoms, since they may notice symptoms that you are not aware of.

⁴ 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. Dabrafenib; trametinib – Peripheral neuropathy

Authorisation procedure	Centralised
EPITT No	19947
PRAC Rapporteur	David Olsen (NO)
Date of adoption	30 November 2023

Recommendation [see also section 2]

Having considered the available evidence, including the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH for Tafinlar and Mekinist (Novartis Europharm Limited), should submit a variation within two months from the publication of the PRAC recommendation, to amend the product information as described below (new text underlined):

Tafinlar (dabrafenib) - Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions

Table 3 (Adverse reactions with dabrafenib monotherapy) and Table 4 (Adverse reactions with dabrafenib in combination with trametinib)

Nervous system disorders

Common: Peripheral neuropathy (including sensory and motor neuropathy)

Tafinlar (dabrafenib) - Package leaflet

4. Possible side effects

Possible side effects in patients taking Tafinlar alone and Possible side effects when Tafinlar and trametinib are taken together

Common side effects (may affect up to 1 in 10 people)

Problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet and/or muscle weakness (peripheral neuropathy)

Mekinist (trametinib) - Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions

Table 4 (Adverse reactions with trametinib monotherapy) and Table 5 (Adverse reactions with trametinib in combination with dabrafenib)

Nervous system disorders (new SOC for table 4)

Common: Peripheral neuropathy (including sensory and motor neuropathy)

Mekinist (trametinib) - Package leaflet

4. Possible side effects

Possible side effects in patients taking Mekinist alone and Side effects when Mekinist and dabrafenib are taken together

Common side effects (may affect up to 1 in 10 people)

Problem with the nerves that can produce pain, loss of sensation or tingling in hands and feet and/or muscle weakness (peripheral neuropathy)

1.3. Pirfenidone – Drug reaction with eosinophilia and systemic symptoms (DRESS)

Authorisation procedure	Centralised and non-centralised ⁵
EPITT No	19920
PRAC Rapporteur	Rhea Fitzgerald (IE)
Date of adoption	30 November 2023

Recommendation

Having considered the known association of pirfenidone with severe skin reactions and the available new evidence on drug reaction with eosinophilia and systemic symptoms (DRESS), including the cumulative review submitted by the MAH of Esbriet (Roche Registration GmbH), the PRAC has agreed that the MAHs for pirfenidone-containing products⁵ 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

Severe skin reactions

Stevens-Johnson syndrome (SJS), ~~and~~ toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with *<product name>* treatment. If signs and symptoms suggestive of these reactions appear, *<product name>* should be withdrawn immediately. If the patient has developed SJS, ~~or~~ TEN or DRESS with the use of *<product name>*, treatment with *<product name>* must not be restarted and should be permanently discontinued.

4.8. Undesirable effects

Skin and subcutaneous tissue disorders SOC

Frequency: Not known - Stevens-Johnson syndrome¹; toxic epidermal necrolysis¹; drug reaction with eosinophilia and systemic symptoms (DRESS)¹

Footnote ¹: Identified through post-marketing surveillance (see section 4.4)

⁵ The scope of the signal was extended to all pirfenidone-containing products on 17 January 2024.

Package leaflet

2. Warning and precautions

- Stevens-Johnson syndrome, ~~and~~ toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in association with *<product name>* treatment. Stop using *<product name>* and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

4. Possible side effects

Stop taking *<product name>* and ~~tell your doctor~~ seek medical attention immediately if you notice any of the following symptoms or signs

- ~~If you experience s~~Swelling of the face, lips and/or tongue, itching, hives, difficulty breathing or wheezing, or feeling faint, which are signs of angioedema, a serious allergic reaction or anaphylaxis.
- ~~If you experience y~~Yellowing of the eyes or skin, or dark urine, potentially accompanied by itching of the skin, pain on the upper right side of your stomach area (abdomen), loss of appetite, bleeding or bruising more easily than normal, or feeling tired. These may be signs of abnormal liver function and could indicate liver injury, which is an uncommon side effect of *<product name>*.
- ~~If you experience r~~Reddish non-elevated, or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals, and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms. ~~These signs and symptoms may indicate~~ (Stevens-Johnson syndrome, or toxic epidermal necrolysis).
- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Afatinib	Growth of eyelashes (19987)	Ulla Wändel Liminga (SE)	Assess in the next PSUR (submission by 24 December 2023)	Boehringer Ingelheim International GmbH
Brolucizumab	Scleritis (20016)	Gabriele Maurer (DE)	Assess in the next PSUR (submission by 15 December 2023)	Novartis Europharm Limited
Dabrafenib; trametinib	Peripheral neuropathy (19947)	David Olsen (NO)	<ul style="list-style-type: none"> · See section 1.2 · Assess cases of Guillain-Barre syndrome and related terms in the next PSUR (submission by 7 August 2024) 	Novartis Europharm Limited
Doxycycline	Suicidality (19997)	Liana Gross-Martirosyan (NL)	Supplementary information requested (submission by 7 February 2024)	Pharmanovia A/S
Ethambutol	Drug reaction with eosinophilia and systemic symptoms (DRESS) (20018)	Sonja Hrabcik (AT)	Supplementary information requested (submission by 7 February 2024)	Teofarma S.R.L.
Glatiramer	Anaphylaxis with a long latency (19990)	Karin Erneholm (DK)	Assess in the next PSUR (submission by 28 February 2024)	Teva Pharmaceuticals Ltd
Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide; exenatide; liraglutide; insulin degludec, liraglutide; lixisenatide; insulin glargine, lixisenatide; semaglutide	Suicidal ideation and self-injurious ideation (19946)	Menno van der Elst (NL)	Supplementary information requested (submission by 10 January 2024)	Novo Nordisk A/S, AstraZeneca AB, Eli Lilly Nederland B.V., Sanofi Winthrop Industrie

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Elexacaftor, tezacaftor, ivacaftor; ivacaftor; lumacaftor, ivacaftor; tezacaftor, ivacaftor	Intracranial pressure increased (20000)	Martin Huber (DE)	Supplementary information requested (submission by 7 February 2024)	Vertex Pharmaceuticals (Ireland) Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Axicabtagene ciloleucel	Progressive multifocal leukoencephalopathy (PML) (19940)	Karin Erneholm (DK)	<ul style="list-style-type: none"> · See section 1.1 · Include PML in the PSUR list of safety concerns and follow-up as pertinent 	Kite Pharma EU B.V.