10 June 2024[1]
EMA/PRAC/222449/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 13-16 May 2024 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 13-16 May 2024 (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 (27-30 May 2024) 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. Baricitinib – Hypoglycaemia in diabetic patients

Authorisation procedure	Centralised
EPITT No	20038
PRAC Rapporteur	Adam Przybylkowski (PL)
Date of adoption	16 May 2024

Recommendation

Having considered the available evidence in EudraVigilance, published literature including the study by Waibel et al. as well as data submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of Olumiant (Eli Lilly Nederland 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):

Summary of product characteristics

4.4 Special warnings and precautions for use

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of JAK inhibitors, including baricitinib, in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycaemia occurs.

Package leaflet

2. What you need to know before you take OLUMIANT

Other medicines and OLUMIANT

Tell your doctor or pharmacist if you are taking, have recently taken, or might take, any other medicines.

In particular, tell your doctor or pharmacist before taking Olumiant if you are taking any other medicine such as:

(…)

- medicines to treat diabetes or if you have diabetes. Your doctor may decide if you need less anti-diabetic medicine while taking Olumiant.

[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. Dabrafenib; trametinib – Acute febrile neutrophilic dermatosis

Authorisation procedure	Centralised
EPITT No	20022
PRAC Rapporteur	David Olsen (NO)
Date of adoption	16 May 2024

Recommendation

Having considered the available evidence in EudraVigilance, the literature and including the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the product information for the combination dabrafenib/trametinib as well as dabrafenib monotherapy should be updated. The MAH of Tafinlar, Finlee, Mekinist and Spexotras, (Novartis Europharm Limited) 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 ~~strikethrough~~.

Summary of product characteristics

Tafinlar

4.8 Undesirable effects

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

Skin and subcutaneous tissue disorders

Frequency Uncommon: Acute febrile neutrophilic dermatosis

Mekinist

4.8 Undesirable effects

Table 5 Adverse reactions with trametinib in combination with dabrafenib

Skin and subcutaneous tissue disorders

Frequency Uncommon: Acute febrile neutrophilic dermatosis

Finlee

4.8 Undesirable effects

Adverse reactions ~~in the integrated paediatric safety population~~ (Table 4) are listed below by MedDRA system organ class….

Table 4 Adverse reactions ~~reported in the integrated paediatric safety population of~~ with dabrafenib in combination with trametinib ~~(n=171)~~

Skin and subcutaneous tissue disorders	
Uncommon	Acute febrile neutrophilic dermatosis[10], s~~S~~kin fissures,
Musculoskeletal and connective tissue disorders	
Common	Myalgia*, muscle spasms*[11~~0~~]

General disorders and administration site conditions	
Very common	Pyrexia*, fatigue*[12~~1~~], weight increased
Investigations	
Very common	Transaminases increased*[13~~2~~]

[10] Acute febrile neutrophilic dermatosis is an adverse drug reaction seen also with dabrafenib monotherapy (Tafinlar)

[11~~0~~] muscle spasms include musculoskeleteal stiffness

[12~~1~~] fatigue includes malaise and asthenia

[13~~2~~] transaminases increased includes aspartate aminotransferase (AST) increased and alanine aminotransferase (ALT) increased

Spexotras

4.8 Undesirable effects

Adverse reactions ~~in the integrated paediatric safety population~~ (Table 5) are listed below by MedDRA system organ class…

Table 5 Adverse reactions ~~reported in the integrated paediatric safety population of~~ with trametinib in combination with dabrafenib ~~(n=171)~~

Skin and subcutaneous tissue disorders	
Uncommon	Acute febrile neutrophilic dermatosis, s~~S~~kin fissures,

Package leaflet

Tafinlar

4. Possible side effects

Possible side effects in patients taking Tafinlar alone

Uncommon side effects (may affect up to 1 in 100 people)

- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

Possible side effects when Tafinlar and trametinib are taken together

Uncommon side effects (may affect up to 1 in 100 people)

- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

Mekinist

4. Possible side effects

Side effects when Mekinist and dabrafenib are taken together

Uncommon side effects (may affect up to 1 in 100 people)

- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

Finlee and Spexotras

4. Possible side effects

Other possible side effects

Uncommon side effects (may affect up to 1 in 100 people)

- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

1.3. Manidipine – Ascites

Authorisation procedure	Non-centralised
EPITT No	20026
PRAC Rapporteur	Amelia Cupelli (IT)
Date of adoption	16 May 2024

Recommendation

Having considered the available evidence in EudraVigilance, company safety database and literature, including the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAHs of manidipine should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below. Taking into account the already existing wording in some nationally authorised products the text needs to be adapted by MAHs to individual products. (new text underlined):

Summary of product characteristics

4.4 Special warnings and precautions for use

Peritoneal Dialysis

Manidipine has been associated with the development of cloudy peritoneal effluent in patients on peritoneal dialysis. The turbidity is due to an increased triglycerides concentration in the peritoneal effluent and tends to resolve after discontinuation of manidipine. This is an important association to recognise as cloudy peritoneal effluent can be mistaken for infective peritonitis with consequential unnecessary hospitalisation and empiric antibiotic administration.

4.8 Undesirable effects

Under SOC Gastrointestinal disorders with frequency "Not known"

Peritoneal cloudy effluent

Package leaflet

2. What you need to know before you take <*Product name*>

Warnings and precautions

Talk to your doctor before taking <*Product name*>

- [...]
- If you are undergoing peritoneal dialysis

4. Possible side effects

Frequency not known (frequency cannot be estimated from the available data): […], cloudy fluid (when performing dialysis through a tube into your abdomen)

1.4. Propofol – Hepatic failure

Authorisation procedure	Non-centralised
EPITT No	20020
PRAC Rapporteur	Karen Pernille Harg (NO)
Date of adoption	16 May 2024

Recommendation

Having considered the available evidence in EudraVigilance and literature, including the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAHs of propofol containing products should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below, taking into account the already existing wording in some nationally authorised products the text needs to be adapted by MAHs to individual products (new text underlined):

Summary of product characteristics

4.8 Undesirable effects

Frequency: not known

Hepatitis, acute hepatic failure.

Footnote to section 4.8: After both long- and short-term treatment and in patients without underlying risk factors.

Package leaflet*

4. Possible side effects

Not known (frequency cannot be estimated from the available data):

Hepatitis (inflammation of the liver), acute liver failure (symptoms can include yellowing skin and eyes, itching, dark coloured urine, stomach pain and liver tenderness (indicated by pain under the front of the rib cage on your right-hand side), sometimes with loss of appetite).

*If package leaflets distinguish between adverse reactions that could occur during anaesthesia and adverse reactions that could occur after anaesthesia, these ADRs are recommended to be included amongst ADRs that could occur after anaesthesia.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adagrasib	Febrile neutropenia (20080)	Kimmo Jaakkola (FI)	Assess in the next PSUR (submission by 20 August 2024)	Bristol-Myers Squibb Pharma EEIG
Aflibercept	Nephropathy toxic after intravitreal administration (20024)	Nathalie Gault (FR)	Assess in the next PSUR (submission by 28 February 2026)	Bayer AG, Viatris Limited
Eptinezumab; erenumab; fremanezumab; galcanezumab	Insomnia (20077)	Kirsti Villikka (FI)	Supplementary information requested (submission by 31 July 2024)	H. Lundbeck A/S, Novartis Europharm Limited, TEVA GmbH, Eli Lilly Nederland B.V.
Erenumab	Hypertension (20081)	Kirsti Villikka (FI)	Assess in the next PSUR (submission by 25 July 2024)	Novartis Europharm Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Clobazam	Drug reaction with eosinophilia and systemic symptoms (DRESS) (20041)	Kimmo Jaakkola (FI)	Monitor in PSUR	MAHs of clobazam containing products
Ivacaftor, tezacaftor, elexacaftor; ivacaftor; lumacaftor, ivacaftor; tezacaftor, ivacaftor	Intracranial pressure increased (20000)	Martin Huber (DE)	· For the combination ivacaftor/tezacaftor/ elexacaftor: follow up in the next PSUR (submission by 29 June 2024) · For the other products: routine pharmacovigilance	Vertex Pharmaceuticals (Ireland) Limited