5 February 2024[1]
EMA/PRAC/2748/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 8-11 January 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 8-11 January 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 (22-25 January 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.

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. Amphotericin B – Hyperkalaemia

Authorisation procedure	Non-centralised
EPITT No	19966
PRAC Rapporteur	Maria del Pilar Rayon (ES)
Date of adoption	11 January 2024

Recommendation

Having considered the available evidence in EudraVigilance, literature and cumulative reviews submitted by Marketing Authorisation Holders (MAHs), PRAC has agreed that no further action is deemed warranted at this stage for non-lipid Amphotericin B i.e. Fungizone, powder for infusion 50 mg (Cheplapharm Arzneimittel GmbH). The MAHs for Amphotericin B, lipid formulations i.e. AmBisome 50 mg, powder for dispersion for infusion (Gilead) and Abelcet 5 mg/ml concentrate for suspension for infusion (Teva) should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as applicable (taking into account the already existing wording in some nationally authorised products), and described below (new text underlined, text to be adapted by MAHs to individual products)*:

AmBisome

Summary of product characteristics

4.4 Special warnings and precautions for use

AmBisome has been shown to be substantially less toxic than conventional amphotericin B, particularly with respect to nephrotoxicity; however, adverse reactions, including renal adverse reactions, may still occur.

In studies comparing AmBisome 3mg/kg daily with higher doses (5, 6 or 10 mg/kg daily), it was found that the incidence rates of increased serum creatinine, hypokalaemia and hypomagnesaemia were notably higher in the high dose groups.

Regular laboratory evaluation of serum electrolytes, particularly potassium and magnesium, as well as renal, hepatic and haematopoietic function should be performed ~~in patients receiving concomitant nephrotoxic medications as well as other patients treated with AmBisome (see section 4.5)~~. Due to the risk of hypokalaemia, appropriate potassium supplementation may be required during the course of AmBisome administration. If clinically significant reduction in renal function or worsening of other parameters occurs, consideration should be given to dose reduction, treatment interruption or discontinuation. Cases of hyperkalaemia (some of them leading to cardiac arrhythmias and cardiac arrest) have been reported. Most of them occurred in patients with renal impairment, and some cases after potassium supplementation in patients with previous hypokalaemia. Therefore, renal function and laboratory evaluation of potassium, should be measured before and during treatment. This is particularly important in patients with pre-existing renal disease, who have already experienced renal failure, or in patients receiving concomitant nephrotoxic medications (see section 4.5).

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

4.8 Undesirable effects

Under SOC Metabolism and nutrition disorders with frequency "Common"

Hyperkalaemia

Package leaflet

2. What you need to know before you use AmBisome

Warning and precautions

- **If you are taking other medicines that may cause kidney damage**, see the section *Other medicines and AmBisome*. AmBisome may cause damage to the kidney. Your doctor or nurse will take ~~regular~~ blood samples to measure your creatinine (a chemical in the blood that reflects kidney function), and electrolyte levels (particularly potassium and magnesium) before and during the treatment with AmBisome because both of these can be abnormal if you have changes in your kidney function. This is particularly important if you have previous renal damage or if you are taking other medicines that can affect the way your kidney functions. The blood samples will also be tested for changes in your liver, and your body's ability to produce new blood cells and platelets. **If blood tests show a change in kidney function**, or other important changes your doctor may give you a lower dose of AmBisome or stop treatment.
- **If blood tests show that your potassium levels are low.** If this happens, your doctor may prescribe a potassium supplement for you to take while you are treated with AmBisome.
- **If blood test shows that your potassium levels are high** you may suffer irregular heartbeat, sometimes severe.

4. Possible side effects

- Common side effects (may affect up to 1 in 10 people treated)
- ……
- High blood potassium levels

Abelcet

Summary of product characteristics

4.4 Special warnings and precautions for use

Since Abelcet is a potentially nephrotoxic drug, monitoring of renal function should be performed before initiating treatment and during the treatment. This is particularly important in patients with pre-existing renal disease, ~~or~~ who have already experienced renal failure, or in patients receiving nephrotoxic medications. Laboratory evaluation of serum electrolytes, particularly potassium ~~as well as renal function~~ should be performed regularly before and during therapy. Cases of hyperkalaemia (some of them leading to cardiac arrhythmias and cardiac arrest) have been reported. Some of them occurred in patients with renal impairment, or after potassium supplementation in patients with previous hypokalaemia.

4.8 Undesirable effects

Under SOC Metabolism and nutrition disorders with frequency "Common"

Hyperkalaemia*

Package leaflet

2. What you need to know before you use Abelcet

Warning and precautions

If you are treated with Abelcet lipid complex, your doctor will monitor the function of the kidneys and the electrolytes such as potassium prior and during treatment with Abelcet. This is particularly important if you have previous kidney damage or if you are taking other medicines that can affect the way your kidney functions. If blood test show that your potassium levels are high you may suffer irregular heartbeat, sometimes severe.

Your doctor will regularly monitor the function of your ~~kidneys and~~ liver ~~and have regular blood tests~~, especially if you have had liver disease in the past ~~have had kidney problems~~.

4. Possible side effects

Common side effects

……

High blood potassium levels*

** Due to differences in the national SmPCs and Package Leaflets, it is acknowledged that text already included in the product information will have to be modified/adjusted in order to accommodate the new text stated in this PRAC recommendation.*

1.2. Avatrombopag – Antiphospholipid syndrome

Authorisation procedure	Centralised
EPITT No	19954
PRAC Rapporteur	Monica Martinez Redondo
Date of adoption	11 January 2024

Recommendation *[see also section 3]*

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 MAH of Doptelet, Swedish Orphan Biovitrum AB 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

Thrombotic/thromboembolic events

> […] Doptelet was not studied in patients with prior thromboembolic events. Consider the potential increased thrombotic risk when administering Doptelet to patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (e.g. Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency), acquired risk factors (e.g. antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, […]

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

Authorisation procedure	Non-centralised
EPITT No	19960
PRAC Rapporteur	Sonja Hrabcik (AT)
Date of adoption	11 January 2024

Recommendation

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

Summary of product characteristics

4.4 Special warnings and precautions for use

The current text should be replaced with the following:

Severe skin reactions

Severe cutaneous adverse reactions (SCARs) including acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with cefotaxime treatment.

At the time of prescription patients should be advised of the signs and symptoms for skin reactions.

If signs and symptoms suggestive of these reactions appear, cefotaxime should be withdrawn immediately. If the patient has developed AGEP, SJS, TEN or DRESS with the use of cefotaxime, treatment with cefotaxime must not be restarted and should be permanently discontinued.

In children, the presentation of a rash can be mistaken for the underlying infection or an alternative infectious process, and physicians should consider the possibility of a reaction to cefotaxime in children that develop symptoms of rash and fever during therapy with cefotaxime.

4.8 Undesirable effects

Under SOC Skin and subcutaneous tissue disorders with frequency "Not known"

Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

Package leaflet

2. What you need to know before you take [product name]

Do not take [product name] if:

……

You have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking cefotaxime or other cephalosporins.

Do not have this [product name] or tell your doctor if any of these apply to you.

Warning and precautions

Take special care with [product name]

Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) have been reported in association with cefotaxime treatment. Stop using cefotaxime 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

The current text should be replaced with the following:

Stop taking cefotaxime and tell your doctor immediately if you notice any of the following symptoms:

- Reddish non-elevated, target-like 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 (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).
- A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (acute generalised exanthematous pustulosis).

1.4. Cobimetinib; vemurafenib – Aphthous ulcer, mouth ulceration, stomatitis

Authorisation procedure	Centralised
EPITT No	19961
PRAC Rapporteur	Ulla Wändel Liminga (SE)
Date of adoption	11 January 2024

Recommendation

Having considered the available evidence in EudraVigilance, clinical studies and the literature, including the cumulative review submitted by the Marketing Authorisation Holder, the PRAC has agreed that the MAH for COTELLIC and ZELBORAF (Roche Registration GmbH) 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):

- **Zelboraf (vemurafenib)**

Summary of product characteristics

4.8 Undesirable effects

System organ class	Very common	Common	Uncommon	Rare
Gastrointestinal disorders	Diarrhoea, vomiting, nausea, constipation	Stomatitis	Pancreatitis(2)	

Package leaflet: Information for the user

4. Possible side effects

Common (may affect up to 1 in 10 people):

<…>

- Sore mouth or mouth ulcers, inflammation of mucous membranes (stomatitis)

- **Cotellic (cobimetinib)**

Summary of product characteristics

4.8 Undesirable effects

System organ class	Very common	Common	Uncommon	Rare

Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Stomatitis			

Package leaflet: Information for the user

4. Possible side effects

Very common (may affect more than 1 in 10 people):

<…>

- Sore mouth or mouth ulcers, inflammation of mucous membranes (stomatitis)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Aflibercept; ranibizumab	Nephropathy toxic after intravitreal administration (20024)	Nathalie Gault (FR)	· Aflibercept: supplementary information requested (submission by 13 March 2024) · Ranibizumab: no action for MAH	Bayer AG, Viatris Limited
Axicabtagene ciloleucel; idecabtagene vicleucel; lisocabtagene maraleucel; ciltabtagene autoleucel; tisagenlecleucel; brexucabtagene autoleucel	Secondary malignancy of T-cell origin (20040)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 7 February 2024)	Bristol-Myers Squibb Pharma EEIG, Janssen-Cilag International NV, Novartis Europharm Limited, Kite Pharma EU B.V.
Baricitinib	Hypoglycaemia in diabetic patients (20038)	Adam Przybylkowski (PL)	Supplementary information requested (submission by 13 March 2024)	Eli Lilly Nederland B.V.
Canagliflozin; dapagliflozin; empagliflozin;	Polycythaemia (20019)	Mari Thörn (SE)	· Dapagliflozin: assess in the ongoing PSUR (submission by 17 April 2024)	AstraZeneca AB

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
empagliflozin, metformin			· Canagliflozin; empagliflozin; empagliflozin, metformin: no action for MAH	
Clobazam	Drug reaction with eosinophilia and systemic symptoms (DRESS) (20041)	Kimmo Jaakkola (FI)	Supplementary information requested (submission by 13 March 2024)	Sanofi - Produtos Farmaceuticos Lda
Dabrafenib; trametinib	Acute febrile neutrophilic dermatosis (20022)	David Olsen (NO)	Supplementary information requested (submission by 13 March 2024)	Novartis Europharm Limited
Ixazomib	Vasculitis (20023)	Ulla Wändel Liminga (SE)	Assess in the next PSUR (submission by 28 January 2024)	Takeda Pharma A/S
Manidipine	Ascites (20026)	Amelia Cupelli (IT)	Supplementary information requested (submission by 13 March 2024)	Chiesi Farmaceutici S.P.A.
Propofol	Hepatic failure (20020)	Pernille Harg (NO)	Supplementary information requested (submission by 13 March 2024)	Aspen Pharma Trading Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Avatrombopag	Antiphospholipid syndrome (19954)	Monica Martinez Redondo	· See section 1.2 · Monitor the topics of antiphospholipid syndrome (APS) / catastrophic antiphospholipid syndrome (CAPS) in the next PSUR	Swedish Orphan Biovitrum AB (publ)