22 February 2018
EMA/PRAC/59224/2018 Rev[1]
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 5-8 February 2018 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 5-8 February 2018 (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 February 2018) 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] The PRAC recommendation for the signal of interaction with levothyroxine on page 4 was revised on 12 July 2018.
[2] The relevant EPITT reference number should be used in any communication related to a signal.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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. Filgrastim; lenograstim; lipegfilgrastim; pegfilgrastim – Aortitis

Authorisation procedure	Centralised and non-centralised
EPITT No	18940
PRAC rapporteur(s)	Patrick Batty (UK)
Date of adoption	8 February 2018

Recommendation

Having considered the evidence from MAHs of filgrastim, lenograstim, lipegfilgrastim and pegfilgrastim, the PRAC agreed that there is at least a reasonable possibility of a causal association between aortitis and G-CSF treatment. The PRAC recommended that MAHs of filgrastim-, lenograstim-, lipegfilgrastim- and pegfilgrastim-containing products should submit a variation within 2 months* to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Warnings and precautions

Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF. See also section 4.8.

4.8. Undesirable effects

Vascular disorders

Aortitis [rare frequency]

Package leaflet

2. Warnings and precautions

Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) has been reported rarely in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience these symptoms.

4. Possible side effects

[Rare frequency] Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body), see section 2.

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

*Applicants for products under authorisation should update their product information accordingly during evaluation.

Note: Rare frequency is applicable for filgrastim & pegfilgrastim; for lipegfilgrastim and lenograstim the frequency is to be calculated by the MAHs.

1.2. Hydroxycarbamide – Cutaneous lupus erythematosus

Authorisation procedure	Centralised
EPITT No	18939
PRAC rapporteur(s)	Laurence de Fays (BE)
Date of adoption	8 February 2018

Recommendation

Having considered the evidence from MAHs of hydroxycarbamide, the PRAC recommended that MAHs of hydroxycarbamide-containing products should submit a variation within 2 months to amend the product information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Systemic and cutaneous lupus erythematous (frequency very rare)

Package leaflet

4. Possible side effects

Inflammation of the skin causing red scaly patches and possibly occurring together with pain in the joints

1.3. Ritonavir; lopinavir, ritonavir; levothyroxine – Interaction possibly leading to decreased levothyroxine efficacy and hypothyroidism[4]

Authorisation procedure	Centralised and non-centralised
EPITT No	18896
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of adoption	8 February 2018

Recommendation

Having considered the available evidence, including data from EudraVigilance and the literature, the response from the MAH for Norvir and Kaletra (AbbVie Ltd) and the advice from the Pharmacokinetics Working Party (PKWP), the PRAC has concluded that an interaction between levothyroxine and

[4] The PRAC agreed on 12 July 2018 that this recommendation is not applicable to ombitasvir/paritaprevir/ritonavir (Viekirax).

ritonavir cannot be ruled out based on spontaneous reports and should therefore be reflected in the product information of ritonavir- and levothyroxine-containing medicinal products.

The MAHs for medicinal products containing ritonavir and lopinavir/ritonavir and those levothyroxine-containing products whose product information does not mention a possible interaction with protease inhibitors, should submit a variation within 3 months to amend the product information as described below (new text underlined).

The PRAC also recommended that Member States should consider communicating the outcome of the signal assessment to appropriate patient organisations at national level.

Summary of product characteristics

[Ritonavir and lopinavir/ritonavir containing products, and levothyroxine-containing products whose SPC section 4.5 does not mention a possible interaction with protease inhibitors:]

4.5. Interaction with other medicinal products and other forms of interaction

Post-marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.

Package leaflet

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

- *[Levothyroxine-containing products whose package leaflet does not mention a possible interaction with protease inhibitors:]*

The following may affect the way that levothyroxine works:

- Ritonavir - used to control HIV and chronic hepatitis C virus

- *[Ritonavir containing products:]*

There are medicines that may not mix with [product] because their effects could increase or decrease when taken together. In some cases your doctor may need to perform certain tests, change the dose or monitor you regularly. This is why you should tell your doctor if you are taking any medicines, including those you have bought yourself or herbal products, but it is especially important to mention these:

- Levothyroxine (used to treat thyroid problems)

- *[Lopinavir/ritonavir containing products:]*

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

- Levothyroxine (used to treat thyroid problems)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Biotin	Interference with clinical laboratory tests (19156)	Valerie Straßmann (DE)	Supplementary information requested (submission by 11 April 2018)	Baxter
Varenicline	Loss of consciousness (19146)	Doris Stenver (DK)	Supplementary information requested (submission by 11 April 2018)	Pfizer Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Apixaban; dabigatran; edoxaban; rivaroxaban	Cholesterol embolisms (19078)	Menno van der Elst (NL)	Routine pharmacovigilance	Boehringer Ingelheim International GmbH; Bristol-Myers Squibb; Daiichi Sankyo Europe GmbH; Bayer AG
Baricitinib	Pneumonia (18950)	Patrick Batty (UK)	Submission of a variation; supplementary information in the PSUR (submission by 24 April 2018)	Eli Lilly Nederland B.V.
Human coagulation (plasma-derived) factor VIII: human coagulation factor VIII (antihemophilic factor A); human coagulation factor VIII (inhibitor bypassing	Inhibitor development in previously untreated patients (PUPs) with haemophilia A treated with plasma-derived *vs* recombinant coagulation factor VIII concentrates (18701)	Brigitte Keller-Stanislawski (DE)	Monitor in PSUR	MAHs of human coagulation (plasma-derived) factor VIII and recombinant factor VIII

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
fraction); human coagulation factor VIII, human von Willebrand factor; Recombinant factor VIII: antihemophilic factor (recombinant); efmoroctocog alfa; lonoctocog alfa; moroctocog alfa; octocog alfa; simoctocog alfa; susoctocog alfa; turoctocog alfa				
Paracetamol	Paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus (17796)	Laurence de Fays (BE)	No action at this stage	Not applicable