11 June 2019[1]
EMA/PRAC/265212/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 13-16 May 2019 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 2019 (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 (27-29 May 2019) 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] Intended 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. Clopidogrel; clopidogrel, acetylsalicylic acid – Interaction with boosted antiviral human immunodeficiency virus (HIV) therapy leading to insufficient inhibition of platelet aggregation

Authorisation procedure	Centralised and non-centralised
EPITT No	19325
PRAC rapporteur(s)	Márcia Silva (PT)
Date of adoption	16 May 2019

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH(s) of clopidogrel-containing medicinal products should submit a variation within 3 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

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

A significantly lower exposure to clopidogrel active metabolite and reduced platelet inhibition have been demonstrated in HIV-infected patients treated with ritonavir- or cobicistat-boosted anti-retroviral therapies (ART). Although the clinical relevance of these findings is uncertain, there have been spontaneous reports of HIV-infected patients treated with boosted ART, who have experienced re-occlusive events after de-obstruction or have suffered thrombotic events under a clopidogrel loading treatment schedule. Exposure of clopidogrel and average platelet inhibition can be decreased with concomitant use of ritonavir. Therefore, concomitant use of clopidogrel with boosted ART should be discouraged.

Package leaflet

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

Other medicines and [X]

[…]

You should specifically tell your doctor if you take:

[…]

- anti-retroviral medicines (medicines to treat HIV infections).

[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. Pantoprazole – Colitis microscopic

Authorisation procedure	Centralised and non-centralised
EPITT No	19342
PRAC rapporteur(s)	Rugile Pilviniene (LT)
Date of adoption	16 May 2019

Recommendation

Having considered the available evidence from EudraVigilance, the literature, the cumulative review provided by the Takeda, as well as the fact that colitis microscopic is included in the label of other proton pump inhibitors and is a likely class effect, the PRAC has agreed that the MAH(s) of pantoprazole-containing medicinal products should submit a variation within 3 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions

Gastrointestinal disorders

Frequency not known: Microscopic colitis

Package leaflet

4. Possible side effects

Frequency not known:

Inflammation in the large bowel, that causes persistent watery diarrhoea

1.3. Serotonin and noradrenaline reuptake inhibitors (SNRI)[4]; selective serotonin reuptake inhibitors (SSRI)[5] [6] – Persistent sexual dysfunction after drug withdrawal

Authorisation procedure	Centralised and non-centralised
EPITT No	19277
PRAC rapporteur(s)	Liana Gross-Martirosyan (NL)
Date of adoption	16 May 2019

Recommendation

Having considered the available evidence from EudraVigilance, literature, social media and cumulative reviews provided by MAHs for duloxetine, fluoxetine (Eli Lilly), citalopram, vortioxetine, escitalopram (Lundbeck), fluvoxamine (Mylan), sertraline, desvenlafaxine (Pfizer), paroxetine (GSK), venlafaxine (Almirall), milnacipram (Pierre Fabre) and clomipramine (Alfasigma) the PRAC has agreed that all MAHs of products containing citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline (Selective serotonin reuptake inhibitors (SSRIs)) and all MAHs of products containing duloxetine, venlafaxine, desvenlafaxine, milnacipram (Serotonin–norepinephrine reuptake inhibitors (SNRIs)) should submit a variation within 2 months[6], to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Package leaflet

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

Warnings and precautions

Medicines like [Invented name] (so called SSRIs/SNRIs) may cause symptoms of sexual dysfunction (see section 4). In some cases, these symptoms have continued after stopping treatment.

[4] Desvenlafaxine; duloxetine; milnacipran; venlafaxine
[5] Citalopram; escitalopram; fluoxetine; fluvoxamine; paroxetine; sertraline
[6] Clomipramine and vortioxetine were part of the signal assessment but are not concerned by the recommendation to update the product information.

1.4. Sertraline – Maculopathy

Authorisation procedure	Non-centralised
EPITT No	19341
PRAC rapporteur(s)	Liana Gross-Martirosyan (NL)
Date of adoption	16 May 2019

Recommendation

Based on the review of the data on the risk of maculopathy with sertraline, the PRAC has agreed that the MAH(s) of sertraline-containing medicinal product(s) 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

Eye disorders

Not known: maculopathy

Package leaflet

4. Possible side effects

Rare: spots in front of eyes, glaucoma, double vision, light hurts eye, blood in the eye, unequal sized pupils, vision abnormal, tear problem

Not known: partial loss of vision

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Direct acting antivirals (DAAV)[7]	Autoimmune hepatitis (19395)	Ana Sofia Martins (PT)	Supplementary information requested (submission by 31 July 2019)	AbbVie Deutschland GmbH Co. KG, Bristol-Myers Squibb Pharma EEIG, Gilead Sciences Ireland UC, Merck Sharp & Dohme B.V.
Febuxostat	Gynaecomastia (19412)	Jan Neuhauser (AT)	Assess in the next PSUR (submission by 29 June 2019)	Menarini International Operations Luxembourg S.A.
Ferric carboxymaltose; iron; iron dextran; iron (III) isomaltoside; iron sucrose; sodium ferric gluconate	Arteriospasm coronary (19408)	Zane Neikena (LV)	Supplementary information requested (submission by 3 July 2019)	Vifor, Pharmacosmos, Sanofi
Ibuprofen	Acute generalised exanthematous pustulosis (AGEP) (19409)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 3 July 2019)	Reckitt Benckiser
Ibuprofen; ketoprofen	Serious exacerbation of infections (19415)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 31 July 2019)	Reckitt Benckiser, Sanofi-Aventis, Orphan Europe S.A.R.L.
Lithium	Drug induced lichenoid reaction (19389)	Martin Huber (DE)	Supplementary information requested (submission by 31 July 2019)	Teofarma

[7] Daclatasvir; dasabuvir; elbasvir, grazoprevir; glecaprevir, pibrentasvir; ledipasvir, sofosbuvir; ombitasvir, pariteprevir, ritonavir; sofosbuvir; sofosbuvir, velpatasvir; sofosbuvir, velpatasvir, voxilaprevir

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Sebelipase alfa	Nephrotic syndrome (19410)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 31 July 2019)	Alexion Europe SAS
Tigecycline	Bradycardia (19394)	Pilar Rayón (ES)	Supplementary information requested (submission by 31 July 2019)	Pfizer Europe MA EEIG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
5 alfa-reductase inhibitors (5ARIs): finasteride; dutasteride	Type 2 diabetes mellitus (19424)	Annika Folin (SE)	No action at this stage	Not applicable
Amino acids and/or lipids with or without admixture of vitamins or trace elements[8]	Adverse outcomes in neonates treated with solutions not protected from light (19423)	Ulla Wändel Liminga (SE)	· Provide comments on the proposed updates to the product information (submission by 7 June 2019) · Collaborate in the drafting of a single direct healthcare professional communication (DHPC) and communication plan (submission by 7 June 2019)	MAHs of parenteral nutrition solutions containing amino acids and/or lipids with or without admixture of vitamins or trace elements
Mesalazine	Nephrolithiasis (19405)	Martin Huber (DE)	Provide comments on the proposed updates to the product information (submission by 7 June 2019)	Innovator MAHs for mesalazine containing products
Tocilizumab	Facial paralysis (19295)	Brigitte Keller-Stanislawski (DE)	Routine pharmacovigilance	Roche Registration GmbH

[8] For parenteral nutrition

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Tofacitinib	Increased risk of pulmonary embolism and overall mortality arising from a post-authorisation safety study in patients with cardiovascular risk factors treated for rheumatoid arthritis with tofacitinib 10 mg twice daily (19382)	Liana Gross-Martirosyan (NL)	Review under Article 20 of Regulation (EC) No 726/2004	Pfizer Europe MA EEIG
Vascular endothelial growth factor (VEGF) inhibitors[9]	Artery dissections and aneurysms (19330)	Annika Folin (SE)	· For MAHs of VEGF inhibitors for systemic administration: provide comments on the proposed updates to the product information (submission by 7 June 2019) · For MAHs of VEGF inhibitors for intravitreal administration: supplementary information requested (submission by 31 July 2019)	· Roche Registration GmbH, Ipsen Pharma, Genzyme Europe BV, Eli Lilly Nederland BV, EUSA Pharma (Netherlands) BV, Incyte Biosciences Distribution BV, Pfizer Europe MA EEIG, Eisai GmbH, Amgen Europe BV, Bayer AG, Boehringer Ingelheim International GmbH, Novartis Europharm Limited, sanofi-aventis groupe · Bayer AG, Novartis Europharm Limited

[9] Aflibercept; axitinib; bevacizumab; cabozantinib; lenvatinib; nintedanib; pazopanib; ponatinib; ramucirumab; ranibizumab; regorafenib; sorafenib; sunitinib; tivozanib; vandetanib