26 November 2018[1]
EMA/PRAC/758152/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 29-31 October 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 29-31 October 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 (12-15 November 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] 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. Tacrolimus systemic formulation – Hepatitis E infection

Authorisation procedure	Centralised and non-centralised
EPITT No	19246
PRAC rapporteur(s)	Rhea Fitzgerald (IE)
Date of adoption	31 October 2018

Recommendation

Having considered the available evidence from EudraVigilance and the literature as well as the cumulative review submitted by Astellas (MAH innovator), the PRAC has agreed that the MAHs for tacrolimus systemic formulation should submit a variation within 3 months to amend the product information as described below (new text underlined, current text to be deleted ~~struck through~~). No changes to the package leaflet are considered necessary in view of the existing warning on infections.

Summary of product characteristics

4.4. Special warnings and precautions for use

Infections including opportunistic infections

Patients treated with immunosuppressants, including tacrolimus are at increased risk for infections including opportunistic infections (bacterial, fungal, viral and protozoal)~~. Among these conditions are~~ such as BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). Patients are also at an increased risk of infections with viral hepatitis (for example, hepatitis B and C reactivation and de novo infection, as well as hepatitis E, which may become chronic). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating hepatic or renal function or neurological symptoms. Prevention and management should be in accordance with appropriate clinical guidance.

[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. Xylometazoline – Serious ventricular arrhythmia in patients with long QT syndrome

Authorisation procedure	Non-centralised
EPITT No	19242
PRAC rapporteur(s)	Zane Neikena (LV)
Date of adoption	31 October 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH(s) of xylometazoline-containing medicinal products should submit a variation within 3 months, to amend the product information as applicable (taking into account the already existing wording in some nationally authorised products), in order to include the text as described below (new text underlined, text to be adapted by MAHs to individual product <in brackets>):

Summary of product characteristics

4.4. Special warnings and precautions for use

Patients with long QT syndrome treated with xylometazoline may be at increased risk of serious ventricular arrhythmias.

Package leaflet

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

Warnings and precautions

Talk to your doctor or pharmacist before using <Product name>

· if you suffer from a heart disease (e.g. long QT syndrome)

Note: in the package leaflet the text '(e.g. long QT syndrome)' should be added to the bullet point mentioning heart disease, taking into account the already existing wording for nationally authorised medicinal products. For package leaflets which do not mention 'heart disease', a bullet point on 'heart disease (e.g. long QT syndrome)' should be added, in line with the wording above.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Clomipramine; serotonin and noradrenaline reuptake inhibitors (SNRI)[4]; selective serotonin reuptake inhibitors (SSRI)[5]; vortioxetine	Persistent sexual dysfunction after drug withdrawal (19277)	Liana Gross-Martirosyan (NL)	Supplementary information requested (submission by 13 February 2019)	Eli Lilly, Lundbeck, Mylan, Pfizer, GSK, Almirall, Pierre Fabre, Alfasigma
Dabigatran	Hallucinations (19298)	Anette Kristine Stark (DK)	Assess in the next PSUR (submission by 27 May 2019)	Boehringer Ingelheim International GmbH
Mepolizumab	Hypertensive crisis and hypertension (19301)	Brigitte Keller-Stanislawski (DE)	Assess in the next PSUR (submission by 2 December 2018)	GlaxoSmithKline Trading Services Limited
Niraparib	Sepsis (19311)	Patrick Batty (UK)	Assess in the next PSUR (submission by 5 December 2018)	Tesaro UK Limited
Nivolumab	Hypoparathyroidism (19310)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 9 January 2019)	Bristol-Myers Squibb Pharma EEIG
Paracetamol	Maternal paracetamol use during pregnancy and premature ductus arteriosus closure in offspring (19297)	Laurence de Fays (BE)	Supplementary information requested (submission by 1 January 2019)	Teva, GlaxoSmithKline, Bristol-Myers Squibb, Aurobindo, Stada, Fresenius, PanPharma, Novartis, Sanofi and Johnson & Johnson

[4] Desvenlafaxine; duloxetine; milnacipran; venlafaxine
[5] Citalopram; escitalopram; fluoxetine; fluvoxamine; paroxetine; sertraline

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Peramivir	Hepatic failure (19314)	Ulla Wändel Liminga (SE)	Assess within the ongoing PSUR (submission by 14 December 2018)	Biocryst UK Limited
Rivaroxaban; apixaban; dabigatran; edoxaban;	Recurrent thrombosis in patients with antiphospholipid syndrome (19320)	Ulla Wändel Liminga (SE)	Supplementary information, including list of questions requested (submission by 9 January 2019)	Bayer AG, Bristol-Myers Squibb / Pfizer EEIG, Boehringer Ingelheim International GmbH, Daiichi Sankyo Europe GmbH

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Paracetamol	Paracetamol use in pregnancy and child neurodevelopment and effects on the urogenital apparatus (17796)	Laurence de Fays (BE)	Provide comments on the proposed updates to the product information (submission by 1 January 2019)	Teva, GlaxoSmithKline, Bristol-Myers Squibb, Aurobindo, Stada, Fresenius, PanPharma, Novartis, Sanofi and Johnson & Johnson