25 November 2019[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 28-31 October 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 28-31 October 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 (11-14 November 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. Iron sucrose; iron carboxymaltose; iron isomaltoside; iron dextran; sodium ferric gluconate – Arteriospasm coronary

Authorisation procedure	Non-centralised
EPITT No	19408
PRAC rapporteur(s)	Zane Neikena (LV)
Date of adoption	31 October 2019

Recommendation

Having considered the data from clinical trials and post–marketing use provided by the MAHs, together with the available evidence from literature, the PRAC has agreed that the strengths of the causal relationship of Kounis syndrome with the use of iron containing medicinal products for intravenous administration is sufficient enough to add a warning to the product information of iron sucrose, ferric carboxymaltose, iron isomaltoside, iron dextran and sodium ferric gluconate containing medicinal products.

Therefore all MAHs of iron sucrose, iron carboxymaltose, iron isomaltoside, iron dextran and sodium ferric gluconate containing medicinal products 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

Hypersensitivity reactions

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

4.8. Undesirable effetcs

Cardiac disorders

Frequency 'Not known': Kounis syndrome

Package leaflet

4. Possible side effects

Allergic reactions

Tell your doctor immediately if you experience any of the following signs and symptoms that may indicate a serious allergic reaction ……. And chest pain which can be a sign of a potentially serious allergic reaction called Kounis syndrome.

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

2. Recommendations for submission of supplementary information

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)	Supplementary information requested (submission by 8 January 2020)	Merck Sharp & Dohme Ltd, GlaxoSmithKline
Adalimumab	Autoimmune encephalitis (19483)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 8 January 2020)	AbbVie Deutschland GmbH & Co. KG
Ceftriaxone	Encephalopathy (19492)	Zane Neikena (LV)	Supplementary information requested (submission by 8 January 2020)	Roche
Mycophenolic acid; mycophenolate mofetil	Posterior reversible encephalopathy syndrome (PRES) (19473)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 8 January 2020)	Novartis Pharma N.V., Roche Registration GmbH
Paroxetine	Microscopic colitis (19474)	Liana Gross-Martirosyan (NL)	Supplementary information requested (submission by 8 January 2020)	GlaxoSmithKline
Pazopanib	Tumour lysis syndrome (TLS) (19494)	Hans Christian Siersted (DK)	Assess in the next PSUR (submission by 27 December 2019)	Novartis Europharm Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Azacitidine	Progressive multifocal leukoencephalopathy (PML) (19422)	Menno van der Elst (NL)	Routine pharmacovigilance	Celgene Europe BV
Buprenorphine, naloxone	Drug-drug interaction with serotonergic drugs leading to serotonin syndrome (19475)	Martin Huber (DE)	No action at this stage	Not applicable
Ibuprofen; ketoprofen and fixed-dose combinations[4]	Serious exacerbation of infections (19415)	Anette Kirstine Stark (DK)	No action at this stage	Not applicable
Imiquimod	Pemphigus (19441)	Adam Przybylkowski (PL)	Monitor in PSUR	MAHs of imiquimod-containing medicinal products
Infliximab and all other tumour necrosis factor alpha inhibitors: adalimumab; etanercept; certolizumab pegol; golimumab	Kaposi's sarcoma (19480)	Ulla Wändel Liminga (SE)	No action at this stage	Not applicable
Tigecycline	Bradycardia (19394)	Maria del Pilar Rayon (ES)	Monitor in PSUR	MAHs of tigecycline-containing medicinal products
Vascular endothelial growth factor (VEGF) inhibitors for intravitreal use: aflibercept; ranibizumab	Artery dissections and aneurysms (19330)	Annika Folin (SE)	Monitor in PSUR	Novartis Europharm Limited, Bayer AG

[4] Chlorphenamine, ibuprofen, phenylephrine; dimenhydrinate, ibuprofen, caffeine; ibuprofen, ascorbic acid; ibuprofen, caffeine; ibuprofen, codeine; ibuprofen, hydrocodone; ibuprofen, paracetamol; ibuprofen, phenylephrine; ibuprofen, pseudoephedrine; ketoprofen, omeprazole; ketoprofen, sucralfate