26 January 2017
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 9-12 January 2017

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 9-12 January 2017 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][1] 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 (23-26 January 2017) 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 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[2]

1.1. Azacitidine – Pericarditis and pericardial effusion

Authorisation procedure	Centralised
EPITT No	18733
PRAC rapporteur(s)	Sabine Straus (NL)
Date of adoption	12 January 2017

Recommendation

Having considered the data submitted by the MAH of Vidaza, the PRAC has agreed that the available evidence suggests a possible causal association between azacitidine and pericardial effusion that warrants a summary of product characteristics update. The MAH is requested to submit a variation within 2 months to update the product information as described below (new text underlined). The proposed assigned frequency is "common" based on the pooled clinical trial data.

Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions

System Organ Class	Very common	Common	Uncommon	Rare	Not known
Cardiac disorders		Pericardial effusion			

Package leaflet

4. Possible side effects

Common side effects (may affect up to 1 in 10 people)

- Collection of fluid around the heart (pericardial effusion)

[2] 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. Propofol; valproate – Pharmacokinetic drug interaction leading to an increased propofol exposure

Authorisation procedure	Non-centralised
EPITT No	18696
PRAC rapporteur(s)	Helga Olsen (NO)
Date of adoption	12 January 2017

Recommendation

Having considered the available evidence in the literature on the drug interaction between propofol and valproate, the PRAC has agreed that the MAHs of propofol-containing medicinal products should submit a variation within 2 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 need for lower propofol doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of propofol may be considered.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amoxicillin; amoxicillin, clavulanic acid	Drug rash eosinophilia systemic symptoms (DRESS) syndrome (18802)	Jan Neuhauser (AT)	Supplementary information requested (submission by 2 March 2017)	GlaxoSmithKline
Fluconazole	Spontaneous abortion and stillbirth (18666)	Doris Irene Stenver (DK)	Supplementary information requested (submission by 23 January 2017)	Pfizer
Gabapentin	Respiratory depression without concomitant opioid use (18814)	Martin Huber (DE)	Supplementary information requested (submission by 2 March 2017)	Pfizer; Glenmark
Pembrolizumab	Sarcoidosis (18806)	Sabine Straus (NL)	Assess within ongoing PSUSA procedure (submission by 8 March 2017)	Merck Sharp & Dohme Limited

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Sodium iodide [^{131}I]	Hyperparathyroidism and parathyroid adenomas (18820)	Ana Sofia Martins (PT)	Assess in the next PSUR (submission by 30 May 2017)	MAHs of sodium iodide [^{131}I]

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Darbepoetin alfa	Incorrect use of device associated with adverse reactions including underdose, drug dose omission, accidental exposure to product and injection site reactions (18718)	Valerie Straßmann (DE)	Submission of a variation and supplementary information by 16 June 2017	Amgen Europe B.V.
Lenalidomide	Hemophagocytic lymphohistiocytosis (HLH) (18689)	Claire Férard (FR)	Routine pharmacovigilance	Celgene Europe Limited
Paracetamol	Paracetamol use in pregnancy and child neurodevelopment (17796)	Laurence de Fays (BE)	Routine pharmacovigilance	MAHs of paracetamol-containing products
Proton pump inhibitors (PPIs): dexlansoprazole; esomeprazole; lansoprazole; omeprazole ; pantoprazole; rabeprazole	Incident chronic kidney disease (CKD) and progression to end stage renal disease (ESRD) (18698)	Rafe Suvarna (UK)	Routine pharmacovigilance	MAHs of PPIs