23 June 2016
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 6-9 June 2016

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 6-9 June 2016 (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 (20-23 June 2016) 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. Riociguat – Increased mortality and serious adverse events (SAEs) in patients with pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) in a single clinical trial

Authorisation procedure	Centralised
EPITT No	18681
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	9 June 2016

Recommendation *[see also section 2]*

Based on the available evidence, including the data submitted by the MAH of Adempas (riociguat) in response to the List of Questions dated 20 May 2016, the PRAC has recommended [that the] MAH should submit within 30 days a variation to amend the product information as described below (new text underlined) to contraindicate its use in patients with pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP). The interim results of the RISE-IIP study (increase in mortality and serious adverse events (SAEs) in riociguat treated patients and the absence of clinically significant beneficial effects in these patients) should also be included in the summary of product characteristics. The package leaflet should also be updated to reflect the contraindication.

Summary of product characteristics

Section 4.3 – Contraindications

- Patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) (see Section 5.1)

Section 5.1 - Pharmacodynamic properties

Clinical efficacy and safety

Patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP)

A randomised, double blind, placebo-controlled phase II study (RISE-IIP) to evaluate the efficacy and safety of riociguat in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) was terminated early. Interim results showed an increased risk of mortality and serious adverse events in subjects receiving riociguat compared to those receiving placebo. The available data do not indicate a clinically significant benefit from riociguat treatment in these patients.

Riociguat is therefore contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (see section 4.3).

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

Package leaflet

Section 2 - What you need to know before you take Adempas

Do NOT take Adempas:

- If you have increased pressure in your pulmonary circulation associated with scarring of the lungs, of unknown cause (idiopathic pulmonary pneumonia).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Cisplatin	Peripheral arterial thromboembolic events (ATEs) and arterial occlusion (18560)	Doris Irene Stenver (DK)	Assess in the next PSUR (submission by 18 March 2018)	MAHs of cisplatin containing medicinal products (restricted to MAHs who submit PSURs)
Dasabuvir; ombitasvir, paritaprevir, ritonavir	Depression and suicidal ideation (18670)	Dolores Montero Corominas (ES)	Assess in the next PSUR (submission by 22 September 2016)	AbbVie Ltd
Direct-acting antivirals indicated for the treatment of hepatitis C: daclatasvir; dasabuvir; ombitasvir, paritaprevir, ritonavir; simeprevir; sofosbuvir; sofosbuvir, ledipasvir; boceprevir, telaprevir *[see also section 3]*	Drug interaction with fluindione leading to a reduced international normalized ratio (INR) (18654)	Dolores Montero Corominas (ES)	Comment on PRAC recommendation for update of the product information (submission by 30 June 2016)	AbbVie Ltd, Bristol-Myers Squibb, Gilead Sciences International Ltd, Janssen-Cilag, Merck Sharp & Dohme Limited
Olanzapine	Restless legs syndrome (RLS) (18659)	Kimmo Jaakkola (FI)	Supplementary information requested (submission by 24 August 2016)	Eli Lilly Nederland B.V.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Pazopanib	Polycythaemia (18660)	Doris Irene Stenver (DK)	Supplementary information requested (submission by 24 August 2016)	Novartis Europharm Ltd
Riociguat *[see also section 1]*	Increased mortality and serious adverse events (SAEs) in patients with pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP) in a single clinical trial (18681)	Julie Williams (UK)	Supplementary information requested (submission by 31 August 2016); update of risk management plan requested (submission by 31 August 2016); Direct Healthcare Professional Communication (DHPC) requested	Bayer Pharma AG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Direct-acting antivirals indicated for the treatment of hepatitis C: daclatasvir; dasabuvir; ombitasvir, paritaprevir, ritonavir; simeprevir; sofosbuvir; sofosbuvir, ledipasvir; boceprevir, telaprevir *[see also section 2]*	Drug interaction with fluindione leading to a reduced international normalized ratio (INR) (18654)	Dolores Montero Corominas (ES)	Monitor possible interactions with vitamin K antagonists in PSUR	AbbVie Ltd, Bristol-Myers Squibb, Gilead Sciences International Ltd, Janssen-Cilag, Merck Sharp & Dohme Limited