28 April 2016
EMA/PRAC/259909/2016
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 11-14 April 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 11-14 April 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 (25-28 April 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. Olanzapine – Drug reaction with eosinophilia and systemic symptoms (DRESS)

Authorisation procedure	Centralised and non-centralised
EPITT No	18534
PRAC rapporteur(s)	Jaakkola Kimmo (FI)
Date of adoption	14 April 2016

Recommendation

Having considered the available evidence from case reports in EudraVigilance and published case reports in the literature, the PRAC has agreed that the MAH(s) of olanzapine containing products should submit a variation within 2 months, to amend the product information as described below (new text underlined).

Summary of Product Characteristics

Section 4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (frequency unknown)

Package Leaflet

4. Possible side effects

Very rare side effects include serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia).

[2] 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
Adalimumab	Acute febrile neutrophilic dermatosis (Sweet's syndrome) (18630)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 30/06/2016)	AbbVie Ltd
Agomelatine	Leukopenia (18638)	Kristin Thorseng Kvande (NO)	Supplementary information requested (submission by 30/06/2016)	Laboratoires Servier
Agomelatine	Urinary retention (18637)	Kristin Thorseng Kvande (NO)	Supplementary information requested (submission by 30/06/2016)	Laboratoires Servier
Cobicistat containing products: cobicistat; cobicistat, atazanavir sulfate; cobicistat, darunavir; cobicistat elvitegravir, emtricitabine, tenofovir alafenamide; cobicistat, elvitegravir, emtricitabine, tenofovir disoproxil fumarate	Drug interaction with corticosteroids leading to adrenal suppression (18647)	Rafe Suvarna (UK)	Supplementary information requested (submission by 30/06/2016)	Gilead Sciences International Ltd; Bristol-Myers Squibb Pharma EEIG; Janssen-Cilag International N.V.
Fulvestrant	Interference with oestradiol assay leading to false oestradiol results (18636)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 30/06/2016)	AstraZeneca UK Ltd

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Iomeprol	Haemolysis (18625)	Ingebjørg Buajordet (NO)	Supplementary information requested (submission by 30/06/2016)	Bracco

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Canagliflozin; canagliflozin, metformin	Potential increased risk of lower limb amputations	Valerie Strassmann (DE)	Circulation of a Direct Healthcare Professional Communication (DHPC); further action to be addressed within the procedure under Article 20 of Regulation (EC) No 726/2004 on canagliflozin	Janssen-Cilag International N.V.
Direct-acting antivirals indicated for the treatment of hepatitis C: daclatasvir; dasabuvir; ombitasvir, paritaprevir, ritonavir; simeprevir; sofosbuvir; sofosbuvir, ledipasvir	Unexpected early hepatocellular carcinoma recurrence (18653)	Dolores Montero Corominas (ES)	To be addressed within the procedure under Article 20 of Regulation (EC) No 726/2004 on direct-acting antivirals against hepatitis C	AbbVie Ltd, Bristol-Myers Squibb Pharma EEIG, Gilead Sciences International Ltd, Janssen-Cilag International N.V.
Flucloxacillin and other penicillins of the beta-lactamase resistant group: cloxacillin; dicloxacillin; nafcillin; oxacillin	Metabolic acidosis following administration of flucloxacillin in association with paracetamol (18514)	Margarida Guimarães (PT)	Routine pharmacovigilance	MAHs of flucloxacillin and other penicillin containing products

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Recombinant Factor VIII: antihemophilic factor (recombinant); moroctocog alfa; octocog alfa	Inhibitor development in previously untreated patients (18134)	Brigitte Keller-Stanislawski (DE)	Monitor published studies on drug inhibitor development with the aim of keeping the product information up to date	Bayer Pharma AG, Baxter AG, Pfizer Limited, various