14 September 2017
EMA/PRAC/407007/2017 Corr[1]
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 29 August-1 September 2017 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 August-1 September 2017 (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 September 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] Please see page 4 for corrections implemented on 6 October 2017 in the pramipexole package leaflet.
[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. Mesalazine – Risk of photosensitivity reactions

Authorisation procedure	Non-centralised
EPITT No	18869
PRAC rapporteur(s)	Patrick Batty (UK)
Date of adoption	1 September 2017

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH(s) of mesalazine-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

4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Frequency 'rare': Photosensitivity*

*see section c)

Photosensitivity

More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

Package leaflet

4. Possible side effects

Rare side effects

- Increased sensitivity of your skin to sun and ultraviolet light (photosensitivity).

[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. Pramipexole – Dystonia

Authorisation procedure	Centralised and non-centralised
EPITT No	18866
PRAC rapporteur(s)	Doris Irene Stenver (DK)
Date of adoption	1 September 2017

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, and the known association of pramipexole with axial dystonia, the PRAC has agreed that the MAHs of pramipexole-containing products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Dyskinesia

[...]

Dystonia

Axial dystonia including antecollis, camptocormia and pleurothotonus (Pisa Syndrome) has occasionally been reported in patients with Parkinson's disease following initiation or incremental dose increase of pramipexole. Although dystonia may be a symptom of Parkinson's disease, the symptoms in these patients have improved after reduction or withdrawal of pramipexole. If dystonia occurs, the dopaminergic medication regimen should be reviewed and an adjustment in the dose of pramipexole considered.

Package leaflet

2. What you need to know before you take <product name>

Warnings and precautions

Talk to your doctor before taking <product name>. Tell your doctor if you have (had) or develop any medical conditions or symptoms, especially any of the following:

[...]

- Dyskinesia

[...]

- Dystonia[4] (inability of keeping your body and neck straight and upright (axial dystonia)). In particular, you may experience forward flexion of the head and neck (also called antecollis), forward bending of the lower back (also called camptocormia) or sidewards bending of the back (also called pleurothotonus or Pisa Syndrome). If this happens, your doctor may want to change your medication.

[4] The two bullet points have been merged and brackets have been added after 'dystonia'.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Azithromycin	Increased rate of relapses of haematological malignancies and mortality in hematopoietic stem cell transplantation (HSCT) patients (18907)	Kimmo Jaakkola (FI)	Supplementary information requested (submission by 9 November 2017)	Pfizer
Cefalexin	Acute generalized exanthematous pustulosis (AGEP) (18911)	Dolores Montero (ES)	Supplementary information requested (submission by 9 November 2017)	Eurocept International BV
Dexmedetomidine	Polyuria (18926)	Julie Williams (UK)	Assess in currently ongoing PSUSA procedure	Orion Corporation
Dulaglutide	Gastrointestinal stenosis and obstruction (18931)	Carmela Macchiarulo (IT)	Supplementary information requested (submission by 9 November 2017)	Eli Lilly Nederland B.V.
Filgrastim; lenograstim; lipegfilgrastim; pegfilgrastim	Aortitis (18940)	Overall Rapporteur: Patrick Batty (UK); Individual assessments - filgrastim: Kirsti Villikka (FI); lenograstim: Ghania Chamouni (FR); lipegfilgrastim, pegfilgrastim: Patrick Batty (UK)	Supplementary information requested (submission by 9 November 2017)	MAHs of filgrastim, lenograstim, lipegfilgrastim and pegfilgrastim containing products
Hydroxycarbamide	Cutaneous lupus erythematosus (18939)	Laurence de Fays (BE)	Supplementary information requested (submission by 9 November 2017)	MAHs of hydroxycarbamide-containing products
Ipilimumab	Histiocytosis haematophagic (18929)	Sabine Straus (NL)	Assess in currently ongoing PSUSA procedure (submission by 27 September 2017)	Bristol-Myers Squibb Pharma EEIG

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Megestrol; vitamin K antagonists (acenocoumarol, fluindione, phenindione, phenprocoumon, warfarin)	Drug interaction leading to elevated international normalised ratio (INR)/ haemorrhage with megestrol and vitamin K antagonists (18910)	Almath Spooner (IE)	Supplementary information requested (submission by 9 November 2017)	Laboratoire Theramex S.A.M.; Sandoz B.V.; Merck Santé S.A.S.; Mercury Pharma Group Ltd; Meda AS; Teofarma S.R.L.
Methotrexate	Pulmonary alveolar haemorrhage (18850)	Martin Huber (DE)	Supplementary information requested (submission by 9 November 2017)	Pfizer
Pemetrexed	Nephrogenic diabetes insipidus (18930)	Ghania Chamouni (FR)	Supplementary information requested (submission by 9 November 2017)	Eli Lilly Nederland B.V.
Rivaroxaban	Increased risk of bleeding following drug interaction between rivaroxaban and macrolide antibiotics (18934)	Qun-Ying Yue (SE)	Assess in the next PSUR (submission by 24 November 2017)	Bayer AG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amlodipine; rifampicin	Drug interaction between amlopdine and rifamipicin leading to reduced antihypertensive effect of amlodipine (18933)	Doris Irene Stenver (DK)	No action at this stage	Not applicable
Azithromycin; tobramycin *inhaled*	Possible interaction between tobramycin and azithromycin leading to lower effectiveness of tobramycin (18855)	Menno van der Elst (NL)	No action at this stage (assess results of TEACH trial when available, ClinicalTrials.gov NCT02677701)	Novartis Europharm Ltd; PARI Pharma GmbH

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Doxycycline	Doxycycline induced Jarisch-Herxheimer reaction (18937)	Martin Huber (DE)	Provide comments on proposed updates to the product information (submission by 15 September 2017)	Pfizer
Meningococcal group B vaccine (rDNA, component, adsorbed)	Arthritis and synovitis (18764)	Qun-Ying Yue (SE)	· Update RMP · Address list of questions in next PSUR (submission by 24 March 2018)	GSK Vaccines S.r.l