21 July 2016
EMA/PRAC/452657/2016 Corr[1]
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 4-8 July 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 4-8 July 2016 (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 (18-21 July 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] Please see footnote on page 3 regarding ferrous sulfate.
[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. Ferrous sulfate – Mouth ulceration

Authorisation procedure	Non-centralised
EPITT No	18623
PRAC rapporteur(s)	Leonor Chambel (PT)
Date of adoption	7 July 2016

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the data submitted by the MAHs, and the known association of ferrous sulfate with local mucosal irritation, the PRAC has agreed that the MAH(s) of ferrous sulfate tablets should submit a variation within 3 months, to amend the product information as described below:

Summary of product characteristics

4.2. Posology and method of administration

Method of administration:

The tablets should not be sucked, chewed or kept in the mouth, but swallowed whole with water.

Tablets should be taken before meals or during meals, depending on gastrointestinal tolerance.[4]

4.4. Special warnings and precautions for use

Due to the risk of mouth ulcerations and tooth discolouration, tablets should not be sucked, chewed or kept in the mouth, but swallowed whole with water.

4.8. Undesirable effects

Post-marketing: The following ADRs have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Gastrointestinal disorders:

mouth ulceration*
* in the context of incorrect administration, when the tablets are chewed, sucked or kept in mouth. Elderly patients and patients with deglutition disorders may also be at risk of oesophageal lesions or of bronchial necrosis, in case of false route.

Package leaflet

2 - What you need to know before you take [Product name]

[3] Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.
[4] This sentence should be implemented in line with existing information on tolerability and the type of food (see also 4.5) as taking with certain foods may lower iron absorption.

Warnings and precautions

Due to the risk of mouth ulceration and tooth discolouration, tablets should not be sucked, chewed or kept in the mouth but swallowed whole with water. If you cannot follow this instruction or have difficulty swallowing, please contact your doctor.

3 - How to take [Product name]

Swallow the tablet whole with water. Do not suck, chew or keep the tablet in your mouth.

4 - Possible side effects

Not known (frequency cannot be estimated from the available data)
Mouth ulceration (in case of incorrect use, when tablets are chewed, sucked or left in the mouth)
Elderly patients and patients with difficulty swallowing may also be at risk of ulceration of the throat, oesophagus (the tube that connects your mouth with your stomach) or bronchus (the major air passages of the lungs) if the tablet enters the airways.

1.2. Proton pump inhibitors (PPIs): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – Elevated circulating levels of Chromogranin A

Authorisation procedure	Centralised and non-centralised
EPITT No	18614
PRAC rapporteur(s)	Rafe Suvarna (UK)
Date of adoption	7 July 2016

Recommendation

Having considered the available evidence in EudraVigilance, the reviews submitted by Janssen/EISAI, Takeda and AstraZeneca including data from non-clinical and clinical trial sources, their safety database and the literature, as well as the existence of a plausible biological mechanism, the PRAC has agreed that the MAH(s) of rabeprazole, lansoprazole, dexlansoprazole, pantoprazole, esomeprazole and omeprazole containing products should submit a variation within 3 months, to amend the product information as described below:

Summary of product characteristics

4.4. Special warnings and precautions for use

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, [Product name] treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

5.1. Pharmacodynamic properties

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Package leaflet

2 - What you need to know before you take [Product name]

Warnings and precautions

Tell your doctor before taking this medicine, if:

- [...]
- You are due to have a specific blood test (Chromogranin A)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Acenocoumarol; phenprocoumon; fluindione; phenindione	Calciphylaxis (18710)	Martin Huber (DE)	Supplementary information requested (submission by 28 September 2016)	Meda Pharma; Merck Santé S.A.S; Novartis, Merus Labs Luxco; Mercury Pharma Group
Aripiprazole	Compulsive shopping (18683)	Leonor Chambel (PT)	Assess in the next PSUR (submission by 24 September 2016)	Otsuka Pharmaceutical Europe Ltd
Exenatide	Incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia (18688)	Yue Qun-Ying (SE)	Supplementary information requested (submission by 28 September 2016)	AstraZeneca AB

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ipilimumab	Type 1 diabetes mellitus (18674)	Sabine Straus (NL)	Supplementary information requested in the ongoing PSUSA procedure	Bristol-Myers Squibb Pharma EEIG
Loperamide	QT prolongation and torsade de pointes with high doses of loperamide from abuse and misuse (18339)	Nectaroula Cooper (CY)	Supplementary information requested (submission by 28 September 2016)	Johnson & Johnson Consumer B.V.
Methylphenidate	Priapism (18719)	Julie Williams (UK)	Supplementary information requested (submission by 28 September 2016)	Novartis pharma GmbH; Janssen-Cilag; SHIRE Pharmaceuticals; Sandoz; Johnson & Johnson; Alternova A/S; Proton Pharma S.A.; Medice Arzneimittel Putter GmbH & Co. KG; Generics (UK) Limited trading as Mylan; Laboratorios Rubió
Vildagliptin; vildagliptin, metformin	Pemphigoid (18692)	Yue Qun-Ying (SE)	Supplementary information requested (submission by 28 September 2016)	Novartis Europharm Ltd

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ceftriaxone	Drug reaction with eosinophilia and systemic symptoms (DRESS) (18715)	Zane Neikena (LV)	Routine pharmacovigilance	MAHs of ceftriaxone containing products
Fluoroquinolones (for systemic use): ciprofloxacin; enoxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Uveitis (18686)	Martin Huber (DE)	No action at this stage	Not applicable
Human albumin solutions	Increased risk of death in patients with severe traumatic brain injury and in patients with burns (13948)	Brigitte Keller-Stanislawski (DE)	No action for MAH	Not applicable
Human coagulation (plasma-derived) factor VIII: Human coagulation factor VIII (antihemophilic factor A); human coagulation factor VIII (inhibitor bypassing fraction); human coagulation factor VIII,	Inhibitor development in previously untreated patients (PUPs) with haemophilia A treated with plasma-derived *vs* recombinant coagulation factor VIII concentrates (18701)	Brigitte Keller-Stanislawski (DE)	To be addressed within the procedure under Article 31 of Directive 2001/83/EC that has been triggered for medicinal products containing factor VIII	Not applicable

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
human von Willebrand factor. Recombinant factor VIII: antihemophilic factor (recombinant); moroctocog alfa; octocog alfa; simoctocog alfa; turoctocog alfa				
Tramadol; tramadol, paracetamol	Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) (18471)	Julie Williams (UK)	Routine pharmacovigilance	Grünenthal