23 July 2015
EMA/PRAC/450903/2015
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 6-9 July 2015

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 July 2015 (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 July 2015) 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 established procedures and timelines for submission of variation applications pertaining to generic medicinal products are to be followed.

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. Dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – Subacute cutaneous lupus erythematosus

Authorisation procedure	Centralised and non-centralised
EPITT No	18119
PRAC rapporteur(s)	Rafe Suvarna (UK)
Date of adoption	9 July 2015

Recommendation

Having considered the cases from the global safety databases of Takeda, Janssen/Eisai and AstraZeneca, as well as the comments received from these MAHs, the PRAC has confirmed that there is sufficient evidence that indicates that Subacute Cutaneous Lupus Erythematosus (SCLE) is likely to be a class effect for proton pump inhibitors.

Taking into consideration the relevant data across all substances in the class, including the cases with positive re-challenge, the evidence from published literature, and the likelihood of under-reporting given that photosensitivity is a known side effect of proton pump inhibitors, the PRAC agreed that the MAH(s) of medicinal products containing omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole and dexlansoprazole should submit a variation within 3 months to amend the product information as described below (new text underlined):

Summary of Product Characteristics (both prescription and non-prescription)

Section 4.4 - Special warnings and precautions for use

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping {Drug name}. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Section 4.8 - Undesirable effects

Skin and subcutaneous tissue disorders

Frequency 'not known': Subacute cutaneous lupus erythematosus (see section 4.4).

Package Leaflet (both prescription and non-prescription)

Section 2: What you need to know before you take {Drug name}

Warnings and precautions

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

Talk to your doctor before taking {Drug name}:

- if you have ever had a skin reaction after treatment with a medicine similar to {Drug name} that reduces stomach acid.

If you get a rash on your skin, especially in areas exposed to the sun tell your doctor as soon as you can, as you may need to stop your treatment with {Drug name}. Remember to also mention any other ill-effects like pain in your joints.

Section 4: Possible side effects

- Frequency 'not known': rash, possibly with pain in the joints

1.2. Donepezil – Rhabdomyolysis

Authorisation procedure	Non-centralised
EPITT No	18261
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	9 July 2015

Recommendation

Having considered the available evidence, including the data submitted by the MAH, the PRAC has agreed that the MAHs of donepezil-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

Section 4.8 - Undesirable effects

Musculoskeletal, connective tissue and bone disorders

Frequency 'very rare': Rhabdomyolysis*

(To be inserted in the table footnote): * Rhabdomyolysis has been reported to occur independently of neuroleptic malignant syndrome and in close temporal association with donepezil initiation or dose increase.

Package Leaflet

Section 4: Possible side effects

Serious side effects:

You must tell your doctor immediately if you notice these serious side effects mentioned. You may need urgent medical treatment.

- Muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell, have a high temperature or have dark urine. They may be caused by an abnormal muscle breakdown which can be life threatening and lead to kidney problems (a condition called rhabdomyolysis).

2. Recommendations for submission of supplementary information

The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a **causal relationship** between the medicine and the reported adverse event.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Convulsion (18211)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 07/08/2015)	AbbVie Ltd
Human fibrinogen / human thrombin	Intestinal obstruction (18373)	Brigitte Keller Stanislawski (DE)	Supplementary information requested (submission by 03/09/2015)	Takeda Austria GmbH
Ipilimumab	Vogt-Koyanagi-Harada syndrome (18403)	Sabine Straus (NL)	Supplementary information to be requested in the preliminary assessment report of the PSUSA	Bristol-Myers Squibb Pharma EEIG
Palifermin	Infection (18401)	Rafe Suvarna (UK)	Supplementary information requested (submission by 03/09/2015)	Swedish Orphan Biovitrum AB (publ)
Saxagliptin; saxagliptin/metformin	Acute kidney injury (18379)	Menno van der Elst (NL)	Supplementary information requested (submission by 01/10/2015)	AstraZeneca AB
Warfarin	Bone density decreased (18173)	Torbjörn Callreus (DK)	Supplementary information requested (submission by 03/09/2015)	Bristol Myers Squibb, Takeda, Nycomed, Teofarma

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amiodarone	Pancreatitis (18216)	Menno van der Elst (NL)	Recommendation for product information update to be addressed within the scope of the PSUR single assessment procedure (PSUSA/00000166/201412)	MAHs of amiodarone-containing products
Infliximab	Rhabdomyolysis (18129)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	Hospira UK Limited, Janssen Biologics B.V., Celltrion Healthcare Hungary Kft.