27 February 2015
EMA/PRAC/107418/2015 Corr.[3]
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 9-12 February 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 9-12 February 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 (23-26 February 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. Amiodarone – Syndrome of inappropriate antidiuretic hormone secretion[3] (SIADH)

Substance (invented name)	Amiodarone
Authorisation procedure	Non-centralised
EPITT No	18091
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of adoption	12 February 2015

Recommendation

Having considered the available evidence the PRAC has agreed that the MAHs of amiodarone for intravenous administration should submit a variation within 2 months, to amend the product information as described below (new text underlined). The package leaflets should be updated accordingly.

Summary of product characteristics (SmPC)

Section 4.8:

Endocrine disorders:

Very rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Package leaflet

4. Possible side effects

Very rare (affects less than 1 in 10,000 people)

Feeling unwell, confused or weak, feeling sick (nausea), loss of appetite, feeling irritable. This could be an illness called 'syndrome of inappropriate anti-diuretic hormone secretion' (SIADH).

[2] Translations in EU languages of the adopted PRAC recommendations for update of the product information will be made available to MAHs via the EMA website. The translations will be reviewed by National Competent Authorities of the Member States and thereafter published. It is expected that this will occur within 3 weeks of publishing this document.
[3] Word missing in the initial version published on 3 March 2015.

1.2. Aripiprazole – Hyperprolactinaemia

Substance (invented name)	Aripiprazole (Abilify; EMEA/H/C/000471), (Abilify Maintena; EMEA/H/C/002795)
Authorisation procedure	Centralised
EPITT No	18086
PRAC rapporteur(s)	Margarida Guimarães (PT)
Date of adoption	12 February 2015

Recommendation

Having considered the available evidence in EudraVigilance, the MAH's clinical trials and pharmacovigilance databases and the literature, the PRAC has agreed that the MAH of Abilify and Abilify Maintena should submit variations within 2 months, to amend the product information as described below (new text underlined). In addition, the MAH should describe the data on hyper- and hypoprolactinaemia in the SmPCs' sections 5.1. Following the variations of the marketing authorisations for these products, the MAH for any product with the same active substance should submit a respective variation application.

SmPC:

Section 4.8 – Undesirable effects:

Tabulated list of adverse reactions:

Endocrine disorders

Frequency 'uncommon': Hyperprolactinaemia

Description of selected adverse reactions:

Hyperprolactinaemia

In clinical trials for the approved indication(s) and post-marketing, both increase and decrease in serum prolactin as compared to baseline was observed with aripiprazole (section 5.1).

Package leaflet:

Section 4: Possible side effects

Uncommon side effects (may affect up to 1 in 100 people):

Increased blood levels of the hormone prolactin.

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
Aliskiren	Severe hyponatraemia leading to neurological symptoms (18212)	Carmela Macchiarulo (IT)	Assess in the PSUR (submission of supplementary information by 11/03/2015)	Novartis Europharm Ltd
Everolimus	Lymphoedema (18197)	Martin Huber (DE)	Assess in the next PSUR (submission by 09/06/2015)	Novartis Europharm Ltd
Teriparatide	Angina Pectoris (18203)	Julie Williams (UK)	Supplementary information requested (submission by 11/04/2015)	Eli Lilly Nederland B.V.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Paliperidone	Accidental exposure of children to oral formulation (18069)	Qun-Ying Yue (SE)	Routine pharmacovigilance	Janssen-Cilag International N.V.
Sodium-containing effervescent, dispersible and soluble medicines	Cardiovascular events (17931)	Julie Williams (UK)	No action at this stage	Not applicable