27 March 2015
EMA/PRAC/176901/2015 Corr[3]
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 9-12 March 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 March 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 March 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. Aripiprazole – Aggression and related events

Substance (invented name)	Aripiprazole (Abilify EMEA/H/C/000471, Abilify Maintena EMEA/H/C/002755)
EPITT No	18127
PRAC rapporteur(s)	Margarida Guimarães (PT)
Date of adoption	12 March 2015

Recommendation

Having considered the available evidence in the literature and from individual case safety reports, the PRAC has agreed that the MAH(s) of aripiprazole-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:

Tabulated list of adverse reactions

Psychiatric disorders

Frequency 'not known': aggression

Package Leaflet:

Section 4: Possible side effects

The following side effects have been reported since the marketing of oral aripiprazole but the frequency for them to occur is not known: Aggression

The PRAC has further agreed that the MAH for Abilify and Abilify Maintena should submit in the next PSUR (data lock point 16/07/2015), a cumulative review of aripiprazole overdose and the risk of aggression and related events.

[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.

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 09/05/2015)	AbbVie Ltd
Amiodarone	Pancreatitis (18216)	Menno Van der Elst (NL)	Supplementary information requested (submission by 09/05/2015)	Sanofi
Bisphosphonates (alendronic acid; alendronic acid, colecalciferol; etidronic acid; ibandronic; neridronic acid; pamidronic acid; risedronic acid; tiludronic acid; zoledronic acid); Denosumab	Osteonecrosis of the external auditory canal (18256)	Julie Williams (UK)	Supplementary information requested (submission by 09/05/2015)	Merck, Roche, Novartis, Bioprojet Europe, Warner Chilcott, Abiogen Pharma, Hospira UK, Sanofi-Aventis, Amgen
Donepezil hydrochloride	Rhabdomyolysis (18261)	Julie Williams (UK)	Supplementary information requested (submission by 09/05/2015)	Eisai Ltd
Fingolimod	Occurrence of one case of progressive multifocal leukoencephalopathy (PML)	Arnaud Batz (FR)	Supplementary information (submission by 06/04/2015) and direct healthcare professional communication (DHPC) requested	Novartis Europharm Ltd

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Infliximab	Rhabdomyolysis (18129)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 09/05/2015)	Janssen Biologics B.V.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Aflibercept	Higher systemic exposure compared to ranibizumab after intravitreal injection (18112)	Arnaud Batz (FR)	Study protocol for PASS (submission by 11/07/2015)	Bayer Pharma AG[3]
Palifermin	Increased mortality for unlicensed use in acute lung injury (18160)	Rafe Suvarna (UK)	Routine pharmacovigilance	Swedish Orphan Biovitrum AB
Recombinant Factor VIII: antihemophilic factor (recombinant); moroctocog alfa; octocog alfa	Inhibitor development in previously untreated patients (18134)	Brigitte Keller-Stanislawski (DE)	No action at this stage	Bayer Pharma AG, Baxter AG, Pfizer Limited, various
Sodium-containing effervescent, dispersible and soluble medicines	Cardiovascular events (17931)	Julie Williams (UK)	No action at this stage	Not applicable
Sorafenib	Acute generalised exanthematous pustulosis (18109)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	Bayer Pharma AG
Warfarin	Bone density decreased (18173)	Torbjörn Callreus (DK)	No action at this stage	Not applicable

[3] The name of the MAH was corrected on 9 April 2015.