22 June 2017
EMA/PRAC/337620/2017
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 6-9 June 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 6-9 June 2017 (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 (19-22 June 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] 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[2]

1.1. Gabapentin – Respiratory depression without concomitant opioid use

Authorisation procedure	Non centralised
EPITT No	18814
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	9 June 2017

Recommendation

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

4.4. Special warnings and precautions for use

Concomitant use with opioids

[...]

Respiratory depression

Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

4.8. Undesirable effects

Respiratory, thoracic and mediastinal disorders

Frequency 'rare': Respiratory depression

Package leaflet

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

Warnings and precautions

Talk to your doctor or pharmacist before taking <brand name>

- if you suffer from kidney problems your doctor may prescribe a different dosing schedule

[...]

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

- if you have nervous system disorders, respiratory disorders, or you are more than 65 years old, your doctor may prescribe you a different dosing regimen

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular, tell your doctor (or pharmacist) if you are taking or have been recently taking any medicines for convulsions, sleeping disorders, depression, anxiety, or any other neurological or psychiatric problems.

4. Possible side effects

Contact your doctor immediately if you experience any of the following symptoms after taking this medicine as they can be serious:

[...]

- breathing problems, which if severe you may need emergency and intensive care to continue breathing normally

Rare (may affect up to 1 in 1,000 people):

[...]

- Trouble breathing, shallow breaths (respiratory depression)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amitriptyline	Risk of drug induced liver injury (DILI) and hepatocellular injury (18890)	Agni Kapou (EL)	Supplementary information requested (submission by 23 August 2017)	Lundbeck Austria GmbH
Dasatinib; warfarin	Serious adverse drug reactions (ADRs) including bleeding events following potential drug interaction between dasatinib and warfarin (18894)	Doris Stenver (DK)	Assess in the next PSUR (submission by 5 September 2017)	Bristol-Myers Squibb Pharma EEIG
Ledipasvir, sofosbuvir	Blood cholesterol increased, low density lipoprotein increased (18903)	Ana Sofia Diniz Martins (PT)	Assess in the ongoing PSUR (submission by 27 September 2017)	Gilead Sciences International Ltd

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Levonorgestrel intrauterine device (IUD)	Anxiety, panic attacks, mood changes, sleep disorders and restlessness (18849)	Martin Huber (DE)	Supplementary information requested (submission by 23 August 2017)	Allergan, Bayer
mTOR inhibitors: everolimus, sirolimus, temsirolimus	Optic neuropathy and papilloedema (18901)	Martin Huber (DE)	Supplementary information requested (submission by 23 August 2017)	Novartis Europharm Ltd, Pfizer Limited
Phenprocoumon	Risk of birth defects and foetal loss following first trimester exposure as a function of the time of withdrawal (18902)	Martin Huber (DE)	Supplementary information requested (submission by 23 August 2017)	MEDA Pharma GmbH & Co. KG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Dabigatran	Major haemorrhage following dabigatran interaction with simvastatin or lovastatin (18819)	Torbjörn Callréus (DK)	Monitor based on data from ongoing clinical trials and observational studies	Boehringer Ingelheim International GmbH
Dabrafenib; trametinib	Sepsis (18779)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	Novartis Europharm Ltd
Docetaxel	Unexpected seriousness of reported adverse drug reactions (ADRs) with docetaxel in particular neutropenic enterocolitis and suspicion of an increase in ADR reporting rate in France with docetaxel-containing products (12059)	Claire Férard (FR)	Routine pharmacovigilance	MAHs of docetaxel containing products

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Intravenous fluids containing electrolytes and/or carbohydrates	Hyponatraemia (18631)	Doris Irene Stenver (DK)	No action at this stage	Not applicable
Prednisolone; prednisone	Induced scleroderma renal crisis (18888)	Doris Stenver (DK)	Provide comments on proposed updates to the product information (submission by 23 June 2017)	Agepha Pharma S.R.O, Merck
Telmisartan; telmisartan, hydrochlorothiazide; telmisartan, amlodipine	Risk of psoriasis or exacerbation of psoriasis (18882)	Carmela Macchiarulo (IT)	Routine pharmacovigilance	MAHs of telmisartan containing products
Tick-borne encephalitis vaccine (inactivated)	Potential vaccination failure in children (18825)	Brigitte Keller-Stanislawski (DE)	Routine pharmacovigilance	MAHs of tick-borne encephalitis vaccines