25 June 2015
EMA/PRAC/383371/2015
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 8-11 June 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 8-11 June 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 (22-25 June 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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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]

None

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
Anakinra	Thrombocytopenia (18337)	Torbjörn Callreus (DK)	Supplementary information requested (submission by 08/08/2015)	Swedish Orphan Biovitrum AB
Boceprevir	Hyponatraemia (18350)	Isabelle Robine (FR)	Supplementary information requested (submission by 08/08/2015)	Merck Sharp & Dohme Ltd
Enfuvirtide	Amyloidosis (18347)	Qun-Ying Yue (SE)	Assess in the ongoing PSUSA procedure (submission by 10/07/2015)	Roche Registration Ltd
Fluoroquinolones: ciprofloxacin; enoxacin; flumequine; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Retinal detachment (15914)	Valerie Strassmann (DE)	Supplementary information requested (submission by 08/08/2015)	Angelini, Bayer, Delta, Gerda, MSD, Pierre Fabre, Rottapharm, S.F. and Sanofi-Aventis

[2] Translations in EU languages of the adopted PRAC recommendations for update of the product information are also available to MAHs on the EMA website.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Nalmefene	Suicidal ideation (18333)	Martin Huber (DE)	Assess in the ongoing PSUR procedure (submission by 12/08/2015)	H. Lundbeck A/S
Oxybutynin	Psychiatric disorders (18342)	Veerle Verlinden (BE)	Supplementary information requested (submission by 08/08/2015)	Nicobrand Ltd
Pregabalin	Hyponatremia and syndrome of inappropriate antidiuretic hormone (SIADH) (18334)	Sabine Straus (NL)	Assess in the ongoing PSUSA procedure (submission by 12/08/2015)	Pfizer Ltd

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Atypical antipsychotics: aripiprazole; asenapine; clozapine; lurasidone; olanzapine; paliperidone; quetiapine; risperidone; sertindole; ziprasidone; zotepine	Acute renal failure (18102)	Qun-Ying Yue (SE)	Monitor in PSUR	Janssen-Cilag International N.V.; Eli Lilly Nederland B.V.; Otsuka Pharmaceutical Europe Ltd; Takeda Pharma A/S; N.V. Organon; Novartis Pharmaceuticals UK Ltd; Janssen-Cilag International N.V.; Lundbeck; Astrazeneca UK Ltd; Pfizer; Astellas
Canagliflozin; canagliflozin, metformin; dapagliflozin; dapagliflozin,	Diabetic ketoacidosis (18375)	Valerie Strassmann (DE)	Direct Healthcare Professional Communication (DHPC) and Article 20 procedure	Janssen-Cilag International N.V, AstraZeneca AB, Boehringer Ingelheim

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
metformin; empagliflozin; empagliflozin, metformin				International GmbH
Clopidogrel; prasugrel	Safety of dual antiplatelet therapy (18184)	Margarida Guimarães (PT)	No action	Sanofi-aventis groupe, Sanofi Clir SNC, Eli Lilly Nederland B.V.
HMG-CoA reductase inhibitors: atorvastatin; fluvastatin; lovastatin; pitavastatin; pravastatin; rosuvastatin; simvastatin	Lichenoid drug eruption (18299)	Valerie Strassmann (DE)	Monitor in PSUR	MAHs of HMG-CoA reductase inhibitors
Hormone replacement therapy medicinal products containing oestrogens or oestrogens and progestogens in combination; bazedoxifene, oestrogens conjugated	Increased risk of ovarian cancer (18258)	Menno van der Elst (NL)	No action at this stage	Not applicable
Pertuzumab	Acute renal failure (18322)	Doris Irene Stenver (DK)	Address in the ongoing PSUR procedure	Roche Registration Ltd
Teriparatide	Angina pectoris (18203)	Julie Williams (UK)	Routine pharmacovigilance	Eli Lilly Nederland B.V.