19 November 2015
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 3-6 November 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 3-6 November 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 (16-19 November 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 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

Palifermin – Signal of infection (EPITT no 18401): request for a type II variation (see section 3 on page 5).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Axitinib	Nephrotic syndrome (18484)	Ingebjørg Buajordet (NO)	Supplementary information requested (submission by 13/01/2016)	Pfizer Limited
Bevacizumab	Generalized tonic-clonic seizures (18485)	Doris I. Stenver (DK)	Assess in the next PSUR (submission by 05/05/2016)	Roche Registration Ltd
Human fibrinogen, human thrombin	Intestinal obstruction (18373)	Brigitte Keller-Stanislawski (DE)	Proposal for summary of product characteristics wording and communication plan requested (submission by 18/11/2015)	Takeda Austria GmbH
Human normal immunoglobulin	Posterior reversible encephalopathy syndrome (PRES)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 13/01/2016)	Baltic Therapeutic Service, Baxter / Baxalta Innovations, Bio Products Laboratory, Biomed-Lublin Wsisz, Biotest Pharma GmbH / Vianex S.A., CSL Behring, Demo Abee, Grifols, Hi-Med Solutions (Cyprus) Ltd / Jana Pharm D.O.O. / Octapharma AG, Human Bioplazma Manufacturing and Trading LLC, Imed Poland SP.Z.O.O., Jasika D.O.O. / Kedrion S.p.A., LFB Biomedicaments, Narodowe centrum badań jądrowych, Oxbridge Pharma Limited, Sanquin/CAFDCF

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Mercaptopurine; azathioprine	Lymphoproliferative disorders (18503)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 13/01/2016)	Aspen Pharma
Methotrexate	Congenital cardiovascular anomaly (18481)	Doris I. Stenver (DK)	Supplementary information requested (submission by 13/01/2016)	Pfizer
Oxybutynin	Psychiatric disorders (18342)	Veerle Verlinden (BE)	Proposal for summary of product characteristics wording (including frequencies) requested (submission by 10/12/2015)	Nicobrand Limited
Selective serotonin reuptake inhibitors (SSRIs) and Serotonin–norepinephrine reuptake inhibitors (SNRIs): citalopram; duloxetine; escitalopram; fluoxetine ; fluvoxamine; mirtazapine; paroxetine; sertraline; venlafaxine	Risk of autism spectrum disorders (ASD) after maternal use of SSRI/SNRI (14082)	Isabelle Robine (FR)	Supplementary information requested (submission by 10/02/2016)	Lundbeck, Eli Lilly, Abbott, GlaxoSmithKline, Organon, Pfizer
Somatropin	Hypersensitivity reactions (18486)	Torbjörn Callreus (DK)	Assess in the next PSUR (submission by 29/12/2015)	Ipsen Pharma, Sandoz GmbH, BioPartners GmbH, Pfizer , Novo Nordisk A/S, Merck KGaA, Eli Lilly Nederland B.V., Ferring Pharmaceuticals

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Tigecycline	Hypofibrinogenaemia (18479)	Miguel A. Maciá (ES)	Supplementary information requested (submission by 13/01/2016)	Pfizer Limited

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Aflibercept	Higher systemic exposure compared to ranibizumab after intravitreal injection (18112)	Isabelle Robine (FR)	No action	Bayer Pharma AG
Palifermin	Infection (18401)	Rafe Suvarna (UK)	Submission of type II variation including update of product information, Direct Healthcare Professional Communication, drug utilisation study and update of risk management plan	Swedish Orphan Biovitrum AB (publ)
Selective serotonin reuptake inhibitors (SSRIs): citalopram; escitalopram; fluoxetine ; fluvoxamine; paroxetine; sertraline	New malformative risks in newborn (14082)	Isabelle Robine (FR)	Routine pharmacovigilance	MAHs of SSRIs
Warfarin	Bone density decreased (18173)	Torbjörn Callreus (DK)	Routine pharmacovigilance	MAHs of warfarin-containing products