19 May 2014
EMA/PRAC/272621/2014
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 5-8 May 2014

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 5-8 May 2014 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][1] reference numbers).

PRAC recommendations to provide additional data 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 May 2014) 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

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
Atazanavir	Haemolytic anaemia (17921)	Isabelle Robine (FR)	Supplementary information requested (submission by 12/07/2014)	Bristol-Myers Squibb Pharma EEIG
Azithromycin	Potentially fatal heart events (16156)	Terhi Lehtinen (FI)	Supplementary information requested (submission by 31/05/2014)	Pfizer
Leuprorelin, suspension for injection	Medication error - wrong technique in drug usage process (17753)	Carmela Macchiarulo (IT)	Supplementary information requested (submission by 12/07/2014)	Astellas
Quetiapine	Possible misuse and abuse (17960)	Sabine Straus (NL)	Supplementary information requested (submission by 31/10/2014)	AstraZeneca
Temozolomide	Diabetes insipidus (17951)	Martin Huber (DE)	Supplementary information requested (submission by 10/10/2014)	Merck Sharp & Dohme Limited
Valproate and related substances	Mitochondrial toxicity (17956)	Martin Huber (DE)	Supplementary information requested (submission by 09/08/2014)	Sanofi-Aventis

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Androgen deprivation therapy	QT interval prolongation due to long-term use (13886)	Martin Huber (DE)	No action at this stage	Not applicable
Bisphosphonates, strontium ranelate	Heart valves disorders (13832)	Julie Williams (UK)	No action at this stage	Not applicable
Fentanyl, transdermal patch	Accidental exposure (17778)	Sabine Straus (NL)	Direct healthcare professional communication (DHPC)	Johnson and Johnson
Fluticasone furoate	Oral and upper respiratory fungal infection (17769)	Adam Przybylkowski (PL)	Monitor in PSUR	Glaxo Group Ltd
Ivabradine	Cardiovascular risk (17961)	Sabine Straus (NL)	Under consideration*	Laboratoires Servier
Paracetamol	Drug exposure in pregnancy – publication by *Brandlistuen et al.*; Int. J. Epidemiol., 2013 (17796)	Veerle Verlinden (BE)	Routine pharmacovigilance	MAHs of paracetamol-containing products
Sitagliptin; sitagliptin, metformin; angiotensin-converting enzyme (ACE) inhibitors	Angioedema due to interaction between sitagliptin and ACE inhibitors (17608)	Menno van der Elst (NL)	Routine pharmacovigilance	Merck Sharp & Dohme Limited
Tiotropium bromide	Increased mortality from cardiovascular disease and all-cause mortality – results of TIOSPIR trial (17406)	Sabine Straus (NL)	Follow-up on the outcome of the initiated variation procedure	Boehringer Ingelheim

* The review of ivabradine (Procoralan/Corlentor) has been initiated at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004.