10 December 2013
EMA/PRAC/773133/2013
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 2-5 December 2013

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 2-5 December 2013.

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 (16-19 December 2013) 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.

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.

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1. Recommendations for update of the product information

1.1. Thiopental - Hypokalaemia and rebound hyperkalamaemia

Substance (invented name)	Thiopental
Authorisation procedure	Non-centralised
PRAC rapporteur(s)	Ruchika Sharma (IE)
Date of adoption	5 December 2013

Recommendation

The Marketing Authorisation Holder(s) for thiopental-containing products should submit a variation within 2 months to the national competent authorities to amend the product label as follows:

Summary of Products Characteristics

Section 4.4

Use in neurological patients with raised intracranial pressure

Thiopental has been associated with reports of severe or refractory hypokalaemia during infusion; severe rebound hyperkalaemia may occur after cessation of thiopental infusion. The potential for rebound hyperkalaemia should be taken into account when stopping thiopental therapy.

Section 4.8

Include the MedDRA preferred terms hypokalaemia and hyperkalaemia under the 'Metabolism and nutrition disorders SOC' with a frequency "not known".

Package Leaflet

Section 4 Possible side effects

Thiopental has been associated with reports of decreased potassium blood levels during infusion and increased potassium blood levels after stopping thiopental infusion.

2. Recommendations for submission of additional data

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	PRAC Rapporteur	Action for MAH	MAH
Cabazitaxel	Medication error potentially leading to inappropriate dose	Isabelle Robine (FR)	Assess in the next PSUR	Sanofi Aventis
Clindamycin	Drug interaction with warfarin leading to international normalised ratio (INR) increased	Julie Williams (UK)	Additional data requested (submission by 08 February 2014)	Pfizer
Fentanyl, transdermal patch	Accidental exposure	Sabine Straus (NL)	Additional data requested (submission by 08 February 2014)	Johnson and Johnson Pharmaceuticals
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Complex regional pain syndrome (CRPS) linked to the process of vaccination	Jean-Michel Dogné (BE)	Additional data requested (submission by 08 February 2014)	GlaxoSmithKline Biologicals S.A.
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Complex regional pain syndrome (CRPS) linked to the process of vaccination	Qun-Ying Yue (SE)	Additional data requested (submission by 08 February 2014)	Sanofi Pasteur
Sitagliptin; Sitagliptin, metformin; Angiotensin-converting enzyme (ACE) inhibitors	Angioedema due to interaction between sitagliptin and ACE inhibitors	Menno van der Elst (NL)	Additional data requested (submission by 08 February 2014)	Merck Sharp & Dohme Limited
Strontium ranelate	Eye disorders	Ulla Wändel Liminga (SE)	Assess in on-going PSUR	Les Laboratoires Servier
Tiotropium bromide	Increased mortality from cardiovascular disease and all-cause mortality – results of TIOSPIR trial	Sabine Straus (NL)	Additional data requested (submission by 08 February 2014)	Boehringer Ingelheim

3. Other recommendations

INN	Signal	PRAC Rapporteur	Action for MAH	MAH
Lamotrigine	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Sabine Straus (NL)	Recommendation for product information change to be addressed in the PSUR work-sharing procedure	MAHs for lamotrigine-containing products involved in the PSUR work-sharing procedure