19 December 2014
EMA/PRAC/734095/2014
Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 1-4 December 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 1-4 December 2014 (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 (15-18 December 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

1.1. Vildagliptin; Vildagliptin, metformin – Myalgia

Substance (invented name)	Vildagliptin; Vildagliptin, metformin (Galvus EMEA/H/C/000771, Eucreas EMEA/H/C/000807, Jalra EMEA/H/C/001048, Xiliarx EMEA/H/C/001051, Icandra EMEA/H/C/001050, Zomarist EMEA/H/C/001049)
Authorisation procedure	Centralised
EPITT No	17959
PRAC rapporteur(s)	Qun-Ying Yue (SE)
Date of adoption	04 December 2014

Recommendation

Based on preclinical findings, clinical trials and EudraVigilance data and assessment of further clarifications provided by the MAH for Galvus (innovator of vildagliptin) and Eucreas (innovator of vildagliptin/metformin) the PRAC has agreed that there is insufficient evidence for an association between vildagliptin and rhabdomyolysis at the moment, however the MAH for Galvus and Eucreas should submit a variation to the EMA within 2 months to include in the SOC Musculoskeletal, connective tissue and bone disorders '<u>myalgia</u>' in section 4.8 of the SmPCs. The relevant frequency should be assigned according to current guidelines and the patient information leaflets should be updated accordingly. The MAH(s) of other products containing vildagliptin should update their product information in line with that of the reference product.

With the next PSUR of Galvus (Data Lock Point 28.02.2015) events of muscle events / myopathy / rhabdomyolysis in association with vildagliptin and vildagliptin/metformin should be closely monitored. In addition, full case narratives (CIOMS) for rhabdomyolysis cases in clinical trials should be provided.

In the RMP for Galvus and Eucreas the important potential risk should be updated to include rhabdomyolysis specifically: "muscle events/myopathy/rhabdomyolysis, in particular with current statin use".

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
Interferon alfa-2a; Interferon alfa-2b; Interferon beta-1a; Interferon beta-1b; Peginterferon alfa-2a; Peginterferon alfa-2b; Peginterferon beta-1a	Pulmonary arterial hypertension (18059)	Qun-Ying Yue (SE)	Supplementary information requested (submission by 07/02/2015)	Merck Sharp & Dohme Limited; Biogen Idec; Merck Serono Europe Limited; Bayer Pharma AG; Novartis Europharm Ltd; Roche Registration Limited
Lenalidomide	Parkinson's disease (18135)	Arnaud Batz (FR)	Assess in the next PSUR (submission by 06/03/2015)	Celgene Europe Limited
Natalizumab	Anaemia (18137)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 07/02/2015)	Biogen Idec Ltd
Trabectedin	Capillary leak syndrome (18115)	Torbjörn Callreus (DK)	Supplementary information requested (submission by 07/02/2015)	Pharma Mar, S.A.

3. Other recommendations

None.