21 November 2014
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Pharmacovigilance Risk Assessment Committee

PRAC recommendations on signals

Adopted at the PRAC meeting of 3-6 November 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 3-6 November 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 (17-20 November 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. Dimethyl fumarate – Progressive multifocal leukoencephalopathy (PML)

Substance (invented name)	Dimethyl fumarate (Tecfidera EMEA/H/C/002601), fumaric acid esters (Fumaderm initial, Fumaderm, nationally authorised in Germany)
Authorisation procedure	Centralised and non-centralised
EPITT No	18136
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	6 November 2014

Recommendation

PRAC considered the well described case of first occurrence of PML after long-term treatment with Tecfidera in a patient experiencing severe long-term lymphopenia and the life-threatening nature of progressive multifocal leukoencephalopathy (PML), including case reports in EudraVigilance relating to fumaric acid esters used for treatment of psoriasis, and concluded that the well-described case of PML during treatment with Tecfidera provides sufficient evidence for immediate communication and an immediate request for submission of a variation to update the product information.

Therefore, the PRAC recommended that the MAH for Tecfidera should submit a proposal for a Direct Healthcare Professional Communication (DHPC) to be adopted as early as possible by CHMP.

The PRAC also considered the need for further evaluation and discussion of the available evidence and necessary risk minimisation for all products containing fumaric acid esters including updates of the product information and recommended that variations including an updated RMP should be submitted for both Tecfidera and the nationally authorised products Fumaderm initial and Fumaderm. In the present case a worksharing variation involving the centrally and nationally authorised products held by the same MAH should be considered and submitted to the EMA and NCAs. Within the variation application, a response and discussion should be provided addressing [a list of questions].

1.2. Leuprorelin – Medication error - wrong technique in drug usage process

Substance (invented name)	Leuprorelin (Eligard)
Authorisation procedure	Non-centralised
EPITT No	17753
PRAC rapporteur(s)	Carmela Macchiarulo (IT)
Date of adoption	6 November 2014

Recommendation

Having considered Eudravigilance data, the literature, post-marketing reports, study results and plans to manage this risk submitted by Astellas, (the MAH of Eligard), as well as the ongoing variation to add the sentence "Lack of clinical efficacy may occur due to incorrect reconstitution of the product (see section 4.2)" to the product information and to allow storage of the product at room temperature for up to 1 month, the PRAC has agreed the following:

1. The MAH should distribute a dear healthcare professional communication (DHPC) according to the text and communication plan agreed with the PRAC.
2. The MAH should submit by December 2014 a variation modifying the device so that it will be impossible to remove the blue plunger rod without removing the grey stopper.
3. The MAH should submit, together with the above mentioned variation, an update of the Risk Management Plan with appropriate routine and additional pharmacovigilance and risk minimisation measures regarding the risk of lack of efficacy due to medication error. This should include an update of the product information as appropriate, a poster, video, periodic surveys of targeted healthcare providers regarding their knowledge of this risk, an effectiveness check on the DHPC and a detailed plan for a new product presentation with fewer and easier handling steps, with the submission of the feasibility study results by end of October 2015.

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
Aripiprazole	Aggression and related events (18127)	Margarida Guimarães (PT)	Supplementary information requested (submission by 10/01/2015)	Otsuka Pharmaceutical Europe Ltd
Gadodiamide; Gadopentetic acid; Gadoversetamide	Nephrogenic systemic fibrosis in patients with acute kidney injury (408)	Rafe Suvarna (UK)	Supplementary information requested (submission by 21/11/2014)	GE Healthcare AS, Bayer, Mallinckrodt Deutschland GmbH
Infliximab	Rhabdomyolysis (18129)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 10/01/2015)	Janssen Biologics B.V.
Methylprednisolone	Hepatotoxicity after high dose intravenous use (18121)	Harald Herkner (AT)	Assess in the next PSUR (submission by 28/02/2015)	Pfizer Limited
Paliperidone and other atypical antipsychotics: olanzapine; aripiprazole; lurasidone; asenapine; clozapine; risperidone; sertindole; quetiapine; ziprasidone; zotepine	Acute renal failure (18102)	Qun-Ying Yue (SE)	Supplementary information requested (submission by 10/01/2015)	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

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Pantoprazole	Subacute cutaneous lupus erythematosus (SCLE) (18119)	Rafe Suvarna (UK)	Supplementary information requested (submission by 10/01/2015)	Takeda GmbH
Radium-223 dichloride	Cerebral haemorrhage (18142)	Rafe Suvarna (UK)	Assess in the next PSUR (submission by 23/01/2015)	Bayer Pharma AG
Sorafenib	Acute generalised exanthematous pustulosis (18109)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 10/01/2015)	Bayer Pharma AG
Vemurafenib	Dupuytren's contracture (18111)	Ulla Wändel Liminga (SE)	Assess in the PSUR (submission of supplementary information by 11/02/2015)	Roche Registration Ltd
Vildagliptin; Vildagliptin, metformin	Renal failure (18106)	Qun-Ying Yue (SE)	Assess in the next PSUR (submission by 29/05/2015)	Novartis Europharm Ltd

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Bisphosphonates; strontium ranelate	Heart valves disorders (13832)	Julie Williams (UK)	Routine pharmacovigilance	MAHs of bisphosphonate and strontium ranelate containing products
Octocog alfa	Inhibitor development in previously untreated patients (18134)	Brigitte Keller-Stanislawski (DE)	No action at this stage	Bayer Pharma AG

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Sildenafil	Increased risk of incident melanoma (17997)	Menno van der Elst (NL)	Routine pharmacovigilance	Pfizer Limited
Simvastatin; pravastatin; fluvastatin; pitavastatin; lovastatin	Immune-mediated necrotizing myopathy (IMNM) (18140)	Arnaud Batz (FR)	No action at this stage	Not applicable
Vildagliptin; Vildagliptin, metformin	Interstitial lung disease (17793)	Qun-Ying Yue (SE)	Monitor in PSUR	Novartis Europharm Ltd