21 April 2017
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 3-6 April 2017 PRAC meeting

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 April 2017 (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 (18-21 April 2017) 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[2]

1.1. Albiglutide – Acute kidney injury

Authorisation procedure	Centralised
EPITT No	18778
PRAC rapporteur(s)	Julie Williams (UK)
Date of adoption	6 April 2017

Recommendation

Having considered the evidence from case reports in EudraVigilance and the data provided by the MAH, the PRAC has agreed that the MAH of Eperzan (GlaxoSmithKline Trading Services Limited) should submit to the EMA a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4 – Special warnings and precautions for use

Dehydration

Dehydration, sometimes leading to renal impairment and acute renal failure, has been reported in patients treated with albiglutide and has occurred in patients without gastrointestinal side effects. Patients treated with albiglutide should be advised of the potential risk of dehydration, and take precautions to avoid fluid depletion.

Package leaflet

2 - What you need to know before you use Eperzan

Warnings and precautions

When initiating treatment with albiglutide, you may experience fluid loss from vomiting, nausea, diarrhoea or dehydration. It is important to avoid dehydration by drinking plenty of fluids.

1.2. Leflunomide; teriflunomide – Falsely decreased ionised calcium levels

Authorisation procedure	Centralised and non-centralised
EPITT No	18787
PRAC rapporteur(s)	Sabine Straus (NL)
Date of adoption	6 April 2017

[2] Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH(s) of teriflunomide and leflunomide-containing products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4 - Special warning and precautions for use

Interference with determination of ionised calcium levels

The measurement of ionised calcium levels might show falsely decreased values under treatment with leflunomide and/or teriflunomide (the active metabolite of leflunomide) depending on the type of ionised calcium analyser used (e.g. blood gas analyser). Therefore, the plausibility of observed decreased ionised calcium levels needs to be questioned in patients under treatment with leflunomide or teriflunomide. In case of doubtful measurements, it is recommended to determine the total albumin adjusted serum calcium concentration.

Package leaflet

2 - What you need to know before you take {Drug Name}

Warnings and precautions

Talk to your doctor before taking {Drug Name}

- if you are due to have a specific blood test (calcium level). Falsely low levels of calcium can be detected.

1.3. Temozolomide – Meningoencephalitis herpetic

Authorisation procedure	Centralised
EPITT No	18785
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	6 April 2017

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH(s) of temozolomide-containing products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4 - Special warnings and precautions for use

Meningoencephalitis herpetic

In post marketing cases, meningoencephalitis herpetic (including fatal cases) has been observed in patients receiving TMZ in combination with radiotherapy, including cases of concomitant steroids administration.

4.8 - Undesirable effects

Infections and infestations

Frequency 'uncommon': Meningoencephalitis herpetic (including cases with fatal outcome)

Package leaflet

4 - Possible side effects

Other side effects:

New or reactivated (recurring) cytomegalovirus infections and reactivated hepatitis B virus infections have been uncommonly reported. Cases of brain infections caused by herpes virus (meningoencephalitis herpetic), including fatal cases, have been uncommonly reported.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Azithromycin; tobramycin *inhaled*	Possible interaction between tobramycin and azithromycin leading to lower effectiveness of tobramycin (18855)	Sabine Straus (NL)	Supplementary information requested (submission by 29 June 2017)	Novartis Europharm Ltd; PARI Pharma GmbH
Flucloxacillin	High anion gap metabolic acidosis (HAGMA) (18844)	Ana Sofia Martins (PT)	Supplementary information requested (submission by 29 June 2017)	Actavis Group PTC ehf.
Gefitinib	Recall phenomenon (18857)	Ulla Wändel-Liminga (SE)	Supplementary information requested (submission by 29 June 2017)	AstraZeneca AB
Meningococcal group B vaccine (rDNA, component, adsorbed)	Arthritis and synovitis (18764)	Yue Qun-Ying (SE)	Supplementary information requested (submission by 29 June 2017)	GSK Vaccines S.r.l

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Mesalazine	Risk of photosensitivity reactions (18869)	Patrick Batty (UK)	Supplementary information requested (submission by 29 June 2017)	DR FALK
Methotrexate	Pulmonary alveolar haemorrhage (18850)	Martin Huber (DE)	Supplementary information requested (submission by 29 June 2017)	Pfizer; Nordic Group B.V.
Pramipexole	Dystonia (18866)	Doris Irene Stenver (DK)	Supplementary information requested (submission by 29 June 2017)	Boehringer Ingelheim International GmbH

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Docetaxel	Unexpected seriousness of reported adverse drug reactions (ADR) with docetaxel and suspicion of an increase in ADR reporting rate in France with docetaxel-containing products (12059)	Claire Férard (FR)	No action at this stage	Not applicable
Intravenous fluids containing electrolytes and/or carbohydrates	Hyponatraemia (18631)	Doris Irene Stenver (DK)	No action at this stage	Not applicable
Selexipag	Fatal cases in patients with pulmonary arterial hypertension (PAH) (18833)	Julie Williams (UK)	Monitor in PSUR	Actelion Registration Ltd.