23 February 2017
EMA/PRAC/68642/2017
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the PRAC meeting of 6-9 February 2017

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 6-9 February 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 (20-23 February 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. Fluconazole – Spontaneous abortion and stillbirth

Authorisation procedure	Non-centralised
EPITT No	18666
PRAC rapporteur(s)	Doris Irene Stenver (DK)
Date of adoption	9 February 2017

Recommendation

Having considered the available evidence, including the review and assessment of the register-based cohort study "*Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth", Mølgaard-Nielsen D et al, JAMA 2016; 315(1); 58-67,* the cumulative review of all available data from clinical trials, post-marketing data and literature publications concerning the risk following exposure to fluconazole during pregnancy, as well as the MAH innovator for fluconazole (Pfizer) proposal for update to SPC Section 4.6, the PRAC has agreed that the MAHs of fluconazole containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text is underlined and deleted text appears as ~~struck through~~). The PRAC considered there was insufficient justification for adding a requirement for effective contraception. The MAHs of fluconazole should also submit an update to the Risk Management Plan at the next regulatory opportunity. This PRAC recommendation applies to all fluconazole formulations.

Summary of product characteristics

4.6. Fertility, pregnancy and lactation

Pregnancy
An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.

There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Studies in animals have shown reproductive toxicity (see section 5.3).

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

~~Data from several hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole, administered as a single or repeated dose in the first trimester, show no increased risk of undesirable effects in the foetus.~~

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.
Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

1.2. Nivolumab – Pemphigoid

Authorisation procedure	Centralised
EPITT No	18759
PRAC rapporteur(s)	Brigitte Keller-Stanislawski (DE)
Date of adoption	9 February 2017

Recommendation

Having reviewed the avalaible evidence from Eudravigilance and the literature, and considering that pemphigoid is already listed in the SmPC of Keytruda (pembrolizumab) -another anti-programmed death-1 (PD-1) receptor- the PRAC has agreed that the MAH of Opdivo (Bristol-Myers Squibb Pharma EEIG) should submit a variation within 2 months to amend the product information as described below (new text underlined, text to be removed ~~struck-through~~):

Summary of product characteristics

4.8. Undesirable effects

[e] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, ~~and~~ drug eruption and pemphigoid.

Package leaflet

4 - Possible side effects

Skin rash sometimes with blisters, itching

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Dabigatran	Major haemorrhage following dabigatran interaction with simvastatin or lovastatin (18819)	Torbjörn Callréus (DK)	Supplementary information requested (submission by 6 April 2017)	Boehringer Ingelheim International GmbH
Darbepoetin alfa; epoetin alfa; epoetin beta; epoetin theta; epoetin zeta; methoxy polyethylene glycol-epoetin beta	Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (18846)	Valerie Straßmann (DE)	Supplementary information requested (submission by 6 April 2017)	Amgen Europe B.V., Medice Arzneimittel Pütter GmbH & Co. KG, Sandoz GmbH, Hexal AG, Janssen-Cilag NV, Janssen-Cilag Pharma GmbH, Janssen-Cilag GmbH, Roche Registration Limited, Teva GmbH, Ratiopharm GmbH, Hospira UK Limited, Stada Arzneimittel AG
Exenatide	Incorrect use of device associated with (serious) adverse reactions including hyperglycaemia and hypoglycaemia (18688)	Qun-Ying Yue (SE)	Supplementary information requested (submission by 6 April 2017)	AstraZeneca AB
Ipilimumab	Pemphigoid (18759)	Sabine Straus (NL)	Assess in the next PSUR (submission by 2 June 2017)	Bristol-Myers Squibb Pharma EEIG
Levonorgestrel intrauterine device (IUD)	Anxiety, panic attacks, mood changes, sleep disorders and restlessness (18849)	Martin Huber (DE)	Supplementary information requested (submission by 6 April 2017)	MAHs of all levonorgestrel IUD
Selexipag	Fatal cases in patients with pulmonary arterial hypertension (PAH) (18833)	Rafe Suvarna (UK)	Supplementary information requested (submission by 3 March 2017)	Actelion Registration Ltd.
Tick-borne encephalitis vaccine (inactivated)	Potential vaccination failure in children (18825)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 6 April 2017)	MAHs of tick-born vaccine products

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Dexlansoprazole; lansoprazole	Unexpected histopathological findings from a juvenile rat toxicity study (18645)	Kirsti Villikka (FI)	Routine pharmacovigilance	Takeda