9 July 2018[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 11-14 June 2018 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 11-14 June 2018 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] 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 (25-28 June 2018) 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] Intended publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] 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[3]

1.1. Nabumetone – Drug reaction with eosinophilia and systemic symptoms (DRESS)

Authorisation procedure	Non-centralised
EPITT No	19241
PRAC rapporteur(s)	Sabine Straus (NL)
Date of adoption	14 June 2018

Recommendation

Having considered the available evidence in EudraVigilance (i.e. well-documented post-marketing spontaneous cases) with regards to the risk of Drug reaction with eosinophilia and systemic symptom (DRESS) with nabumetone, the PRAC has agreed that the MAH(s) of nabumetone-containing medicinal product(s) 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

4.4. Special warnings and precautions for use

Serious skin reactions, ~~some of them fatal,~~ including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported ~~very~~ rarely in association with the use of NSAIDs, including nabumetone (see section 4.8).

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, nabumetone should be withdrawn immediately and an alternative treatment considered (as appropriate).

Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first two months of treatment. Nabumetone should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of nabumetone, treatment with nabumetone must not be restarted in this patient at any time.

4.8. Undesirable effects

Summary of safety profile

Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with nabumetone treatment (see section 4.4).

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

Table of ADRs

Skin and subcutaneous tissue disorders

Very rare: Bullous reactions including toxic epidermal necrolysis, Stevens Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, angioedema, pseudoporphyria, alopecia

Package leaflet

4. Possible side effects

Widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (drug reaction with eosinophilia and systemic symptoms which is also known as DRESS or drug hypersensitivity syndrome). Stop using <medicine> if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 2.

1.2. Varenicline – Loss of consciousness

Authorisation procedure	Centralised
EPITT No	19146
PRAC rapporteur(s)	Doris Stenver (DK)
Date of adoption	14 June 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards the risk of loss of consciousness, the PRAC has agreed that the MAH for Champix (Pfizer Limited) 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

4.7. Effects on ability to drive and use machines

CHAMPIX may have minor or moderate influence on the ability to drive and use machines.

CHAMPIX may cause dizziness, somnolence and transient loss of consciousness, and therefore may influence the ability to drive and use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8. Undesirable effects

Nervous system disorders

Very common	Headache
Common	Somnolence, dizziness, dysgeusia
Uncommon	Seizure, tremor, lethargy, hypoaesthesia
Rare	Cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder
Not known	Transient loss of consciousness

Package leaflet

2. What you need to know before you take CHAMPIX

Driving and using machines

CHAMPIX may be linked with ~~produce~~ dizziness, sleepiness and transient loss of consciousness. You should not drive, operate complex machinery or engage in any other potentially hazardous activities until you know whether this medicine affects your ability to perform these activities.

4. Possible side effects

- Not known
  - o Transient loss of consciousness

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Biotin	Interference with clinical laboratory tests (19156)	Valerie Straßmann (DE)	Supplementary information requested (submission 29 August 2018)	Essential Pharmaceuticals, Fresenius Kabi, Alfasigma, Baxter, Quiris Healthcare, Dr. Kleine Pharma, Krauterhaus Sanct Bernhard, Bio-H-Tin Pharma, FAR.G.IM, Bayer
Carbimazole; thiamazole	New information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy (19238)	Valerie Straßmann (DE)	Supplementary information requested (submission 29 August 2018)	Amdipharm, Aspen pharma, Meda, Sandoz, Takeda, Sanóbia-centro de saúde e estética, Teofarma, Uni-pharma Kleon Tsetis
Dolutegravir	Evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women (19244)	Julie Williams (UK)	Supplementary information requested (submission 29 August 2018)	ViiV Healthcare B.V.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Dulaglutide; exenatide; liraglutide	Diabetic ketoacidosis (19237)	Amelia Cupelli (IT)	Supplementary information requested (submission 29 August 2018)	Eli Lilly Nederland B.V., AstraZeneca AB, Novo Nordisk A/S
Nivolumab	Keratoacanthoma (19250)	Brigitte Keller-Stanislawski (DE)	Assess in the next PSUR (submission by 11 September 2018)	Bristol-Myers Squibb Pharma EEIG
Rivaroxaban	Acquired haemophilia (19240)	Qun-Ying Yue (SE)	Assess in the next PSUR (submission by 24 November 2018)	Bayer AG
Tacrolimus (systemic formulations)	Hepatitis E infection (19246)	Almath Spooner (IE)	Assess in the ongoing PSUR (submission by 1 August 2018)	Astellas Pharma Europe B.V.
Xylometazoline	Serious ventricular arrhythmia in patients with long QT syndrome (19242)	Zane Neikena (LV)	Supplementary information requested (submission 29 August 2018)	GlaxoSmithKline

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Hydrochlorothiazide	Skin cancer (19138)	Kirsti Villikka (FI)	Submit proposal for product information updates (submission by 25 June 2018)	MAHs of originator products containing hydrochlorothiazide