



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3 April 2018¹
EMA/PRAC/136563/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 5-8 March 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 5-8 March 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 (19-22 March 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.



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 information³

1.1. Cefalexin – Acute generalised exanthematous pustulosis (AGEP)

Authorisation procedure	Non-centralised
EPI TT No	18911
PRAC rapporteur(s)	Dolores Montero (ES)
Date of adoption	8 March 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of cefalexin with acute generalised exanthematous pustulosis (AGEP), the PRAC has agreed that that the MAH(s) of cefalexin-containing medicinal 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

Acute generalised exanthematous pustulosis (AGEP) has been reported in association with cefalexin treatment. 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, cefalexin should be withdrawn immediately and an alternative treatment considered. Most of these reactions occurred most likely in the first week during treatment.

4.8. Undesirable effects

Table of ADRs:

Skin and subcutaneous tissue disorders (frequency: not known)

Acute generalised exanthematous pustulosis (AGEP)

Package leaflet

2. What do you need to know before you use cefalexin

TELL YOUR DOCTOR BEFORE TAKING CEFALEXIN:

- If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking cefalexin or other antibacterials

Warnings and precautions – Take special care with cefalexin:

Acute generalised exanthematous pustulosis (AGEP) has been reported with the use of cefalexin. AGEP appears at the initiation of treatment as a red, scaly widespread rash with bumps under the skin and

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

blisters accompanied by fever. The most common location: mainly localized on the skin folds, trunk, and upper extremities. The highest risk for occurrence of this serious skin reaction is within the first week of treatment. If you develop a serious rash or another of these skin symptoms, stop taking cefalexin and contact your doctor or seek medical attention immediately.

4. Possible side effects

Frequency not known:

A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever at the initiation of treatment (acute generalised exanthematous pustulosis). Stop using cefalexin if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 2.

1.2. Norepinephrine – Stress cardiomyopathy

Authorisation procedure	Non-centralised
EPITT No	19172
PRAC rapporteur(s)	Almath Spooner (IE)
Date of adoption	8 March 2018

Recommendation

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

Summary of product characteristics

4.8. Undesirable effects

Cardiac disorders

Frequency 'not known': Stress cardiomyopathy

Package leaflet

No update to the package leaflet is considered necessary as the main symptoms of stress cardiomyopathy are already adequately reflected in Section 4 - Possible side effects.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Antiretrovirals ⁴	Autoimmune hepatitis (18956)	Ana Sofia Diniz Martins (PT)	Supplementary information requested (submission by 8 May 2018)	AbbVie Ltd, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Gilead Sciences International Limited, Janssen-Cilag International N.V., Merck Sharp & Dohme Ltd, Roche Registration Limited, ViiV Healthcare
Clopidogrel	Insulin autoimmune syndrome (19155)	Márcia Silva (PT)	Supplementary information requested (submission by 8 May 2018)	Sanofi Clir SNC
Pembrolizumab	Cholangitis sclerosing (19154)	Sabine Straus (NL)	Assess in the next PSUR (submission by 12 May 2018)	Merck Sharp & Dohme Limited

⁴ Abacavir; abacavir / lamivudine / zidovudine; abacavir / lamivudine; abacavir / dolutegravir / lamivudine; atazanavir; atazanavir / cobicistat; cobicistat; darunavir; darunavir / cobicistat; darunavir / cobicistat / emtricitabine / tenofovir alafenamide; didanosine; dolutegravir; efavirenz; efavirenz / emtricitabine / tenofovir disoproxil fumarate; elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide; elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate; emtricitabine; emtricitabine / rilpivirine / tenofovir alafenamide; emtricitabine / rilpivirine / tenofovir disoproxil fumarate; emtricitabine / tenofovir alafenamide; emtricitabine / tenofovir disoproxil fumarate; enfuvirtide; etravirine; fosamprenavir; indinavir; lamivudine; lamivudine / zidovudine; lopinavir / ritonavir; maraviroc; nevirapine; raltegravir; rilpivirine; ritonavir; saquinavir; stavudine; tenofovir disoproxil fumarate; tipranavir; zidovudine.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amitriptyline	Dry eye (19173)	Agni Kapou (GR)	Provide comments on proposed updates to the product information (submission by 23 March 2018)	MAHs of amitriptyline-containing medicinal products
Hormonal contraceptives	Known association between hormonal contraceptives and a small increase in breast cancer following a recent publication (19143)	Menno van der Elst (NL)	No action at this stage	Not applicable