7 May 2018[1]
EMA/PRAC/211744/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 9-12 April 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 9-12 April 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 (23-26 April 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. Amitriptyline – Dry eye

Authorisation procedure	Non-centralised
EPITT No	19173
PRAC rapporteur(s)	Agni Kapou (GR)
Date of adoption	12 April 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of dry eyes and amitriptyline, the PRAC has agreed that the MAHs of amitriptyline-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

Under SOC 'Eye disorders'

Frequency 'not known': Dry eye

Package leaflet

4. Possible side effects

Frequency 'not known': Dry eyes

1.2. Dasatinib – Cytomegalovirus (CMV) reactivation

Authorisation procedure	Centralised
EPITT No	19111
PRAC rapporteur(s)	Doris I Stenver (DK)
Date of adoption	12 April 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of CMV infections, the PRAC has agreed that the MAH of dasatinib (Sprycel) should submit a variation within 2 months, to amend the product information as described below (new text underlined):

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

Summary of product characteristics

4.8. Undesirable effects

Table 2: Tabulated summary of adverse reactions

Infections and infestations

Common: pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection (including cytomegalovirus-CMV), enterocolitis infection, sepsis (including uncommon cases with fatal outcomes)

Package leaflet

4. Possible side effects

Common side effects (may affect up to 1 in 10 people)

Infections: pneumonia, herpes virus infection (including cytomegalovirus-CMV), upper respiratory tract infection, serious infection of the blood or tissues (including uncommon cases with fatal outcomes)

1.3. Lapatinib – Pulmonary hypertension

Authorisation procedure	Centralised
EPITT No	19089
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	12 April 2018

Recommendation

Having considered the available evidence in EudraVigilance and in the literature with regards to the risk of pulmonary arterial hypertension, the PRAC has agreed that the MAH of lapatinib (Tyverb) 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

Frequency not known: pulmonary arterial hypertension

Package leaflet

4. Possible side effects

Frequency not known: pulmonary arterial hypertension (increased blood pressure in the arteries (blood vessels) of the lungs)

1.4. Phenprocoumon – Risk of birth defects and foetal loss following first trimester exposure as a function of the time of withdrawal

Authorisation procedure	Non-centralised
EPITT No	18902
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	12 April 2018

Recommendation

Having considered the available evidence from a recent observational study, the PRAC has agreed that the MAHs of phenprocoumon-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined).

As there are various wordings currently in national summaries of product characteristics (SmPC), for ease of implementation, the entire section 4.6 of the SmPC, as well as the relevant wording in Section 2 of the package leaflet should be updated by the MAHs of phenprocoumon.

Summary of product characteristics

4.6. Fertility, pregnancy and lactation

Women of childbearing potential / Contraception

Women of childbearing age who are taking <…> have to use effective contraceptive measures during treatment and should continue for 3 months after the last dose.

Women of childbearing potential planning a pregnancy should be switched to a safer alternative treatment prior to pregnancy.

Pregnancy

Based on human experience phenprocoumon may cause birth defects and foetal death when administered during pregnancy. There is epidemiological evidence suggesting that the risk of birth defects and foetal death increases with the increasing duration of exposure to phenprocoumon during the first trimester of pregnancy, with a steep increase of the rate of major birth defects when phenprocoumon treatment is continued beyond the 5th gestational week.

In cases of exposure to phenprocoumon during second and third trimester of pregnancy, the foetus is at an increased risk of intrauterine or parturitional (cerebral) hemorrhage due to foetal anticoagulation.

In humans phenprocoumon crosses the placental barrier.

Phenprocoumon is contraindicated during pregnancy (see section 4.3).

If the patient becomes pregnant while taking <…>, the patient should immediately be switched to a safer alternative treatment (e.g. heparin) and close follow-up including level II ultrasound should be recommended.

Breastfeeding

In nursing mothers, the active ingredient passes into the breast milk, though in such small amounts that no adverse reactions are likely to occur in the infant. As a precaution, however, prophylaxis involving the administration of vitamin K1 to the infant concerned is recommended.

Fertility

No information on effects of <…> on fertility is available.

Package leaflet

2. What you need to know before you take <…>

Pregnancy, breastfeeding and fertility

Pregnancy

You must not use <…> when you are pregnant, as it passes from mother to child. This means taking <...> during pregnancy can lead to malformations and even death of your unborn child. There is also a risk of bleeding in the foetus (foetal hemorrhage).

You must prevent becoming pregnant by taking effective contraceptive measures during therapy with <…> and in the period of 3 months after completion of the treatment with <…> due to the increased risk of foetal malformations.

If you wish to get pregnant or if you already became pregnant while taking this medicine, talk to your doctor immediately as you should be switched to a safer alternative treatment (e.g. heparin) if you are planning a pregnancy or immediately after recognition of pregnancy.

Breastfeeding

If you are breastfeeding, <…> passes into the breast milk, though in such small amounts that no adverse reactions are likely to occur to your child. Therefore, if you are breastfeeding, your child should receive vitamin K1.

Fertility

No information is available regarding the influence of <…> on fertility.

1.5. Vortioxetine – Angioedema and urticaria

Authorisation procedure	Centralised
EPITT No	19099
PRAC rapporteur(s)	Laurence de Fays (BE)
Date of adoption	12 April 2018

Recommendation *[see also section 2]*

Having considered the available evidence in EudraVigilance and Lundbeck's safety database, the PRAC has agreed that the MAH(s) of vortioxetine-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

Tabulated list of adverse reactions

Skin and subcutaneous tissue disorders

Frequency 'not known': Angioedema, urticaria

Package leaflet

4. Possible side effects

Not known: frequency cannot be estimated from available data

- Swelling of the face, lips, tongue or throat
- Hives

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Alemtuzumab	Cytomegalovirus (CMV) infection (19193)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 4 July 2018)	Genzyme Therapeutics Ltd
Azithromycin	Increased rate of relapses of haematological malignancies and mortality in hematopoietic stem cell transplantation (HSCT) patients (18907)	Kimmo Jaakkola (FI)	Assess in the next PSUR (submission by 29 July 2020); direct healthcare professional communication (DHPC) requested	MAHs of systemic azithromycin formulations (DHPC to be coordinated by Pfizer)
Belimumab	Lupus nephritis (19174)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 15 June 2018)	Glaxo Group Ltd
Daratumumab	Encephalopathy (19176)	Marcia Silva (PT)	Assess in the next PSUR (submission by 24 July 2018)	Janssen-Cilag International NV
Dimethyl fumarate	Immune thrombocytopenic purpura, thrombocytopenia (19192)	Martin Huber (DE)	Supplementary information requested (submission by 4 July 2018)	Biogen Idec Ltd
Duloxetine	Interstitial lung disease (19175)	Dolores Montero Corominas (ES)	Supplementary information requested (submission by 4 July 2018)	Eli Lilly Nederland B.V.
Emicizumab	New information on the known risk of haemorrhagic events (19214)	Amelia Cupelli (IT)	Assess in the next PSUR (submission by 24 July 2018)	Roche Registration Limited
Olanzapine	Somnambulism (19202)	Kimmo Jaakkola (FI)	Supplementary information requested (submission by 4 July 2018)	Eli Lilly Nederland B.V.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Parathyroid hormone	Nephrolithiasis (19177)	Almath Spooner (IE)	Assess in the next PSUR (submission by 2 July 2018)	Shire Pharmaceuticals Ireland Ltd
Sitagliptin; sitagliptin, metformin hydrochloride	Potential drug interaction between sitagliptin and angiotensin-converting-enzyme (ACE)-inhibitors leading to an increased risk of angioedema (17608)	Menno van der Elst (NL)	Supplementary information requested (submission by 4 July 2018)	Merck Sharp & Dohme Limited
Tocilizumab	Hypofibrinogenaemia (19179)	Brigitte Keller-Stanislawski (DE)	Assess in the next PSUR (submission by 19 June 2018)	Roche Registration GmbH
Vortioxetine	Angioedema and urticaria (19099)	Laurence de Fays (BE)	· See section 1.5 · Assess cases of anaphylactic reaction in the next PSUR	H. Lundbeck A/S

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab; infliximab	Risk of lymphoma in patients with inflammatory bowel disease (19121)	Ulla Wändel Liminga (SE)	No action at this stage	Not applicable
Dienogest, ethinylestradiol	New information on the known risk of venous thromboembolism with combined hormonal contraceptives (CHCs) containing dienogest and ethinylestradiol (DNG/EE) (17409)	Valerie Straßmann (DE)	Issue to be addressed within the ongoing variation procedure	Bayer Vital GmbH
Human normal immunoglobulin	Lupus-like syndrome and related terms (19098)	Brigitte Keller-Stanislawski (DE)	No action at this stage	Not applicable
Pegfilgrastim; lenograstim; lipegfilgrastim	Pulmonary haemorrhage (19181)	Patrick Batty (UK)	Provide comments on proposed updates to the product information (submission by 27 April 2018)	Amgen Europe B.V., Italfarmaco S.P.A, Sanofi, Chugai Pharma, UAB Sicor Biotech