10 February 2020[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 13-16 January 2020 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 13-16 January 2020 (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 (27-30 January 2020) 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] Expected 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. Abiraterone – Interaction with sulphonylureas leading to hypoglycaemia

Authorisation procedure	Centralised
EPITT No	19445
PRAC rapporteur(s)	Eva Segovia (ES)
Date of adoption	16 January 2020

Recommendation *[see also section 2]*

Having considered the available evidence in EudraVigilance and in the literature and also from the cumulative review provided by the MAH for Zytiga (Janssen-Cilag), the PRAC has agreed that the MAH(s) of abiraterone-containing medicinal products should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below (new text underlined, text to be removed with ~~strikethrough~~):

Summary of product characteristics

4.4. Special warnings and precautions for use

Hyperglycaemia

The use of glucocorticoids could increase hyperglycaemia, therefore blood sugar should be measured frequently in patients with diabetes.

Hypoglycaemia

Cases of hypoglycaemia have been reported when ZYTIGA was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see section 4.5); therefore, blood sugar should be measured frequently in patients with diabetes.

4.5. Interaction with other medicinal products and other forms of interaction

Interactions with other medicinal products

Potential to affect exposures to other medicinal products

[…]

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. ~~Although these results indicate that no clinically meaningful increases in exposure are expected when ZYTIGA is combined with medicinal products that are predominantly eliminated by CYP2C8.~~ Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolised by CYP2C8 include pioglitazone and repaglinide (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.

Package leaflet

2. What you need to know before you take Zytiga

Other medicines and ZYTIGA

Ask your doctor or pharmacist for advice before taking any medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is important because ZYTIGA may increase the effects of a number of medicines including heart medicines, tranquilisers, some medicines for diabetes, herbal medicines (e.g., St John's wort) and others. Your doctor may want to change the dose of these medicines. Also, some medicines may increase or decrease the effects of ZYTIGA. This may lead to side effects or to ZYTIGA not working as well as it should.

1.2. Golimumab – Inflammatory myopathy

Authorisation procedure	Centralised
EPITT No	19460
PRAC rapporteur(s)	Ulla Wändel Liminga (SE)
Date of adoption	16 January 2020

Recommendation

Having considered the available evidence from EudraVigilance and the literature as well as the cumulative review submitted by Janssen Biologics B.V, the PRAC has agreed that the product information for golimumab (SIMPONI) should be updated to reflect the risk of worsening of symptoms of dermatomyositis.

The MAH of SIMPONI should submit a variation within two months from the publication of the PRAC recommendation to amend the product information as described hereafter (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Tabulated list of adverse reactions

Skin and subcutaneous tissue disorders

Not known: Worsening of symptoms of dermatomyositis

Package leaflet

4. Possible side effects

The following additional side effects have been observed with Simponi:

Side effects of which the frequency is not known:

Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Abiraterone	Interaction with sulphonylureas leading to hypoglycaemia (19445)	Eva Segovia (ES)	· See section 1.1 · Assess in the next PSUR (submission by 26 July 2021)	Janssen-Cilag International NV
Baricitinib	Diverticulitis (19496)	Adam Przybylkowski (PL)	Supplementary information requested (submission by 11 March 2020)	Eli Lilly Nederland B.V.
Dabrafenib; trametinib	Disseminated intravascular coagulation (DIC) (19510)	Annika Folin (SE)	Supplementary information requested (submission by 11 March 2020)	Novartis Europharm Limited
Desogestrel	Suppressed lactation (19504)	Annika Folin (SE)	Supplementary information requested (submission by 11 March 2020)	Merck Sharp & Dohme BV
Dipeptidyl peptidase-4 (DPP4) inhibitors: alogliptin; vildagliptin	Rhabdomyolysis (19466)	Menno van der Elst (NL)	Supplementary information requested (submission by 11 March 2020)	Takeda Pharma A/S, Novartis Europharm Limited
Dupilumab	Corneal disorders (19509)	Kimmo Jaakkola (FI)	Assess in the next PSUR (submission by 6 June 2020)	Sanofi-aventis groupe
Mirtazapine	Amnesia (19506)	Liana Gross-Martirosyan (NL)	Supplementary information requested (submission by 11 March 2020)	Merck
Nivolumab	Lichen sclerosus (19505)	Brigitte Keller-Stanislawski (DE)	Assess in the next PSUR (submission by 11 September 2020)	Bristol-Myers Squibb Pharma EEIG
Sertraline	Microscopic colitis (19513)	Liana Gross-Martirosyan (NL)	Supplementary information requested (submission by 11 March 2020)	Pfizer

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Pericarditis (19457)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	MAHs of adalimumab containing products
Anastrozole	Hallucinations (19449)	Zane Neikena (LV)	Monitor in PSUR	AstraZeneca
Fluoroquinolones [4]	Heart valve regurgitation (19522)	Martin Huber (DE)	No action at this stage	Not applicable
Hormone replacement therapy (HRT)[5]	New information on the known risk of breast cancer (19482)	Menno van der Elst (NL)	No action at this stage	Not applicable
Immune check point inhibitors: i) Atezolizumab; cemiplimab; durvalumab ii) Atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; nivolumab; pembrolizumab	Tuberculosis (19464)	Brigitte Keller-Stanislawski (DE)	i) Provide comments to the proposed updates to the product information (submission by 7 February 2020) ii) Routine pharmacovigilance	i) Roche Registration GmbH, Regeneron Ireland, AstraZeneca AB ii) Roche Registration GmbH, Merck Europe B.V., Regeneron Ireland, AstraZeneca AB, Bristol-Myers Squibb Pharma EEIG, Merck Sharp & Dohme B.V.
Prasugrel	Severe cutaneous adverse reactions (SCARs) (19463)	Anette Kirstine Stark (DK)	Classify acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) as important potential risks in future PSURs	Daiichi Sankyo Europe GmbH

[4] Ciprofloxacin; delafloxacin; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin
[5] Chlorotrianisene; conjugated estrogens; conjugated estrogens, bazedoxifene; dienestrol; diethylstilbestrol; estradiol; estradiol, norethisterone; estriol; estrone; ethinylestradiol; methallenestril; moxestrol; promestriene; tibolone

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Sacubitril, valsartan	Ventricular arrhythmia (19448)	Anette Kirstine Stark (DK)	Routine pharmacovigilance	Novartis Europharm Limited