28 October 2019[1]
EMA/PRAC/532014/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 30 September-3 October 2019 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 30 September-3 October 2019 (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 (14-17 October 2019) 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.

[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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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.

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. Durvalumab – Myasthenia gravis

Authorisation procedure	Centralised
EPITT No	19451
PRAC rapporteur(s)	David Olsen (NO)
Date of adoption	3 October 2019

Recommendation *[see also section 3]*

Based on the available evidence it is considered that there is an association between durvalumab and myasthenia gravis events, therefore, the PRAC has agreed that the MAH (Astra Zeneca) for the durvalumab containing product (IMFINZI), should submit a variation within 2 months, to amend the Product Information as described below (new text underlined):

Summary of product characteristics

4.2. Posology and method of administration

Adverse reactions	Severity [a]	IMFINZI treatment modification	Corticosteroid treatment unless otherwise specified
Other immune-mediated adverse reactions	Grade 3	Withhold dose	Consider initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by taper
	Grade 4	Permanently discontinue [d]	

c) Permanently discontinue IMFINZI if the adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.

d) For myasthenia gravis, if there are signs of muscular weakness or respiratory insufficiency, IMFINZI should be permanently discontinued.

4.4. Special warnings and precautions for use

Other immune-mediated adverse reactions

Given the mechanism of action of IMFINZI, other potential immune-mediated adverse reactions may occur. The following immune-related adverse reactions were reported in less than 1% of patients treated with IMFINZI monotherapy in clinical trials (n = 1889): myasthenia gravis, myocarditis, myositis, polymyositis. Patients should be monitored for signs and symptoms and managed as recommended in section 4.2.

4.8. Undesirable effects

Nervous system disorders

Rare: Myasthenia gravis

[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. Warnings and precautions

Your doctor may delay the next dose of IMFINZI or stop your treatment with IMFINZI, if you have:

- Inflammation or problems of the muscles: symptoms may include muscle pain, or weakness or rapid fatigue of the muscles;

4. Possible side effects

Rare: a condition in which the muscles become weak and there is a rapid fatigue of the muscles (myasthenia gravis).

1.2. Lithium – Drug-induced lichenoid reaction

Authorisation procedure	Non-centralised
EPITT No	19389
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	3 October 2019

Recommendation

Having considered the available evidence, the PRAC has agreed that the MAH(s) of lithium-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: lichenoid drug reaction

Package leaflet

4. Possible side effects

Frequency not known: eruption of the skin or mucous membranes (lichenoid drug reaction)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Bevacizumab	Guillain–Barré syndrome (GBS) (19472)	Hans Christian Siersted (DK)	Supplementary information requested (submission by 11 December 2019)	Roche Registration GmbH
Nivolumab	Haemophagocytic lymphohistiocytosis (19467)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 11 December 2019)	Bristol-Myers Squibb Pharma EEIG
Vismodegib	Pancreatitis (19470)	Annika Folin (SE)	Supplementary information requested (submission by 11 December 2019)	Roche Registration GmbH

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Direct acting antivirals (DAAV)[4]	Autoimmune hepatitis (19395)	Ana Sofia Martins (PT)	Routine pharmacovigilance	AbbVie Deutschland GmbH Co. KG, Gilead Sciences Ireland UC, Merck Sharp & Dohme B.V.
Durvalumab	Myasthenia gravis (19451)	David Olsen (NO)	· See section 1.1 · Assess in the next PSUR (submission by 8 January 2020) · Update the RMP	AstraZeneca AB
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
Indapamide	Choroidal effusion (19468)	Martin Huber (DE)	No action at this stage	Not applicable

[4] Dasabuvir; elbasvir, grazoprevir; glecaprevir, pibrentasvir; ledipasvir, sofosbuvir; ombitasvir, pariteprevir, ritonavir; sofosbuvir; sofosbuvir, velpatasvir; sofosbuvir, velpatasvir, voxilaprevir
[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
Sebelipase alfa	Nephrotic syndrome (19410)	Ulla Wändel Liminga (SE)	Routine pharmacovigilance	Alexion Europe SAS