9 March 2020[1]
EMA/PRAC/64581/2020 Corr*
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 10-13 February 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 10-13 February 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 (24-27 February 2020)[3] 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] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
* Typo corrected on 30 March 2020 (see page 5).
[2] The relevant EPITT reference number should be used in any communication related to a signal.
[3] The product information update for nivolumab will be adopted by CHMP at their 23-26 March 2020 plenary meeting.

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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[4]

1.1. Nivolumab – Haemophagocytic lymphohistiocytosis

Authorisation procedure	Centralised
EPITT No	19467
PRAC rapporteur(s)	Brigitte Keller-Stanislawski (DE)
Date of adoption	13 February 2020

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH of Opdivo (Bristol-Myers Squibb Pharma EEIG) 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):

Summary of product characteristics

4.4. Special warnings and precautions for use

Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab as monotherapy and nivolumab in combination with ipilimumab. Caution should be taken when nivolumab is administered as monotherapy or in combination with ipilimumab. If HLH is confirmed, administration of nivolumab or nivolumab in combination with ipilimumab should be discontinued and treatment for HLH initiated.

4.8. Undesirable effects

Table 5: Adverse reactions with nivolumab monotherapy

Blood and lymphatic system disorders

Haemophagocytic lymphohistiocytosis (Frequency 'Not known')

Table 6: Adverse reactions with nivolumab in combination with ipilimumab

Blood and lymphatic system disorders

Haemophagocytic lymphohistiocytosis (Frequency 'Not known')

Package leaflet

2. What you need to know before you use OPDIVO

Warnings and precautions:

Haemophagocytic lymphohistiocytosis. A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

[4] Translations in all official EU languages of the new nivolumab product information adopted by PRAC will be published on the EMA website on 6 April 2020.

4. Possible side effects

The following side effects have been reported with nivolumab alone:

A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)

The following side effects have been reported with nivolumab in combination with ipilimumab:

A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Adalimumab	Abnormal weight gain (19520)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 6 May 2020)	AbbVie Deutschland GmbH & Co. KG
Azithromycin	Increased cancer risk among patients with bronchiolitis obliterans after hematopoietic cell transplantation (19528)	Kimmo Jaakkola (FI)	Assess in the next PSUR (submission by 29 July 2020)	Pfizer
Bevacizumab	Guillain-Barré syndrome (19472)	Hans Christian Siersted (DK)	Assess in the upcoming PSURs (submission of next PSUR by 5 May 2020)	MAHs of bevacizumab containing products
Lisdexamfetamine	QT prolongation and cardiac arrhythmia (19533)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 6 April 2020)	Shire Pharmaceuticals
Lorlatinib	Nephrotic syndrome (19518)	Nikica Mirošević Skvrce (HR)	Assess in the responses to the request for supplementary information within the ongoing PSUSA evaluation (submission by 19 March 2020)	Pfizer Europe MA EEIG

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Macrogol 3350[5],[6]; macrogol 4000[5,6]*	Colitis ischaemic (19517)	Ilaria Baldelli (IT)	Supplementary information requested (submission by 6 April 2020)	· All MAHs of macrogol containing products (macrogol 3350 and 4000 with all different combinations) authorised for the bowel preparation · For the literature overview: innovator MAHs (Helsinn Birex, Norgine NV/SA, Ipsen, Alfasigma S.P.A., Polifarmas S.P.A.)
Sevoflurane	Diabetes insipidus (19531)	Ronan Grimes (IE)	Assess in the next PSUR (submission by 30 April 2020)	Abbott, Abbvie, Baxter, Piramal Healthcare UK Limited
Teriparatide	Myeloma (19511)	Ghania Chamouni (FR)	Supplementary information requested (submission by 6 April 2020)	Eli Lilly, Teva, Stada, Gedeon Richter
Tramadol	Hiccups (19529)	Ghania Chamouni (FR)	Assess in the next PSUR (submission by 20 August 2020)	MAHs of tramadol as single ingredient

[5] With or without electrolytes
[6] and combination(s)
* Macrogol 4000[4,5] was replaced by macrogol 4000[5,6] on 30 March 2020.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ifosfamide	Increased risk of encephalopathy (19433)	Annika Folin (SE)	No action	Not applicable
Vismodegib	Pancreatitis (19470)	Annika Folin (SE)	Monitor in PSUR	Roche Registration GmbH