3 July 2023[1]
EMA/PRAC/248309/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 5-8 June 2023 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 June 2023 (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 June 2023) 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. Ipilimumab; nivolumab; pembrolizumab – Capillary leak syndrome (Opdivo, Yervoy, Keytruda) and cytokine release syndrome (Opdivo)

Authorisation procedure	Centralised
EPITT No	19880
PRAC Rapporteur	Menno van der Elst (NL)
Date of adoption	8 June 2023

Recommendation *[see also section 3 for capillary leak syndrome]*

Having considered the available evidence concerning Cytokine release syndrome, including from the cumulative review performed by the Marketing Authorisation Holder (MAH), 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

4.8. Undesirable effects

Table 6: Adverse reactions with nivolumab monotherapy

	Nivolumab monotheraphy
Immune system disorders	
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity (including anaphylactic reaction)

Table 7: Adverse reactions with nivolumab in combination with other therapeutic agents

	Combination with ipilimumab (with or without chemotherapy)	Combination with chemotherapy	Combination with cabozantinib
Immune system disorders			
Common	infusion related reaction (including cytokine release syndrome), hypersensitivity	infusion related reaction (including cytokine release syndrome), hypersensitivity	hypersensitivity (including anaphylactic reaction)
Uncommon			infusion related hypersensitivity reaction

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

1.2. Tofacitinib – Acnes

Authorisation procedure	Centralised
EPITT No	19885
PRAC Rapporteur	Liana Gross-Martirosyan (NL)
Date of adoption	8 June 2023

Recommendation

Having considered the available evidence from EudraVigilance and the literature, the MAH's responses and the Rapporteur's assessment, the PRAC has concluded that there is sufficient evidence to establish a causal relationship between treatment with tofacitinib and acne. Therefore, the PRAC has agreed that an update of the product information is warranted to add acne as an undesirable effect with a frequency 'common'. The MAH for Xeljanz (Pfizer Europe MA EEIG) should submit a variation within 60 days from the publication of the PRAC recommendation, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Skin and subcutaneous tissue disorders

Frequency 'common': Acne

Package leaflet

4. Possible side effects

Common (may affect up to 1 in 10 people): Acne

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amivantamab	Anaphylactic reaction (19928)	Gabriele Maurer (DE)	Supplementary information requested (submission by 23 August 2023)	Janssen-Cilag International N.V.
Dapagliflozin	Acquired phimosis and phimosis (19935)	Mari Thorn (SE)	Supplementary information requested (submission by 23 August 2023)	AstraZeneca AB
Leuprorelin	Severe cutaneous adverse reactions (SCARs) (19930)	Amelia Cupelli (IT)	Assess in the next PSUR (submission by 29 October 2023)	Accord Healthcare S.L.U., AbbVie, Takeda, Recordati Industria Chimica e Farmaceutica S.p.A. and related affiliates

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ipilimumab; nivolumab; pembrolizumab	Capillary leak syndrome (Opdivo, Yervoy, Keytruda) and cytokine release syndrome (Opdivo) (19880)	Menno van der Elst (NL)	· See section 1.1 for cytokine release syndrome and nivolumab (Opdivo) · Routine pharmacovigilance for capillary leak syndrome and all three medicinal products	Bristol-Myers Squibb Pharma EEIG, Merck Sharp & Dohme B.V.