21 November 2022[1]
EMA/PRAC/845793/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 24-27 October 2022 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 24-27 October 2022 (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 (7-10 November 2022) 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. Durvalumab – Myelitis transverse

Authorisation procedure	Centralised
EPITT No	19815
PRAC Rapporteur	David Olsen (NO)
Date of adoption	27 October 2022

Recommendation

Based on the available evidence it is considered that a causal relationship between myelitis transverse and durvalumab is at least a reasonable possibility, therefore, the PRAC has agreed that the MAH (Astra Zeneca AB) 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**
Immune-mediated myelitis transverse	Any grade	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by taper

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 have been observed in patients treated with IMFINZI monotherapy: myasthenia gravis, myelitis transverse, myositis, polymyositis, meningitis, encephalitis, Guillain-Barré syndrome, immune thrombocytopenia, cystitis noninfective and pancreatitis (see section 4.8). Patients should be monitored for signs and symptoms and managed as recommended for other immune-mediated adverse reactions, in section 4.2.

4.8. Undesirable effects

The following adverse reaction: myelitis transverse should be added under the SOC Nervous System Disorders with a frequency not known. The adverse reaction is to be added to table 3:

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

Table 3. Adverse drug reactions in patients treated with IMFINZI monotherapy and IMFINZI in combination with chemotherapy

	IMFINZI Monotherapy			IMFINZI Combined with Chemotherapy		
	Any Grade (%)		Grade 3-4 (%)	Any Grade (%)		Grade 3-4 (%)
Nervous System Disorders						
Myasthenia gravis	Rare[k]	<0.1				
Noninfective encephalitis	Not known[l]					
Meningitis[m]	Rare	<0.1	<0.1			
Guillain-Barré syndrome	Not known					
Myelitis transverse	**Not known[bb]**					

[bb] **events were reported from post-marketing data**

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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;
- inflammation of the spinal cord (transverse myelitis): symptoms may include pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation.

1.2. Elasomeran (COVID-19 mRNA vaccine - Spikevax) – Heavy menstrual bleeding

Authorisation procedure	Centralised
EPITT No	19780
PRAC Rapporteur	Brigitte Keller-Stanislawski (DE)
Date of adoption	27 October 2022

Recommendation

Having considered all the available evidence including spontaneous case reports in EudraVigilance, data from national reviews, observational studies, and provided by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH for COVID-19 mRNA vaccine (nucleoside-modified) Spikevax (Moderna Biotech Spain, S.L.) should submit by 25 November 2022 a variation to amend the product information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

System Organ Class: Reproductive system and breast disorders

[Frequency] Not known: Heavy menstrual bleeding*

[Under table] * Most cases appeared to be non-serious and temporary in nature.

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4. Possible side effects

Not known (cannot be estimated from the available data):

Heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

1.3. Tozinameran (COVID-19 mRNA vaccine - Comirnaty) – Heavy menstrual bleeding

Authorisation procedure	Centralised
EPITT No	19783
PRAC Rapporteur	David Olsen (NO)
Date of adoption	27 October 2022

Recommendation

Having considered all the available evidence, including spontaneous case reports in EudraVigilance, data from national reviews, observational studies, and provided by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH for COVID-19 mRNA vaccine (nucleoside-modified) Comirnaty (BioNTech Manufacturing GmbH) should submit by 25 November 2022 a variation to amend the product information as described below (new text underlined):

Summary of product characteristics

4.8 Undesirable effects

System Organ Class: Reproductive system and breast disorders

[Frequency] Not known: Heavy menstrual bleeding*

[Under table] * Most cases appeared to be non-serious and temporary in nature.

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4. Possible side effects

Not known (cannot be estimated from the available data):

Heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ceftriaxone	Factor V inhibition (19853)	Zane Neikena (LV)	Supplementary information requested (submission by 11 January 2023)	Roche Products LTD
Olaparib	Hepatocellular damage and hepatitis (19846)	Amelia Cupelli (IT)	Supplementary information requested (submission by 11 January 2023)	AstraZeneca AB
Propofol	Medication errors that could potentially lead to life-threatening/fatal cases (19851)	Pernille Harg (NO)	Supplementary information requested (submission by 11 January 2023)	MAHs of all propofol-containing products
Voriconazole	Drug interaction with flucloxacillin leading to subtherapeutic voriconazole levels (19849)	Liana Gross-Martirosyan (NL)	Supplementary information requested (submission by 11 January 2023)	Pfizer Europe MA EEIG

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Ipilimumab; nivolumab	Pure red cell aplasia and aplastic anaemia (19804)	Brigitte Keller-Stanislawski (DE)	Monitor in PSURs	Bristol-Myers Squibb Pharma EEIG
Tildrakizumab	Herpes zoster (19801)	Adam Przybylkowski (PL)	Routine pharmacovigilance	Almirall S.A