26 September 2022[1]
EMA/PRAC/699721/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 29 August – 1 September 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 29 August-1 September 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 (12-15 September 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.

[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.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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. Pneumococcal polysaccharide vaccine (23 serotypes) – Extensive swelling of vaccinated limb

Authorisation procedure	Non-centralised
EPITT No	19768
PRAC Rapporteur	Brigitte Keller-Stanislawski
Date of adoption	1 September 2022

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the MAH(s) of pneumococcal polysaccharide vaccine containing 23 serotypes 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

b. Tabulated list of adverse reactions

[…]

SOC General disorders and administration site conditions

[…]

Frequency rare:

~~Injection site cellulitis~~ Extensive swelling of the vaccinated limb†

[…]

† with short onset time from vaccine administration; defined by clinical review of cases reporting the preferred terms of extensive swelling of the vaccinated limb, injection site cellulitis and cellulitis, all of which described cellulitis-like reactions.

Package leaflet

4. Possible side effects

[…]

Side effects

[…]

Other side effects include:

Rare (may affect up to 1 in 1,000 people):

extensive swelling ~~in~~ of the ~~injected~~ vaccinated limb.

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

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Dabrafenib; trametinib	Haemophagocytic lymphohistiocytosis (19824)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 3 November 2022)	Novartis Europharm Limited
Regorafenib	Thrombotic microangiopathy (19832)	Menno van der Elst (NL)	Supplementary information requested (submission by 3 November 2022)	Bayer AG
Tozinameran (COVID-19 mRNA vaccine) – Comirnaty[4]	Histiocytic necrotizing lymphadenitis (19835)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 26 February 2023)	BioNTech Manufacturing GmbH
Tozinameran (COVID-19 mRNA vaccine) – Comirnaty	Vulval ulceration (19840)	Menno van der Elst (NL)	Supplementary information requested (submission by 3 November 2022)	BioNTech Manufacturing GmbH
Voxelotor	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19833)	Jean-Michel Dogné (BE)	Assess in the next PSUR (submission by 22 October 2022)	Global Blood Therapeutics

[4] The MAHs of two other COVID-19 vaccines, Spikevax (elasomeran) and Vaxzevria (ChAdOx1-S [recombinant]) have also been requested to assess histiocytic necrotizing lymphadenitis in the next PSUR (submission by 26 February 2023 for Spikevax and by 8 March 2023 for Vaxzevria).

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
COVID-19 vaccine (ChAdOx1-S [recombinant]) - Vaxzevria	Corneal graft rejection (19791)	Jean-Michel Dogné (BE)	Routine pharmacovigilance	AstraZeneca AB
Elasomeran (COVID-19 mRNA vaccine) - Spikevax	Corneal graft rejection (19792)	Marie Louise Schougaard Christiansen (DK)	Routine pharmacovigilance	Moderna Biotech Spain, S.L.
Topiramate	Neurodevelopmental disorders due to in utero exposure (19825)	Ulla Wändel Liminga (SE)	Review under Article 31 of Directive 2001/83/EC	MAHs of topiramate-containing products
Tozinameran (COVID-19 mRNA vaccine) - Comirnaty	Corneal graft rejection (19789)	Menno van der Elst (NL)	Routine pharmacovigilance	BioNTech Manufacturing GmbH
Tranexamic acid	Incorrect route of product administration (19844)	Ronan Grimes (IE)	No action	Not applicable