7 February 2022[1]
EMA/PRAC/13254/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 10-13 January 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 10-13 January 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 (24-27 January 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 – Arthralgia

Authorisation procedure	Centralised
EPITT No	19709
PRAC Rapporteur	David Olsen (NO)
Date of adoption	13 January 2022

Recommendation *[see also section 3]*

Having considered the available evidence (e.g. EudraVigilance) it is agreed that there is at least a reasonable possibility of association between durvalumab and arthralgia, therefore, the PRAC concluded that the product information should be updated accordingly.

The MAH of durvalumab-containing medicinal product/ IMFINZI (Astra Zeneca AB) 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

	IMFINZI Monotherapy			IMFINZI Combined with Chemotherapy		
	Any Grade (%)		Grade 3-4 (%)	Any Grade (%)		Grade 3-4 (%)
Musculoskeletal and connective tissue disorders						
<u>Arthralgia</u>	<u>Very common</u>	<u>10.3</u>	<u>0.3</u>	<u>Common</u>	<u>2.6</u>	<u>0.4</u>

Package leaflet

4. Possible side effects

Very common (may affect more than 1 in 10 people)

- infections of the upper respiratory tract
- …
- fever
- <u>joint pain (arthralgia)</u>

[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. Pregabalin – Toxic epidermal necrolysis

Authorisation procedure	Centralised and non-centralised
EPITT No	19723
PRAC Rapporteur	Liana Gross-Martirosyan (NL)
Date of adoption	13 January 2022

Recommendation

Having considered the available evidence from preclinical and clinical studies, EudraVigilance, and the literature, and considering the pathophysiological mechanism and clinical characteristics of TEN, that are the same as for SJS, which is a known ADR for pregabalin, the PRAC has agreed that the MAH(s) of pregabalin-containing medicinal products 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 / text to be removed with ~~strikethrough~~):

Summary of product characteristics

4.4. Special warnings and precautions for use

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported rarely in association with pregabalin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, pregabalin should be withdrawn immediately and an alternative treatment considered (as appropriate).

4.8. Undesirable effects

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders:

Frequency 'rare': Toxic Epidermal Necrolysis

Package leaflet

2. What you need to know before you take <product name>

Serious skin rashes including Stevens-Johnson syndrome, toxic epidermal necrolysis have been reported in association with pregabalin. Stop using pregabalin and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

4. Possible side effects

Frequency 'rare':

Allergic reactions ~~(~~which may include difficulty breathing, inflammation of the eyes (keratitis) and a serious skin reaction characterized by ~~rash, blisters, peeling skin and pain).~~ reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis).

[…]

If you experience swollen face or tongue or if your skin turns red and starts to blister or peel, you should seek immediate medical advice.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Calcitonin gene-related peptide (CGRP) antagonists: eptinezumab; erenumab; fremanezumab; galcanezumab	Raynaud's phenomenon (19766)	Kirsti Villikka (FI)	Supplementary information requested (submission by 2 March 2022)	H. Lundbeck A/S, Novartis Europharm Limited, TEVA GmbH, Eli Lilly Nederland B.V.
COVID-19 mRNA[4] vaccine (nucleoside-modified) – Spikevax; Tozinameran (COVID-19 mRNA[4] vaccine [nucleoside modified]) – Comirnaty	Capillary leak syndrome (19743)	Hans Christian Siersted (DK); Menno van der Elst (NL)	Supplementary information requested (submission by 4 February 2022)	Moderna Biotech Spain, S.L.; BioNTech Manufacturing GmbH
Human normal immunoglobulin for intravenous use	Thrombocytopenia (19764)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 7 April 2022)	MAHs of all approved intravenous immunoglobulins
Osimertinib	Aplastic anaemia (19769)	Menno van der Elst (NL)	Assess in the next PSUR (submission by 10 February 2022)	AstraZeneca AB
Roxadustat	Central hypothyroidism (19757)	Marek Juračka (SK)	Assess in the next PSUR (submission by 24 February 2022)	Astellas Pharma Europe B.V.

[4] Messenger ribonucleic acid

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Durvalumab	Arthralgia (19709)	David Olsen (NO)	· See section 1.1 · Perform a cumulative review of 'arthritis' in the upcoming PSUR (submission by 9 July 2022)	AstraZeneca AB
Tocilizumab	Sarcoidosis (18860)	Brigitte Keller-Stanislawski (DE)	Routine pharmacovigilance	Roche Registration GmbH