2 April 2024[1]
EMA/PRAC/77162/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 4-7 March 2024 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 4-7 March 2024 (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 (18-21 March 2024) 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. Abemaciclib; palbociclib; ribociclib – Erythema multiforme

Authorisation procedure	Centralised
EPITT No	19973
PRAC Rapporteur	Marie Louise Schougaard Christiansen (DK)
Date of adoption	7 March 2024

Recommendation

Having considered the available evidence in EudraVigilance, literature and the cumulative review submitted by the Marketing Authorisation Holders (MAHs), the PRAC has agreed that the MAHs of Kisqali (Novartis Europharm Limited), Ibrance (Pfizer Europe MA EEIG) and Verzenios (Eli Lilly Nederland B.V.), should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below. Regarding section 4.8 of the SmPC, in addition to the inclusion of "Erythema multiforme", the MAHs should amend the headings and/or footnotes of the indicated tables, concerning adverse drug reactions observed post-marketing (new text underlined, text to be removed ~~strike through~~).

Summary of product characteristics

Abemaciclib

4.8 Undesirable effects

Table 8. Adverse reactions reported in the phase 3 studies of abemaciclib in combination with endocrine therapy (N = 3 559) and during post-marketing experience

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

Erythema multiforme

Ribociclib

4.8 Undesirable effects

Table 7. Adverse reactions reported in the three phase III clinical studies and during post-marketing experience

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

Erythema multiforme

~~* Adverse reaction reported during post-marketing experience~~. *[All asterisks applied on adverse events of the table should be removed accordingly]*

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

Palbociclib

4.8 Undesirable effects

Table 4. Adverse reactions based on pooled dataset from 3 randomised studies (N=872) and during post-marketing experience

The following adverse reaction should be added under SOC 'Skin and subcutaneous tissue disorders' with frequency 'uncommon'

Skin and subcutaneous tissue disorders	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Uncommon Erythema multiforme	1 (0.1)	0 (0.0)	0 (0.0)

~~* Adverse drug reaction identified post-marketing.~~ *[All asterisks applied on adverse events of the table should be removed accordingly]*

Package leaflet

4. Possible side effects

Under frequency 'rare' for Abemaciclib and for Ribociclib

Under frequency 'uncommon' for Palbociclib

A skin reaction that causes red spots or patches on the skin that may look like a target or "bullseye" with a dark red centre surrounded by paler red rings (erythema multiforme).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Acetazolamide	Pulmonary oedemas (20050)	Ulla Wändel Liminga (SE)	Supplementary information requested (submission by 8 May 2024)	Amdipharm Limited
Bumetanide	Toxic epidermal necrolysis (20033)	Mari Thörn (SE)	Supplementary information requested (submission by 8 May 2024)	Karo Pharma AB
Dupilumab	Thrombocytopenia (20054)	Kimmo Jaakkola (FI)	Supplementary information requested (submission by 8 May 2024)	Sanofi Winthrop Industrie
Entrectinib	Myocarditis (20059)	Bianca Mulder (NL)	Assess in the next PSUR (submission by 26 August 2024)	Roche Registration GmbH

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Epcoritamab	Progressive multifocal leukoencephalopathy (PML) (20056)	Monica Martinez Redondo (ES)	Assess in the next PSUR (submission by 30 May 2024)	AbbVie Deutschland GmbH & Co. KG
Glofitamab	Immune effector cell-associated neurotoxicity syndrome (20058)	Jana Lukacisinova (CZ)	Supplementary information requested (submission by 8 May 2024)	Roche Registration GmbH
Glucagon-like peptide-1 (GLP-1) receptor agonists: dulaglutide; exenatide; insulin degludec, liraglutide; liraglutide; insulin glargine, lixisenatide; lixisenatide; semaglutide; tirzepatide	Aspiration and pneumonia aspiration (19974)	Mari Thörn (SE)	Supplementary information requested (submission by 8 May 2024)	Eli Lilly Nederland B.V., Novo Nordisk A/S, Sanofi Winthrop Industrie, AstraZeneca AB
Human papillomavirus 9-valent vaccine (recombinant, adsorbed); human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Granuloma (20046)	Jean-Michel Dogné (BE)	Supplementary information requested (submission by 8 May 2024)	Merck Sharp & Dohme B.V.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Elasomeran (COVID-19 mRNA vaccine) - Spikevax	Postmenopausal haemorrhage (20015)	Marie Louise Schougaard Christiansen (DK)	Routine pharmacovigilance	Moderna Biotech Spain, S.L.
Tozinameran (COVID-19 mRNA vaccine) - Comirnaty	Postmenopausal haemorrhage (19989)	Liana Martirosyan (NL)	Routine pharmacovigilance	BioNTech Manufacturing GmbH