



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 June 2023¹
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 10-12 May 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 10-12 May 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 (22-25 May 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.



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 information³

1.1. Lenvatinib – Adrenal insufficiency

Authorisation procedure	Centralised
EPITT No	19870
PRAC Rapporteur	Ulla Wändel Liminga (SE)
Date of adoption	12 May 2023

Recommendation

Having considered all available evidence, including non-clinical data (sinusoidal dilatation and cortical necrosis in the adrenal glands of rats and dogs at clinically relevant exposures), data from literature (including a case of positive de- and re-challenge) and a possible mechanism (inhibition of VEGF), PRAC has agreed that a causal association between lenvatinib and adrenal insufficiency is considered an at least reasonable possibility. The Marketing Authorisation Holder (MAH) for Lenvima and Kisplyx (Eisai GmbH) 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 for Lenvima

4.8. Undesirable effects

Endocrine disorders

Lenvatinib monotherapy: frequency “uncommon”: adrenal insufficiency

Combination with pembrolizumab: frequency “common”: adrenal insufficiency

Summary of product characteristics for Kisplyx

4.8. Undesirable effects

Endocrine disorders

Monotherapy/combination with everolimus: frequency “uncommon”: adrenal insufficiency

Combination with pembrolizumab: frequency “common”: adrenal insufficiency

Package leaflet for Lenvima

4. Possible side effects

The following side effects may happen with this medicine when given alone:

Uncommon (may affect up to 1 in 100 people)

- decreased secretion of hormones produced by the adrenal glands

The following side effects may happen with this medicine when given in combination with pembrolizumab:

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

Common (may affect up to 1 in 10 people)

- decreased secretion of hormones produced by the adrenal glands

Package leaflet for Kisplyx

4 - Possible side effects

Common (may affect up to 1 in 10 people)

- decreased secretion of hormones produced by the adrenal glands

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Azacitidine	Cutaneous vasculitis (19929)	Menno van der Elst (NL)	Supplementary information requested (submission by 26 July 2023)	Bristol-Myers Squibb Pharma EEIG
Baricitinib	Interstitial lung disease (19913)	Adam Przybylkowski (PL)	Supplementary information requested (submission by 26 July 2023)	Eli Lilly Nederland B.V.
Efgartigimod alfa	Anaphylactic reaction (19926)	Rhea Fitzgerald (IE)	Assess in the ongoing PSUR (submission by 7 June 2023)	Argenx
Latanoprost	Choroidal detachment and choroidal effusion (19936)	Jean-Michel Dogné (BE)	Assess in the next PSUR (submission by 29 July 2023)	Viatrix
Mepolizumab	Arthralgia (19919)	Gabriele Maurer (DE)	Assess in the next PSUR (submission by 2 December 2023)	GlaxoSmithKline Trading Services
Pirfenidone	Drug reaction with eosinophilia and systemic symptoms (DRESS) (19920)	Rhea Fitzgerald (IE)	Supplementary information requested (submission by 26 July 2023)	Roche Registration GmbH
Rituximab	Oral lichenoid reaction (19916)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 26 July 2023)	Roche Registration GmbH, Pfizer Europe MA EEIG, Sandoz GmbH, Celltrion Healthcare Hungary Kft.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Elasomeran (COVID-19 mRNA vaccine) - Spikevax	Myositis (19884)	Marie Louise Schougaard Christiansen (DK)	<ul style="list-style-type: none"> · Monitor idiopathic inflammatory myopathies (IIM)/ myositis in PSURs · Follow up on IIM/myositis in the final study report of EU PASS study mRNA-1273-P904 to be submitted in December 2023 	Moderna Biotech Spain, S.L.
Progesterone	Meningioma (19871)	Ulla Wändel Liminga (SE)	Monitor in PSURs (next PSUR to be submitted in the last quarter of 2025)	MAHs of progesterone containing medicinal products (Besins Healthcare S.A., Laboratoires Besins International, Besins Healthcare Germany GmbH, Merck A/S)
Tozinameran (COVID-19 mRNA vaccine) - Comirnaty	Myositis (19883)	Menno van der Elst (NL)	<ul style="list-style-type: none"> · Monitor idiopathic inflammatory myopathies (IIM)/ myositis in PSURs · Follow up on IIM/myositis in any of the ongoing PASS listed in the pharmacovigilance plan 	BioNTech Manufacturing GmbH