10 February 2025[1]
EMA/PRAC/6377/2025
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 13-16 January 2025 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 13-16 January 2025 (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 (27-30 January 2025) 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. Afatinib – Growth of eyelashes

Authorisation procedure	Centralised
EPITT No	19987
PRAC Rapporteur	Mari Thörn (SE)
Date of adoption	13 January 2025

Recommendation

Having considered the available evidence in EudraVigilance, the literature and the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of Giotrif, Boehringer Ingelheim International 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

4.8 Undesirable effects

The following adverse reactions should be added under the SOC Eye disorders with the frequency "uncommon":

Aberrant eyelash growth

Package leaflet

4. Possible side effects

Uncommon side effects (may affect up to 1 in 100 people):

- Abnormal growth of your eyelash (including misdirected growth that may lead to damage to the eye surface)

1.2. Lenvatinib – Tumour lysis syndrome

Authorisation procedure	Centralised
EPITT No	20108
PRAC Rapporteur	Mari Thörn (SE)
Date of adoption	13 January 2025

Recommendation

Having considered the available evidence in EudraVigilance and the literature, including the cumulative review submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of Lenvima and Kisplyx (Eisai GMBH) should submit a variation within 2 months from the publication of

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

the PRAC recommendation to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4 Special warnings and precautions for use

For Lenvima and Kisplyx:

Tumour lysis syndrome (TLS)

Lenvatinib can cause TLS which can be fatal. Risk factors for TLS include but are not limited to high tumour burden, pre-existing renal impairment and dehydration. These patients should be monitored closely and treated as clinically indicated, and prophylactic hydration should be considered.

4.8 Undesirable effects

For Lenvima:

Table 6 Adverse reactions reported in patients treated with lenvatinib§		
System Organ Class (MedDRA terminology)	**Lenvatinib monotherapy**	**Combination with pembrolizumab**
Metabolism and nutrition disorders		
Rare	Tumour lysis syndrome†	Tumour lysis syndrome†

†: Includes cases with a fatal outcome.

For Kisplyx:

Table 4 Adverse reactions reported in patients treated with lenvatinib§			
System Organ Class (MedDRA terminology)	**Lenvatinib monotherapy**	**Combination with everolimus**	**Combination with pembrolizumab**
Metabolism and nutrition disorders			
Rare	Tumour lysis syndrome†	Tumour lysis syndrome†	Tumour lysis syndrome†

†: Includes cases with a fatal outcome.

Package leaflet

For Lenvima and Kisplyx:

2. What you need to know before you take <x>

Conditions you need to look out for

During treatment of your cancer, the breakdown of tumour cells may leak substances into the blood which may lead to a group of complications called tumour lysis syndrome (TLS). This may lead to changes in your kidneys and can be life-threatening. Your doctor will observe and may give you a treatment to reduce the risk. Tell your doctor immediately if you experience signs of TLS (see section 4: Possible side effects).

4. Possible side effects

Tell your doctor straight away if you notice any of the following side effects - you may need urgent medical treatment:

- nausea, shortness of breath, irregular heartbeat, muscular cramps, seizure, clouding of urine and tiredness. These symptoms may be complications due to the breakdown products of dying cancer cells and known as tumour lysis syndrome (TLS).

TLS should be added to the sections, where relevant, of "when given alone", "when given in combination with everolimus" and "when given in combination with pembrolizumab".

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

- Tumour lysis syndrome (TLS)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Axicabtagene ciloleucel; brexucabtagene autoleucel; ciltabtagene autoleucel; idecabtagene vicleucel; lisocabtagene maraleucel; tisagenlecleucel	Immune-mediated enterocolitis (20133)	Jo Robays (BE)	Supplementary information requested (submission by 5 March 2025)	Bristol-Myers Squibb Pharma EEIG, Janssen-Cilag International NV, Novartis Europharm Limited, Kite Pharma EU B.V.
Clozapine	Appendicitis (20139)	Amelia Cupelli (IT)	Assess in the next PSUR (submission by 1 June 2025)	MAHs of clozapine containing products with the obligation to submit PSURs
Clozapine	New aspect of the known risk of neutropenia/agranulocytosis with potential impact on the risk minimisation measures (20141)	Amelia Cupelli (IT)	Supplementary information requested (submission by 11 April 2025)	Viatris Healthcare Limited, Mylan Product Ltd.

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Enzalutamide; digoxin	Laboratory test interference leading to falsely elevated digoxin plasma levels with enzalutamide (20134)	Maria del Pilar Rayon (ES)	Supplementary information requested (submission by 5 March 2025)	Astellas Pharma Europe B.V (enzalutamide); Aspen Pharma Trading Limited (digoxin)
Omalizumab	Hearing losses (20128)	Mari Thörn (SE)	Supplementary information requested (submission by 5 March 2025)	Novartis Europharm Limited
Sertraline	Multiple acyl-coenzyme A dehydrogenase deficiency (20125)	Liana Martirosyan (NL)	Supplementary information requested (submission by 5 March 2025)	Viatris
Sulfamethoxazole, trimethoprim (cotrimoxazole)	Circulatory shock (20135)	Barbara Kovačić Bytyqi (HR)	Supplementary information requested (submission by 5 March 2025)	Eumedica Pharmaceuticals GmbH

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Atezolizumab; avelumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; nivolumab, relatlimab; pembrolizumab; retifanlimab; tislelizumab; tremelimumab	Thrombotic microangiopathy (20090)	Bianca Mulder (NL)	Monitor in PSURs	AstraZeneca AB, Beigene Ireland Limited, Bristol-Myers Squibb Pharma EEIG, GlaxoSmithKline (Ireland) Limited, Incyte Biosciences Distribution B.V., Merck Europe B.V., Merck Sharp & Dohme B.V., Regeneron Ireland Designated Activity, Roche Registration GmbH