7 April 2025[1]
EMA/PRAC/78750/2025
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 10-13 March 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 10-13 March 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 (24-27 March 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. Tegafur, gimeracil, oteracil – Hyperammonaemia

Authorisation procedure	Centralised
EPITT No	20115
PRAC Rapporteur	Bianca Mulder (NL)
Date of adoption	13 March 2025

Recommendation

Having considered the available evidence in EudraVigilance and the literature, the cumulative review submitted by the Marketing Authorisation Holder (MAH) and also biologically plausible mechanism, the PRAC has agreed that a causal association between Teysuno and hyperammonaemia is at least a reasonable possibility. As hyperammonaemia can worsen to hyperammonaemic encephalopathy, which is a serious condition that requires timely recognition and treatment, it is considered that SmPC sections 4.4 and 4.8 as well as the corresponding section in the package leaflet should be updated. Based on the one identified clinical trial case (1/1,800), the frequency 'rare' is proposed.

Therefore the MAH of Teysuno (Nordic Group B.V.) 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

4.4 Special warnings and precautions for use

Hyperammonaemia

Hyperammonaemia has been observed with Teysuno. In patients who develop unexplained neurologic symptoms (like ataxia, lethargy or changes in mental status), ammonia levels should be measured and appropriate clinical management should be initiated. If hyperammonaemia neurologic symptoms worsen to hyperammonaemic encephalopathy, discontinuation of Teysuno should be considered.

4.8 Undesirable effects

SOC Metabolism and nutrition disorders with a frequency 'rare/very rare'

Hyperammonaemia

Package leaflet

2. Warnings and precautions

If you develop lack of energy, confusion, sleepiness, seizures or impaired consciousness, please contact your doctor immediately.

4. Possible side effects

Rare side effects (may affect 1 to 10 in 10,000 people) and very rare side effects (may affect less than 1 in 10,000 people) include:

High blood ammonia levels.

[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
Binimetinib; cobimetinib; dabrafenib; encorafenib; trametinib; vemurafenib	Tattoo associated skin reaction (20160)	Mari Thörn (SE)	Supplementary information requested (submission by 28 May 2025)	Novartis Europharm Limited, Pierre Fabre Medicament, Roche Registration GmbH
Leflunomide	Pulmonary nodule (20155)	Liana Martirosyan (NL)	Supplementary information requested (submission by 7 May 2025)	Sanofi-Aventis Deutschland GmbH

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Canagliflozin; canagliflozin, metformin; dapagliflozin; dapagliflozin, metformin; empagliflozin; empagliflozin, linagliptin; empagliflozin, metformin; ertugliflozin; ertugliflozin, metformin; ertugliflozin, sitagliptin; saxagliptin, dapagliflozin	Sarcopenia (20111)	Mari Thörn (SE)	Routine pharmacovigilance	MAHs of cana-, dapa-, empa-, and ertugliflozin-containing products
Ixekizumab	Demyelinating disorders (20124)	Gabriele Maurer (DE)	Routine pharmacovigilance	Eli Lilly and Co (Ireland) Limited