5 May 2025[1]
EMA/PRAC/111860/2025
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 7-10 April 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 7-10 April 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 (22-25 April 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.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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. Oxytetracycline hydrochloride, hydrocortisone acetate, polymyxin B sulfate (ear/eye drops/suspension/ointment) – Hearing and vestibular disorders

Authorisation procedure	Non-centralised
EPITT No	20120
PRAC Rapporteur	Jo Robays (BE)
Date of adoption	10 April 2025

Recommendation

Having considered the available evidence in EudraVigilance and the literature, including the cumulative review submitted by the Marketing Authorisation Holder (Pfizer), the PRAC has agreed that the MAHs of oxytetracycline hydrochloride/ hydrocortisone acetate/ polymyxin B sulfate ear or ear/eye drops/ointment indicated for auricular use (BAUSCH + LOMB IRELAND LIMITED, FARMASIERRA LABORATORIOS S.L., PFIZER) should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below.

The below text needs to be adapted to existing information for individual nationally authorised products by MAHs considering that the text below is the minimal information to be reflected without affecting existing contraindications or stronger recommendations regarding use in case of eardrum perforation. New text to be added is displayed underlined:

Ear drops, ear/eye drops

Summary of product characteristics

4.2 Posology and method of administration

Auricular use:
The ear canal should be kept clear of exudate, cerumen, or debris during treatment.

4.4 Special warnings and precautions for use

Ear and labyrinth disorders

Not recommended in cases of eardrum perforation. *(Note: this warning should be newly added only for those products with no current contraindication in section 4.3)*

In case of a perforated eardrum, there is a risk of ototoxicity with cochlear or vestibular injury. *Note: for those products with current contraindication in section 4.3 a cross-reference should be added:* (see section 4.3).

Cases of blockage of the external auditory canal due to accumulation of [product name] ear drops, resulting in hearing disorders or dizziness, have been reported. These issues generally resolved by flushing the ear canal or removing the drug residues.

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

4.8 Undesirable effects

The following should be added under the SOC Ear and labyrinth disorders with frequency not known and with footnote:*

Hypoacusis*

Deafness*

Tinnitus*

The following should be added under the SOC Nervous system disorders with frequency not known and with footnote:*

Dizziness*

*blockage of the external auditory canal due to accumulation of [product name] ear drops, resulting in hearing disorders (hypoacusis, deafness, tinnitus) or dizziness (see section 4.4)

Package leaflet

2. What you need to know before you use [product name]

Warnings and precautions

Before you use this medicine, tell your doctor if you have now or have had in the past

- Perforated eardrum *(Note: this warning should be newly added only for those products with no current contraindication in section 2)*

Seek medical care if you experience hearing or balance disorders.

4. Possible side effects

The following should be added under the frequency *not known*:

- Hearing disorders (hearing loss, deafness, ringing or buzzing in the ears) or dizziness due to ear canal blockage (see section 2 Warnings and precautions).

Ear ointment

Summary of product characteristics

4.4 Special warnings and precautions for use

Ear and labyrinth disorders

Not recommended in cases of eardrum perforation. *(Note: this warning should be newly added only for those products with no current contraindication in section 4.3)*

In case of a perforated eardrum, there is a risk of ototoxicity with cochlear or vestibular injury. *Note: for those products with current contraindication in section 4.3 a cross-reference should be added:* (see section 4.3).

Package leaflet

2. What you need to know before you use [product name]

Warnings and precautions

Before you use this medicine, tell your doctor if you have now or have had in the past

- Perforated eardrum *(Note: this warning should be newly added only for those products with no current contraindication in section 2)*

1.2. Regorafenib – Hyperammonaemia, hyperammonaemic encephalopathy

Authorisation procedure	Centralised
EPITT No	20147
PRAC Rapporteur	Bianca Mulder (NL)
Date of adoption	10 April 2025

Recommendation

Having considered the available evidence in EudraVigilance, the literature and the comments submitted by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH of STIVARGA, (Bayer AG) 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

Hyperammonaemic encephalopathy

Hyperammonaemic encephalopathy has been observed with regorafenib, including fatal cases (see section 4.8). In patients who develop unexplained lethargy or changes in mental status, ammonia levels should be measured and appropriate clinical management should be initiated. If hyperammonaemic encephalopathy is confirmed, permanent discontinuation of regorafenib should be considered.

4.8 Undesirable effects

Table 3: Adverse drug reactions (ADRs) reported in clinical trials and post-marketing in patients treated with Stivarga

SOC Nervous system disorders

Hyperammonaemic encephalopathy, frequency not known

Package leaflet

2. What you need to know before you take Stivarga

Take special care with Stivarga (…)

- if you develop a severe and persistent headache, visual disturbances, seizures, lack of energy, sleepiness, impaired consciousness or altered mental status (such as confusion, memory loss or loss of orientation) please contact your doctor immediately.

4. Possible side effects

Frequency not known

- lack of energy, confusion, sleepiness, trembling, impaired consciousness – these symptoms may be signs of brain toxicity caused by high blood levels of ammonia (*hyperammonaemic encephalopathy*).

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Brodalumab	Pyoderma gangrenosum (20162)	Monica Martinez Redondo (ES)	Supplementary information requested (submission by 2 May 2025)	LEO Pharma A/S
Diazoxide	Necrotising enterocolitis neonatal (20163)	Amelia Cupelli (IT)	Supplementary information requested (submission by 27 June 2025)	RPH Pharmaceuticals AB, Merck Sharp & Dohme B.V.)
Ibrutinib	Cough (20161)	Barbara Kovačić Bytyqi (HR)	Assess in the next PSUR (submission by 10 February 2026)	Janssen-Cilag International N.V.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Avelumab; atezolizumab; cemiplimab; dostarlimab; durvalumab; ipilimumab; nivolumab; pembrolizumab; retifanlimab; tislelizumab; toripalimab; tremelimumab	Scleroderma, systemic scleroderma, morphea (20119)	David Olsen (NO)	Monitor in PSUR	Bristol-Myers Squibb Pharma EEIG, Merck Sharp & Dohme B.V., AstraZeneca AB, Merck Europe B.V., Roche Registration GmbH, Regeneron Ireland Designated Activity Company (DAC), GlaxoSmithKline (Ireland) Limited, Beigene Ireland Limited, Incyte Biosciences Distribution B.V., TMC Pharma (EU) Ltd
Emtricitabine, tenofovir disoproxil	Trigeminal neuralgia (20121)	Ana Sofia Diniz Martins (PT)	Monitor in PSUR	Gilead Sciences Ireland UC
Regorafenib	Nephrotic syndrome (20123)	Bianca Mulder (NL)	Include nephrotic syndrome as an important potential risk in PSURs	Bayer AG