5 May 2025[1]
EMA/PRAC/111861/2025
Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 7-10 April 2025 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found on the webpage for PRAC recommendations on safety signals (in English only).

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

1. Oxytetracycline hydrochloride, hydrocortisone acetate, polymyxin B sulfate (ear/eye drops/suspension/ointment) – Hearing and vestibular disorders (EPITT no 20120)

The below text needs to be adapted to existing information for individual nationally authorised products by marketing authorisation holders 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.

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

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.

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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.

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)*

2. Regorafenib – Hyperammonaemia, hyperammonaemic encephalopathy (EPITT no 20147)

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

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*).