Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for macrogol 3350 combinations (oral use), the scientific conclusions are as follows:

In view of available data on seizure from serious spontaneous reports, in some cases a close temporal relationship, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between macrogol 3350 combinations and seizure is ascertained.

The PRAC concluded that the product information of products containing macrogol 3350 combinations indicated in bowel preparation should be amended accordingly, also to include recommendations for Healthcare Professionals to manage such serious risk.

In addition, in view of available data on oesophageal rupture from serious spontaneous reports and literature a close temporal relationship, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between macrogol 3350 combinations and oesophageal perforation (Boerhaave syndrome) is ascertained.

The PRAC concluded that the product information of products containing macrogol 3350 combinations indicated in bowel preparation should be amended accordingly, also to include recommendations for Healthcare Professionals to create awareness of patients to such serious risk ad on the prompt actions to undertake.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for macrogol 3350 combinations (oral use) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing macrogol 3350 combinations (oral use) is unchanged subject to the proposed changes to the product information

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- **SEIZURE**

- **Section 4.4**

A warning should be added as follows:

Cases of seizures associated with use of macrogol 3350 with electrolytes for bowel preparation were observed in patients either with or without prior history of seizures. These cases were mostly associated with electrolyte abnormalities such as severe hyponatraemia (see section 4.8). Use caution when prescribing macrogol 3350 with electrolytes in patients with a history of seizures, at increased risk of seizure or at risk of electrolyte disturbance. In case of neurologic symptoms, fluid and electrolyte abnormalities should be corrected.

- **Section 4.8**

The following adverse reaction should be added under the SOC Nervous system disorders with a frequency not known:

Seizure

- **OESOPHAGEAL RUPTURE**

Section 4.4

Cases of oesophageal rupture (Boerhaave syndrome) associated with excessive vomiting after intake (see section 4.8) of macrogol 3350 with electrolytes for bowel preparation has been reported post-marketing, mostly in elderly patients. Advice patients to stop administration and seek immediate medical assistance if they experience incoercible vomiting and subsequent chest, neck, and abdominal pain, dysphagia, hematemesis or dyspnoea.

- **Section 4.8 Undesirable effects**

The following adverse reaction under SOC "Gastrointestinal Disorders", should be added

Oesophageal rupture (Borheaave syndrome), at frequency not known.

Package Leaflet

- **SEIZURE**

Section 2 What you need to know before you take <product name>

Warning and precautions

Talk to your doctor or pharmacist before taking <product name> if you:

- have epilepsy or a history of convulsions

- have heart failure, severe kidney problems or are taking blood pressure medicine

Section 4 Possible side effects

Stop taking <product name> and immediately contact a doctor if you notice any of the following side effects:

Seizure

- OESOPHAGEAL RUPTURE

Section 2 What you need to know before you take <product name>

Warning and precautions

[…]

If you experience (blood) vomiting followed by sudden chest, neck or abdominal pain, difficulty swallowing or difficulty breathing when taking <product name>, stop taking medicine and promptly contact your doctor.

Section 4 Possible side effects

[…]

Oesophageal rupture due to vomiting frequency not known

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	4 November 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 January 2025