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 chlorphenamine maleate / paracetamol, the scientific conclusions are as follows:

In view of available data on risk of methaemoglobinaemia in case of administration in patients with G6PD deficiency, from the literature and spontaneous cases, and in view of a plausible mechanism of action, a causal relationship between chlorphenamine / paracetamol and methaemoglobinaemia and haemolytic anaemia is considered at least a reasonable possibility.

In view of available data on disseminated intravascular coagulation following overdose of paracetamol, from the literature, including in one case a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, a causal relationship with chlorphenamine / paracetamol is considered at least a reasonable possibility.

The PRAC concluded that the product information of products containing chlorphenamine/paracetamol should be amended accordingly.

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 chlorphenamine maleate / paracetamol the CMDh is of the opinion that the benefit-risk balance of the medicinal products containing chlorphenamine maleate / paracetamol is unchanged subject to the proposed changes to the product information

The CMDh recommends that the terms of the marketing authorisations should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal products

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

- Section 4.4: (only for Zerinol [Zentiva])

A warning should be added as follows:

Paracetamol should be administered with caution in the following situations:

- Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency (may lead to methaemoglobinaemia and haemolytic anaemia)

- Section 4.9 (all products)

The signs or symptoms of overdose should be amended as follows:

- Due to paracetamol:

With overdose, there is a risk of severe liver toxicity, particularly in the elderly, young children, hepatic or renal insufficiency, chronic alcohol consumption, chronic malnutrition, when using enzyme inducing agents and in very lean adults (<50 kg).

Liver toxicity often does not occur until 24 to 48 hours after ingestion. Overdose can be fatal. In case of overdose, a doctor should be consulted immediately, even if there are no symptoms.

Symptoms: Nausea, vomiting, anorexia, pallor, abdominal pain usually occurs within the first 24 hours.

A strong overdose causes severe liver toxicity, with hepatic cytolysis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy, which can lead to coma and death. At the same time, elevated levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin have been observed. **Overdose may also result in disseminated intravascular coagulation.**

Package Leaflet

2. What you need to know before you <take> <use> X

Warnings and Precautions

Talk to your doctor or pharmacist before taking XXX

- in case of Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency (may lead to haemolytic anaemia)

3. How to take X

If you take more X than you should:

- due to paracetamol:

[...]

Overdose can also lead to: coagulation disorders (blood clotting and bleedings).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	20 December 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	27 February 2025