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 paracetamol (IV formulation), the scientific conclusions are as follows:

After reviewing all available data, the PRAC confirmed the risk of high anion gap metabolic acidosis when paracetamol is used concomitantly with flucloxacillin, and recommended in October 2017 (PRAC recommendations on signals adopted at the 25-29 September 2017 PRAC meeting) to update sections 4.4, 4.5 and 4.8 for the PIs of flucloxacillin containing products to mention this risk and a caution in case of concomitantly administration of flucloxacillin and paracetamol.

Given the recommendation from the signal assessed for flucloxacillin and the reported cases, the PRAC recommends to update the PI of paracetamol containing products in order to increase the awareness of the HCPs to this drug-drug interaction which can be severe and fatal.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for paracetamol (IV formulation) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing paracetamol (IV formulation) is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing paracetamol (IV formulation) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

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

Section 4.4

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Section 4.5

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4)

Package Leaflet

2. What you need to know before taking <product name>

[…]

Other medicines and paracetamol

Please inform your doctor or pharmacist if you are taking:

-flucloxacillin (antibiotic), due to a serious risk of blood and fluid abnormality (high anion gap metabolic acidosis) that must have urgent treatment and which may occur particularly in case of severe renal impairment, sepsis (when bacteria and their toxins circulate in the blood leading to organ damage), malnutrition, chronic alcoholism, and if the maximum daily doses of paracetamol are used.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 March 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	12 May 2022