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 hydrochlorothiazide / spironolactone, the scientific conclusions are as follows:

In view of available data on acute respiratory toxicity including acute respiratory distress syndrome from the literature, spontaneous reports with some cases a close temporal relationship, a positive re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between hydrochlorothiazide / spironolactone and acute respiratory distress syndrome established and that warning to inform healthcare professionals on acute respiratory toxicity is necessary. The PRAC concluded that the product information of products containing hydrochlorothiazide / spironolactone should be amended accordingly.

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 hydrochlorothiazide / spironolactone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing hydrochlorothiazide / spironolactone 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 hydrochlorothiazide / spironolactone 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

Hydrochlorothiazide

A warning should be added as follows:

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, X should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Section 4.8

The following adverse reactions should be added under the SOC Respiratory, thoracic and mediastinal disorders with a frequency very rare:

Acute respiratory distress syndrome (ARDS) (see section 4.4)

Package Leaflet

Section 2

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

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> before <taking> <using> X

……

If you experienced breathing or lung problems (including inflammation or fluid in the lungs) following hydrochlorothiazide intake in the past. If you develop any severe shortness of breath or difficulty breathing after taking X, seek medical attention immediately.

4. Possible side effects

Very rare:

Acute respiratory distress (signs include severe shortness of breath, fever, weakness, and confusion).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	1 November 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 December 2021