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 bendroflumethiazide, bendroflumethiazide / potassium chloride, the scientific conclusions are as follows:

By the decrease in tubular calcium excretion, bendroflumethiazide can cause slight increase in calcium serum levels. Hypercalcaemia is a known class effect of thiazide diuretics and a signal of hypercalcaemia was also identified and evaluated for bendroflumethiazide during the reporting period. Based on the review of the mechanism of action, the 4 relevant cases identified in the safety database, and literature review, the signal was confirmed. Therefore the adverse reaction hypercalceamia should be added to the product information of bendroflumethiazide, bendroflumethiazide/ potassium chloride containing products which do not already list it.

In addition, hypercalcaemia is usually mild as normally regulated by decreased intestinal reabsorption due to the decrease in plasma parathyroid hormone production. Based on the reviewed literature data submitted by some Marketing authorisation holders, significant increase in calcium levels can be the sign of underlying hyperparathyroidism. Due to possible interference, PRAC recommends addition of a warning to the product information of all of bendroflumethiazide, bendroflumethiazide/ potassium chloride containing products to inform health care professionals that thiazide diuretics should be discontinued before carrying out parathyroid function tests.

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 bendroflumethiazide, bendroflumethiazide potassium chloride the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing bendroflumethiazide, bendroflumethiazide/ potassium chloride 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 bendroflumethiazide, bendroflumethiazide / potassium chloride are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that 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

All MAHs

- Section 4.4

A warning should be added as follows:

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

MAHs that do not list Hypercalcaemia as adverse drug reaction

- Section 4.8

The following adverse reaction(s) should be added under the SOC Metabolism and nutrition disorders with a frequency 'Not known':

Hypercalcaemia

Package Leaflet

- Section 4

High level of calcium in the blood, with the frequency 'Not known'

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	3 November 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 January 2019