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 hydrocortisone (except for products indicated in adrenal insufficiency in a modified release tablet formulation) the scientific conclusions are as follows:

Hyperthropic cardiomyopathy

In view of available data on hypertrophic cardiomyopathy from clinical trial(s) (Rohr et al (2014)), the literature (Alpert et al.(1984), Sarikabadayi et al. (2013), Scire et al. (2007), Vimala et al. (2011)) and spontaneous reports including cases with a close temporal relationship, and positive de-challenge and re-challenge, the PRAC Lead Member State considers a causal relationship between hydrocortisone (except for products indicated in adrenal insufficiency in a modified release tablet formulation) and hypertrophic cardiomyopathy is at least a reasonable possibility. The PRAC Lead Member State concluded that the product information of products containing hydrocortisone for systemic use (except for products indicated in adrenal insufficiency in a modified release tablet formulation) should be amended accordingly.

Update of section 4.4. (Special warnings and precautions for use) and 4.8. (Undesirable effects) of the SmPC to add the adverse reaction hypertrophic cardiomyopathy with a frequency not known and a warning on hypertrophic cardiomyopathy. The Package leaflet should be updated accordingly.

Weight increased

Based on available data on weight gain from literature (Rice et al. (2017), Roberts et al. (2014). and Kivimäki et al. (2006)) and spontaneous reports including cases with a close temporal relationship, and positive de-challenge, the PRAC Lead Member State considers there is sufficient evidence for establishing a causal relationship between hydrocortisone (except for products indicated in adrenal insufficiency in a modified release tablet formulation) and weight increased. The PRAC Lead Member State concluded that the product information of products containing hydrocortisone for systemic use (except for products indicated in adrenal insufficiency in a modified release tablet formulation) should be amended accordingly.

Update of section 4.8. (Undesirable effects) of the SmPC to add the adverse reaction weight increased with a frequency not known. The Package leaflet should be updated 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 hydrocortisone (except for products indicated in adrenal insufficiency in a modified release tablet formulation) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing hydrocortisone (except for products indicated in adrenal insufficiency in a modified release tablet 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 hydrocortisone (except for products indicated in adrenal insufficiency in a modified release tablet formulation) as EURD list entry} 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~~)

Hydrocortisone formulations for systemic use

a) Hypertrophic cardiomyopathy

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Hypertrophic cardiomyopathy was reported after administration of hydrocortisone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Cardiac disorders with a frequency not known: **hypertrophic cardiomyopathy in prematurely born infants**

Package Leaflet

Section 2. What you need to know before you are given hydrocortisone

Warnings and precautions

If hydrocortisone is given to a prematurely born baby, monitoring of heart function and structure may be needed.

Section 4. Possible side effects

Frequency 'Not known': **Thickening of the heart muscle (hypertrophic cardiomyopathy) in prematurely born babies.**

b) Weight increased
Summary of Product Characteristics

- Section 4.8 Undesirable effects

The following adverse reaction(s) should be added under the SOC Investigations with a frequency 'Not known': **Weight increased**

Package Leaflet

Section 4. Possible side effects

Frequency 'Not known': **Weight increased**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	April 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	14/06/2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	13/08/2020