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 ethosuximide, the scientific conclusions are as follows:

In view of available data on **drug reaction with eosinophilia and systemic symptoms (DRESS)** from the literature and spontaneous reports including in 6 cases a close temporal relationship, a positive de-challenge and/or re-challenge, the RPAC considers that a causal relationship between ethosuximide and DRESS is established. The PRAC concluded that the product information of products containing ethosuximide should be amended accordingly.

In view of available data on **thrombocytopenia** from the literature and spontaneous reports including in 6 cases a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between ethosuximide and thrombocytopenia established. The PRAC concluded that the product information of products containing ethosuximide 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 ethosuximide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing ethosuximide 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 ethosuximide 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

[For SmPCs that do not already have information on the topic, the following warning should be added as follows:]

Severe skin reactions

Serious dermatologic reactions, including Stevens-Johnson Syndrome (SJS) **and drug reaction with eosinophilia and systemic symptoms (DRESS)**, have been reported with ethosuximide treatment. SJS **and DRESS** can be fatal. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Ethosuximide should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

- Section 4.8

Summary of safety profile

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) **and drug reaction with eosinophilia and systemic symptoms (DRESS)** have been reported in association with ethosuximide treatment (see section 4.4).

Tabulated list of adverse reactions

[MAHs which have already listed the below adverse reactions in the product information section 4.8 should maintain the calculated frequency.]

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders with a frequency 'not known':

Drug reaction with eosinophilia and systemic symptoms (DRESS)

The following adverse reaction should be added under the SOC Blood and lymphatic system disorders with a frequency 'not known':

Thrombocytopenia

Package Leaflet

- Section 2 - What you need to know before you use [product name]

Warnings and precautions

Serious skin reactions including Stevens-Johnson syndrome and **drug reaction with eosinophilia and systemic symptoms (DRESS)** have been reported in association with [product name]

treatment. **Stop using [product name] and seek medical attention immediately if you notice any of the symptoms described in section 4.**

- Section 4 – Possible side effects

Serious side effects

Stop using [product name] and seek medical attention immediately if you notice any of the following symptoms:

- Reddish patches on the trunk, the patches are target-like macules or circular, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome).
- **Widespread rash, high body temperature and enlarged lymph nodes (drug reaction with eosinophilia and systemic symptoms (DRESS)).**

[The adverse reaction should be added with a frequency 'not known'. MAHs with similar wording already included in the package leaflet should maintain the calculated frequency]

Seek medical attention if you notice any of the following symptoms:

Not known (frequency cannot be estimated from the available data):

Changes in your blood (**bruising or bleeding more easily,** fever, sore throat, mouth ulcers, fatigue, repeated infections or infections that will not go away). Your doctor may take regular blood samples to test for these effects.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 December 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 February 2021