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 primidone, the scientific conclusions are as follows:

In view of available data on drug reaction with eosinophilia and systemic symptoms (DRESS) from the literature, spontaneous reports and in view of the fact that DRESS is a known adverse reaction of phenobarbital to which primidone is extensively metabolized, the PRAC considers that a causal relationship between primidone and DRESS is at least a reasonable possibility. The PRAC concluded that the product information of products containing primidone 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 primidone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing primidone 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 primidone 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:

Severe skin reactions

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) **and drug reaction with eosinophilia and systemic symptoms (DRESS)** have been reported with the use of primidone.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS, TEN **or DRESS** is within the first weeks of treatment. If symptoms or signs of SJS, TEN **or DRESS** (e.g. progressive skin rash often with blisters or mucosal lesions) are present, primidone treatment should be discontinued.

The best results in managing SJS, TEN **and DRESS** come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS, TEN **or DRESS** with the use of primidone (or phenobarbital), primidone must not be re-started in this patient at any time. (see section 4.8)

- Section 4.8

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

Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

Package Leaflet

- Section 2:

Special warnings & precautions of use

Potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis **or DRESS syndrome**) have been reported with the use of primidone, appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk. Additional signs to look for include ulcers in the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes).

These potentially life-threatening skin rashes are often accompanied by flu-like symptoms. The rash may progress to widespread blistering or peeling of the skin. The highest risk for occurrence of serious skin reactions is within the first weeks of treatment. If you have developed Stevens-Johnson syndrome**,** ~~or~~ toxic epidermal necrolysis **or DRESS syndrome** with the use of primidone or any other medicine containing phenobarbital, you must not be restarted on these medicines at any time.

If you develop a rash or these skin symptoms, stop using primidone and seek immediate advice from a doctor and tell him that you are taking this medicine.*

*The last sentence is already highlighted in bold in the PhVWP wording recommendation and does not present a new addition. The addition is highlighted in red and underlined.

- Section 4:

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

Potentially life-threatening skin rashes (drug rash with eosinophilia and systemic symptoms) have been reported (see section 2).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	February 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 April 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 June 2021