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 valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium, the scientific conclusions are as follows:

Based on identified studies, spontaneous cases, cases retrieved from literature and the clinical trials, there have been reports of cases of patients with diplopia following valproate treatment. Therefore, the MAH proposed to amend the product information (PI) adding this adverse drug reaction (ADR) and PRAC endorses this proposal. PRAC considers that the ADR “diplopia” should be reflected in section 4.8 of the SmPC with frequency ‘rare’ based on the pooled data from the trial reported in the United States Product Information (USPI) and the 9 relevant trials.

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 valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium 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 valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium 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 **<u>underlined and in bold</u>**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.8 - Undesirable effects

The following adverse reaction should be added under the SOC 'nervous system disorders' with a frequency 'rare':

<u>Diplopia</u>

Package leaflet

- Section 4 - Possible side effects

The following adverse reaction should be added with a frequency 'rare':

<u>Double vision</u>

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:	03 November 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	02 January 2019