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:

In view of available data on eye malformations during in utero exposure from literature and spontaneous reports, PRAC considers a causal relationship between valproate and eye malformation is established. 23 cases of retinal fold/retinal rosette/retinal coloboma and coloboma in children exposed to valproate in utero were noted. All cases were serious. In the majority of cases valproate was used as monotherapy and daily valproate dose used by the mothers did not exceed the therapeutic dosage range. In 22/23 (95.7%) cases associated congenital malformations were reported, including 13 cases reporting fetal anticonvulsant syndrome. Narratives provided for the 23 cases indicate that 18 of the cases occurred in children with facial dysmorphism/dysmorphism. PRAC concludes that the product information (SmPC section 4.6 and PIL section 2) of products containing valproate should be amended accordingly.

In addition, in view of the available data, including 2 cases reporting on serum valproate levels and lack of seizure control when valproate was administered in patients on haemodialysis, PRAC considers the cumulative evidence sufficient to include a warning in SmPC section 4.2 that patients with end stage renal failure might experience lack of drug effect when they receive haemodialysis.

Furthermore, in line with information provided in SmPC section 5.3 of other AED, PRAC agrees to include a wording on testicular findings of valproate use in adult and juvenile laboratory animals.

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 **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.6

In utero exposure to valproate may also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.

In utero exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

PIL section 2:

The risks of valproate when taken during pregnancy (irrespective of the disease for which valproate is used):

- Talk to your doctor immediately if you are planning to have a baby or are pregnant.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. **The most frequently reported b**irth defects ~~which have been reported~~ include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects **and multiple associated malformations affecting several organs and parts of the body. Birth defects may result in disabilities which may be severe.**
- Hearing problems or deafness have been reported in children exposed to valproate during pregnancy.
- **Eye malformations have been reported in children exposed to valproate during pregnancy in association with other congenital malformations. These eye malformations may affect vision**.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. […].

Summary of Product Characteristics

- Section 4.2

In patients with renal insufficiency

It may be necessary in patients with renal insufficiency to decrease the dosage, or to increase the dosage in patients on haemodialysis. < active substance> is dialysable (see section 4.9). Dosing should be modified according to clinical monitoring of the patient (see section 4.4).

PIL section 3. How to <take> X

Patients with kidney problems

Your doctor may decide to adjust your dose.

Summary of Product Characteristics

- Section 5.3

In repeat-dose toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration at doses of 1250 mg/kg/day and 150 mg/kg/day, respectively.

In juvenile rats, a decrease in testes weight was only observed at doses exceeding the maximum tolerated dose (from 240 mg/kg/day by intraperitoneal or intravenous route) and with no associated histopathological changes. No effects on the male reproductive organs were noted at tolerated doses (up to 90 mg/kg/day). Based on these data, juvenile animals were not considered more susceptible to testicular findings than adults. Relevance of the testicular findings to paediatric population is unknown.

In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance. However, male infertility has been identified as an undesirable effect in humans (see sections 4.6 and 4.8).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	28 November 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	27 January 2022