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 for the non-interventional imposed PASS final report for the medicinal product(s) containing the active substance valproate and concerned by the PASS final report, the scientific conclusions are as follows:

Having considered the PRAC assessment report for the imposed PASS final report (surveys among health care professionals [HCPs] and patients) investigating the effectiveness of the risk minimisation measures (RMM) implemented after the Article 31 referral completed in 2018 for the medicinal product(s) containing valproate and related active substances, the PRAC scientific conclusions are as follows.

The overall success for effectiveness of both routine and additional (RMM), including PPP implementation, was assessed using three dimensions: awareness, knowledge and behaviour. Although the response rate of both HCPs and patients was very low, and predefined success rates for any of the selected three dimensions were not reached (neither for HCPs or patients), PRAC concluded that, still, successful and less successful areas could be identified from these results and that a variation in the level of awareness, knowledge and self-reported behaviour following implementation of the PPP and additional RMM was observed. Most importantly, the knowledge regarding the contraindication during pregnancy and in WCBP for different indications of valproate was not sufficient. Next, for some of the prescribing conditions, despite sufficient knowledge , PRAC noted a remarkable number of prescribers who reported that they would prescribe valproate not in line with the PPP, e.g. to female children and women of child bearing potential (WCBP) even if alternative treatment options are available, or to some WCBP who do not use effective contraception. Furthermore, the prescribers reported that they would not always conduct pregnancy testing was (i.e. before starting treatment and repeated, as needed, during treatment) and educational materials (EM) did not always reach the targeted audience or were not always used (i.e. ARAF),; the patient guide, described as very comprehensive but text heavy and difficult to read. Patients also reported to rather prefer reading the patient card.

The available interim results of the MAH's consortium drug utilisation study (DUS) and the final results of study EUPAS31001, showing that pregnancies continue to occur in WCBP who use medicinal products containing valproate and related active substances, despite implementation of the (new) risk minimisation measures (RMMs) agreed in the framework of the 2018 Article 31 referral, were also taken into account. In addition, PRAC considered the views and suggestions of representatives of HCPs organisations, learned societies and representatives of patient and carers who attended at the stakeholder's (virtual) meeting held in February 2023.

PRAC concluded that the patient and HCP guides agreed withing the 2018 referral should be revised, to further enhance knowledge on valproate risks, teratogenicity and neurodevelopmental disorders, and adherence to prescribing conditions and PPP.

Furthermore, specifically considering the knowledge deficiency among psychiatrists, as observed in the HCPs survey, and the confusion among general practitioners (GPs) regarding the contraindication for use during pregnancy, as observed in the literature, a boxed presentation of the contraindication should be added on top of SmPC section 4.6, using bullet points, to emphasize the different contraindication per indication.

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 the results of the study for the medicinal product(s) containing the active substance valproate and concerned by the PASS final report , the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) mentioned above is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of the products concerned by this PASS final report should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Summary of Product Characteristics (new text **underlined and in bold,** deleted text ~~strike through~~)

- Section 4.6

Pregnancy

Treatment of epilepsy

- **Valproate is contraindicated during pregnancy, unless there is no suitable alternative treatment**
- **Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4)**

Treatment of bipolar disorder

- **Valproate is contraindicated during pregnancy**
- **Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4)**

~~Valproate is contraindicated as treatment for bipolar disorder during pregnancy. Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4).~~

Annex III

Conditions to the Marketing Authorisation(s)

Changes to be made to the conditions of the marketing authorisation(s) of medicinal product(s) containing the active substance valproate concerned by the non-interventional imposed PASS final report

The marketing authorisation holder(s) shall change the following condition(s) (new text **underlined and in bold,** deleted text ~~strike through~~)

Additional risk minimisation measures

- As part of the pregnancy prevention programme (PPP) the following educational measures for valproate and related active substances containing products have been agreed withing the Article 31 referral procedure completed in 2018: HCP guide, patient guide, annual risk acknowledgement form (ARAF), patient card, visual reminder on the outer package. The following changes to the educational measures are recommended:

  Patient guide

  A revised "core version" of the patient guide is agreed by PRAC. The final version of the revised patient guide should be implemented in each EU Member State (MS) in agreement with the national competent authority (NCA).

  HCP guide

  A new "core version" of the HCP guide is agreed by PRAC. The final version of the revised HCP guide should be implemented in each EU MS in agreement with the NCA.

The following changes to the key elements of the HCP guide are recommended to correct inconsistencies with the SmPC approved in Article 31 referral completed in 2018 (new text **underlined and in bold,** deleted text ~~strike through~~):

Key elements to be addressed in the HCP guide

- The HCP guide should reflect all pregnancy prevention program (PPP) conditions as outlined in the summary of product characteristics (SmPC).
- The role of the different HCPs for implementation of the PPP and educational materials aimed at patients should be provided (as outlined below).
- Information on congenital malformations and developmental disorders including the magnitude of these risks for children exposed to valproate in utero.
- Valproate **should not be used** ~~initiated~~ in female children **unless other treatments are ineffective or not tolerated** ~~only if there is no suitable alternative treatment.~~
- Recommendations for prescribers when valproate is prescribed to female children, in particular the need to:
  - explain the risks of congenital malformations and neurodevelopmental disorders to the parent/caregivers (and children, depending on their age)
  - explain to the parents/caregivers of female girls the importance of contacting the specialist once a female child using valproate experiences menarche
  - reassess the need for valproate therapy at least annually and consider alternative treatment options in female children who experienced menarche

- make efforts to switch the female children to alternative treatment before they reach adulthood.

- Valproate may be initiated in girls and women of childbearing potential only if the conditions of valproate pregnancy prevention program (as outlined in the SmPC) are fulfilled.
- The need to clearly explain to the patient/caregivers the risks of valproate and required actions (in line with valproate PPP) to minimise these risks to all WCBP using valproate and to ensure that the information is well understood.
- The need to use and document the annual risk acknowledgement form, at initiation and during each annual review of valproate treatment by a specialist.
- The need to provide patient educational tools to each **girl and** WCBP using valproate.
- Guidance on the contraception methods (in line with the SmPC recommendations on contraception).
- Recommendations on switching or discontinuing valproate.
- Recommendations on pregnancy planning.
- Recommendations if valproate is the only suitable treatment for a patient who is (planning to become) pregnant.
- *{To be agreed at a national level:}*

  <A link to the dedicated website, indicating to patients where additional online information about valproate use in WCBP can be found.>

Key information to be included for the role of different HCPs in the HCP guide

a. Valproate should be initiated by specialist

b. The patient guide should be provided to the patients by the prescriber

c. The Annual risk acknowledgment form should be used by the specialist at initiation of valproate treatment and during annual treatment reviews

d. The patient card should be provided by the pharmacists

e. Optional for countries where valproate may be unpacked in pharmacies: Avoid unpacking valproate and in the situations where this cannot be avoided, always provide a copy of a package leaflet, patient card and the outer box if available.

The additional details regarding the role of the HCPs (including all relevant HCPs such as GPs, gynecologists, paediatricians, midwifes, pharmacists, etc.) in the implementation of the PPP and educational materials should be assessed on national level taking into account the differences in health care systems in individual Member States.

Annual risk acknowledgement form (ARAF)

The ARAF should be used and documented at initiation and during each annual review of treatment by a specialist. The core version agreed with the Article 31 referral concluded in 2018 remains valid.

Patient card

The patient card is attached to the outer carton to prompt as a reminder for the discussion between the pharmacist and the patient at the time of product dispensing. The core version agreed with the Article 31 referral concluded in 2018 remains valid.

- The MAH(s) should distribute revised versions of the HCP guide, the revised patient guide and the unrevised ARAF in each EU MS, in agreement with the NCA. It is also recommended to include a cover letter with these materials to highlight the reason for distribution of such revised materials.
- To promote access and awareness of valproate and related active substances additional RMM and PPP in each EU MS the MAH(s) should ensure easy access to digital/electronic versions of the EMs in the local language, with and without a QR code included in the packaging material and/or the package leaflet, i.e. via online search on trusted webpages used by patients looking for information on medicines.

Risk management plan

In addition, the MAH(s) should submit an updated risk management plan (RMP) after finalisation of this PASS procedure in order to address the following:

- A qualitative study should be included in the RMP as category 3, in order to investigate
    - barriers and reasons why certain measures part of the PPP are not always followed in clinical practice;
    - the preferred ways of HCPs and patients to receive information on the PPP.

This RMP update should be made accordingly in a separate procedure.

Annex IV

Timetable for the implementation of this position

Timetable for the implementation of the position

Adoption of CMDh position:	September 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	30 October 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	28 December 2023