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 (AR) for the non-interventional imposed post authorisation safety study (PASS) final report, a drug utilisation study extension (DUS ext.) to evaluate the impact of the risk minimisation measures (RMMs) and pregnancy prevention programme (PPP) in women of childbearing potential (WCBP) in Europe, using databases, for the medicinal product(s) containing the active substance valproate and concerned by the PASS final report, the scientific conclusions are as follows:

The findings of the DUS ext. complemented the results of the healthcare professionals (HCPs) and patient's survey (evaluated within procedure number EMEA-H-N-PSR-J-0036) showing that, despite knowledge of risks and prescribing conditions, physicians still reported prescribing valproate to female children and WCBP, even if alternative treatment options are available, or to WCBP who do not use effective contraception.

The PRAC considered that, from a regulatory perspective, the currently implemented additional RMMs (aRMMs) are up to date, complete and user tested, and tailored to all relevant HCP groups and patients. Therefore, no update of valproate aRMMs or risk minimisation strategy is justified at this moment.

Furthermore, PRAC conveyed that further regulatory effort is necessary, aside from the ongoing category 3 qualitative study, conducted to gain input on the potential reasons and barriers for effective uptake of valproate PPP in clinical practice. The results of this study, initially expected in Q3 2026, and now delayed until Q4 2027, are needed to re-evaluate the current aRMMs and valproate overall risk minimisation strategy.

A follow up of the DUS ext. is therefore needed, until Q3/Q4 2024 (at a minimum) or (ideally) 2025, depending on study's feasibility and the due date for submission of the final study results, to allow timely assessment before or in parallel to the category 3 qualitative study outputs. Trend analyses should also be provided to monitor changes over time since the pre-implementation period of the current DUS ext.

Considering the limitations regarding the measurement of compliance to PPP, PRAC agreed that the follow up of this DUS ext. (also a category 3 study) may focus primarily on utilisation patterns in WCBP and analysis of exposed pregnancies. In addition, PRAC requested the MAH(s) to propose a DUS ext. study that would continuously monitor the effectiveness of the PPP, with focus on utilisation patterns in WCBP and incidence rates (IRs) of exposed pregnancies. Such PASS should be planned for a longer period to allow continuous monitoring of PPP performance, and to provide data on important outcomes of PPP with regular time intervals. For the objectives/endpoints related to monitoring compliance with PPP elements, PRAC conveyed to narrow/readjust them to those countries/elements which can be reliably measured, and focus on utilisation patterns in WCBP and incidence rates (IRs) of exposed pregnancies and key PPP elements, to:

- Describe valproate use in WCBP per country, per indication and type of user.

- Provide the proportion of WCBP with prior medication use per country, per indication, type of user.

- Provide the IRs for valproate exposed pregnancies (including women who initiate valproate during pregnancy) per country, per indication and type of user (prevalent and incident). Proportions of women who continue and discontinue valproate during pregnancy should also be provided.

- Provide characteristics of exposed pregnancies (demographic characteristics, indication for use [epilepsy, bipolar disorder, others]), use of prior medication for valproate indications before valproate initiation) in those countries where sufficiently exposed pregnancies are available.

The protocol for the category 3 DUS ext. study should be submitted for PRAC evaluation within 6 months after completion of the current procedure. The MAH(s) should consider and include additional EU

member states (MS) in this study to provide a more representative overview regarding the IRs for valproate-exposed pregnancies across EU countries. Conversely, data from the United Kingdom (UK) may not be necessary, considering it's a jurisdiction outside the EU and where a different type of RMM has been implemented. Putting in place a long-term study protocol would be useful to ensure focused monitoring without requiring reiterated Ethics Committees (EC) protocols' approval.

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 (PI).

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

Annex II

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 remove the following condition(s) (new text **underlined and in bold,** deleted text ~~strike through~~).

~~The MAHs of medicinal products with substances related to valproate shall perform a drug utilisation study to assess the effectiveness of the new risk minimisation measures and to further characterise the prescribing patterns for valproate. MAHs are encouraged to extend the ongoing drug utilisation study (DUS).~~	
~~Protocol to be submitted in accordance with Article 107n (1) of Directive 2001/83/EC :~~	~~Within 6 months of the CMDh agreement/commission decision.~~
~~The first interim report shall be submitted to the PRAC:~~	~~Within 12 months after endorsement of the study protocol.~~
~~Further interim reports should be submitted to the PRAC 6-monthly thereafter for the first 2 years~~	
~~The final study report shall be submitted to the PRAC:~~	~~Within 48 months after endorsement of the study protocol~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of the position

Adoption of CMDh position:	July 2026 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	7 September 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	5 November 2026