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:

Results of this study highlighted that, in women of child-bearing potential (WCBP) with epilepsy or bipolar disorder (BP), the discontinuation of valproate (VPA) after chronic use was maintained in half of the cases, especially in young women with a stabilised disease.

The main conclusion that about half of the discontinuations were sustained was endorsed by PRAC, although major uncertainties remain. Greater disease severity and older age are associated with VPA reintroduction, which may reflect the need to cope with relapses, but also reflect the need or intention to become pregnant. Factors independently associated with successful VPA discontinuation were younger age, shorter history of the disease, better woman management with more clinical and medical examinations, dose-tapering phase before VPA discontinuation, and continued use of previous specific drugs. The limitations and risk of residual confounding were also discussed by PRAC.

PRAC also noted that planned pregnancy associated with a dose-tapering phase was a strong positive factor for successful VPA discontinuation. This is a result that could be expected, but this target population is only a limited part of the target group of the valproate related recommendations and risk minimisation measures.

In conclusion, PRAC agreed that regulatory implications of the results are limited and they do not have an effect on the benefit risk balance of the product, and no regulatory actions can be derived from these results. However, the consortium of marketing authorisation holders (MAHs) is strongly encouraged to publish the results of this study in a scientific journal since sharing these results would be helpful and relevant for future research on this topic.

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.

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

~~Observational study to evaluate and identify the best practices for switching of valproate in clinical practice (VALNAC09344)~~ ~~Study to be conducted by a consortium of MAHs~~	~~Protocol submission~~	~~By 30 Nov 2018~~
	~~First interim report~~	~~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~~
	~~Final study report~~	~~Within 48 months after endorsement of study protocol~~

Annex III

Timetable for the implementation of the position

Adoption of CMDh position:	November 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	22 December 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	22 February 2024