26 October 2023
EMA/580017/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC non-interventional imposed PASS final study report assessment report

Active substance: valproate

Procedure no.: EMEA/H/N/PSP/J/0045

Note

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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Table of contents

1. Background information on the procedure

In order to fulfil the obligation to submit the results of an imposed non-interventional PASS in accordance with Article 107p of Directive 2001/83/EC, the MAH's consortium submitted on 27 July 2023 a PASS final study report (version 1.0, dated 30 June 2023) for valproate to the European Medicines Agency (EMA).

PASS information

Title	Non-Interventional retrospective longitudinal study in the UK and France to investigate the therapeutic strategies after discontinuation of valproate (VPA) and related substances in clinical practice: VALSE study (VALNAC09344)
Final Report version identifier	1.0
DATE OF FINAL REPORT	30 June 2023
Date of last version of protocol	8 November 2022 (v8.0)
EU PAS register number	EUPAS 37438
Active substance	VPA and related substances: ATC code: N03AG01 and N03AG02
Medicinal product	Valproate and related substances*: • magnesium valproate • sodium valproate • valproic acid • sodium valproate / valproic acid • valproate semisodium • valpromide *All substances will be summarized under the term "VPA"
Product reference	Information is detailed in the cover letter's -1
Procedure number	EMA/H/A-31/1454
Marketing authorisation holder(s) / Sponsor	APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH/DR.REDDY'S; CONSILIENT HEALTH, CRESCENT PHARMA, DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; LUPIN HEALTHCARE, MYLAN SAS; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; SANDOZ/HEXAL AG; SANOFI AVENTIS GROUPE; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE; WOCKHARDT UK LIMITED. Of note, Biogaran, Biomo Pharma GMBH and Pharmaswiss Ceska republika s.r.o left the Consortium in 2022.
Joint PASS	Yes
Research question and objectives	The research question was to investigate the therapeutic strategies implemented when VPA is discontinued in clinical practice for Women of Childbearing Potential (WCBP). The objectives and study population were split for each indication of VPA (epilepsy or bipolar disorder) in the overall population of VPA WCBP chronic users and a subpopulation of pregnant women. The primary study objective was to determine the clusters of patients that are the most likely to reflect a success in epilepsy/ bipolar disorder management after VPA discontinuation based on: (i) the description of the overall treatment patterns in the year

	following VPA discontinuation, (ii) the categorisation of patients according to their treatment patterns (clusters), and (iii) the description of patients' and treatment characteristics at baseline, and clinical relapse occurrence, pregnancy occurrence, and other healthcare resources in the follow-up period in each of these clusters. For each cluster, Success/Failure in epilepsy/BD management after VPA discontinuation was defined based on the absence of VPA reintroduction in the follow-up period. This was contextualised according to several clinical and pharmaceutical parameters such as: clinical relapse, number of hospitalisations, and polypharmacy. Results were then discussed with the Scientific Committee to determine which cluster(s) was (were) the most likely to reflect a success in epilepsy/ bipolar disorder management after VPA discontinuation. The secondary study objective was to identify the baseline factors (e.g., patients', Epilepsy/BD treatments, disease characteristics) associated with the potential successful/unsuccessful clusters.
Countries of study	The study was conducted in the United Kingdom (UK) and France

2. Final assessment conclusions and actions

During the plenary meeting held on 23-26 October 2023, PRAC, having considered the PASS final study report version 1.0 (dated 30 June 2023), agreed with the PRAC rapporteur's position.

The main conclusion that about half of the discontinuations were sustained is endorsed, although major uncertainties remain. Greater disease severity and older age are associated with valproate (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. Finally, PRAC 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.

When evaluating the interim study results, PRAC had requested the MAH to discuss the possibility to use the brand name of the products (i.e. in the SNDS database - Système National des Données de Santé - French national health database for reimbursement - via the CIP code - Code Identifiant de Présentation) to identify the indication for use of valproate anSWITCHd limit the proportion of women with identification unknown.

In order to address this request, the MAH's consortium had proposed a sensitivity analysis of the women without database diagnosis to be performed in a second time, to check the consistency with the cohorts of women with a diagnosis of epilepsy or bipolar disorders, or to redo the analyses on 2 cohorts selected using both database diagnosis (epilepsy and bipolar disorders) and valproate brand name when no database diagnosis is available. Those additional analyses would also trigger amendment of both protocol and SAP.

PRAC discussed that such pending analyses might not impact the study conclusions. However, as previously agreed, these analysis are awaited to ensure that the results are representative and

complete as much as possible and will be evaluated separately, in the framework of procedure EMEA/H/N/PSP/J/0074.8.

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 the results. However, the Consortium of 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.

3. Final Recommendations

Based on the review of the PASS final study report version 1.0 dated 30 June 2023, the PRAC considers by consensus that:

☒ The risk-benefit balance of medicinal products containing valproate and related active substances concerned by the PASS final report remains unchanged

4. Other considerations

☒ The recommendations proposed by the PRAC in this report merit careful consideration by CMDh, as they propose e.g. important restrictions of use and/or substantial modifications in the Product Information or Annex II.