



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/334781/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC non-interventional imposed PASS final study report assessment report

Valproate and related substances (sodium valproate, valproic acid, valproate semisodium, valpromide, valproate magnesium)

Procedure no.: EMEA/H/N/PSR/J/0043

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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1. Background information on the procedure

In Europe valproate and related substances (valproic acid, sodium valproate, magnesium valproate, valproate semisodium and valpromide) are licensed since 1967 to treat epilepsy, since 1995 to treat bipolar disorders (BP) and, in some EU member states (MS), also indicated in the prophylaxis of migraine attacks. They have been authorised via national procedures in all EU Member States (MS), and in Norway and Iceland. Worldwide, these products are approved and marketed in more than 120 countries.

Valproate exact mechanism of action is not fully understood. It is thought to act by increasing the level of the neurotransmitter gamma-aminobutyric acid (GABA), which may act as a mood stabiliser.

Valproate may also work by suppressing repetitive neuronal firing through inhibition of voltage-sensitive sodium channels, which has the effect of reducing excessive electrical activity in the brain.

In recent years, in the framework of two referral procedures under article 31 of Directive 2001/83/EC (EMA/H/A-31/1387¹ and EMA/H/A-31/1454²) the use of valproate during pregnancy and in women of childbearing potential (WCBP) has been (further) restricted, due to an increased risk of neurodevelopmental disorders (NDD), including autism spectrum disorders (ASD), and of congenital malformations (CM) in the offspring following in utero exposure. Furthermore, the Pharmacovigilance Risk Assessment Committee (PRAC) has issued (additional) measures to mitigate these risks and imposed to the marketing authorisation holders (MAH) of valproate-containing products in the European Union (EU) to further investigate some additional concerns including the potential impact of paternal use of valproate in the offspring.

In particular, regarding exposure via seminal fluid, in order to fulfil the obligation to submit the results of an imposed non-interventional post-authorisation safety study (PASS) in accordance with Article 107p of Directive 2001/83/EC, on 19 January 2023, Sanofi-Aventis Recherche & Développement, on behalf of a consortium of MAH, submitted to the European Medicines Agency (EMA) a PASS final study report (version 1.0, dated 9 January 2023) for valproate, together with an updated Statistical Analysis Plan (SAP) version 2.0 and an updated protocol version 6.0.

The aim of this PASS (reference number EUPAS34201), a retrospective cohort study using databases from three Nordic countries, was to examine the association between paternal exposure to valproate at conception and the risk of NDD, including ASD (primary objective), as well as congenital malformations (CM) (composite of minor and major; secondary objective) in the offspring. Both descriptive and comparative cohorts were established. In the comparative cohorts, paternal exposure to valproate was compared to paternal exposure to lamotrigine or levetiracetam, which are considered a first-line treatment. In women these drugs are generally associated with lower risk of teratogenicity for their offspring compared to valproate, but it is unknown whether the effect is the same in fathers.

An update to the risk management plan (RMP) resulting from the data presented in this PASS final study report (version 1.0) was not submitted on 19 January 2023.

An update to the Product Information (PI) resulting from the data presented in this PASS final study report (version 1.0) was also submitted on 19 January 2023.

¹ Valproate referral 2014
(http://www.ema.europa.eu/en/documents/press-release/prac-recommends-strengthening-restrictions-use-valproate-women-and-girls_en.pdf)

² Valproate referral 2018
(http://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-prac-recommends-new-measures-avoid-valproate-exposure-pregnancy_en.pdf)

Based on the data presented in the above-mentioned documents, the MAH also submitted (new) educational materials (EM) and a proposal for a direct health care professional communication (DHPC) and DHPC communication plan on 19 January 2023.

On 28 March 2023, due to issues in the statistical programs identified by the MAH, an addendum (version 1.0, dated 20 March 2023) to the final study report (version 1.1, dated 20 March 2023), including the following sensitivity analyses, was submitted:

- sensitivity analyses #2 (risk of Autism Spectrum Disorder) for Denmark and Norway
- exploratory analyses #8 (congenital malformation by target body system organ class)

On 25 May 2023, the MAH informed that part of the Norwegian data considered in this PASS was incorrect, leading to potential bias and misleading results and conclusions.

In its letter dated 23 June 2023, the MAH stated that they would be able to submit the correct data for Norway as a corrigendum and an addendum to the final study report version 1.1, in the second half of October 2023.

On 20 October 2023, as triggered by availability of the corrected Norwegian dataset, the MAH submitted the corrigendum (version 1.0) and the addendum (version 2.0) to the final study report version 1.1, together with the (updated) study protocol version 7.0 (all documents dated 02 October 2023). Based on the data presented in these documents, the MAH also submitted amended versions of the updated PI, (new) EM and a proposal for a DHPC and communication plan (on 20 October 2023).

For an overview of the nationally authorised products covered in the context of this final study report, please see the appendix to this assessment report (AR).

PASS information

Title	A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorders as well as congenital abnormalities in offspring – a population-based retrospective study
Version identifier of the final study report	7.0
Date of last version of the final study report	02 October 2023 (corrigendum v. 1.0 and addendum v 2.0 to the final study report v 1.1).
EU PAS register number	EUPAS34201 ³
Active substance	Antiepileptic drugs (AEDs) including valproate ATC WHO code: N03A
Medicinal product	Refer to the Appendix
Product reference	Information is detailed in the cover letter's Annex 1
Procedure number	EMA/H/N/PSR/J/0043
Marketing authorisation holder(s)	APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; CONSILIENT HEALTH LIMITED; CRESCENT PHARMA; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZ/HEXAL AG;

³ <https://catalogues.ema.europa.eu/node/3611/administrative-details>

Title	A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorders as well as congenital abnormalities in offspring – a population-based retrospective study
	LUPIN; VIATRIS SANTE (LYON) FR;VIATRIS GX /BV/SRL: BE; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; SANOFI R&D; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE; WOCKHARDT UK LIMITED
Joint PASS	Yes
Research question and objectives	Overall aim The aim of this retrospective cohort study is to examine the association between paternal exposure to valproate at conception and the risk of neurodevelopmental disorders (NDD), including autism spectrum disorders (ASD), as well as congenital malformations (CM) in offspring. Paternal exposure to valproate will be compared to paternal exposure to lamotrigine/levetiracetam which are considered first line treatment. Primary objective 1. Investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam (composite monotherapy) treatment at the time of conception. Secondary objectives 2. Investigate the risk of CM in live and non-live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam (composite monotherapy) treatment at the time of conception, in Norway and Denmark. 3. Describe antiepileptic drug (AED) exposure (posology and duration) data and health characteristics of male patients prescribed AEDs (including valproate and lamotrigine/levetiracetam) in treatment of epilepsy and other indications at the time of conception of their offspring, both for NDD and CM cohort. 4. Identify potentially important risk factors for outcomes of interest, in offspring paternally exposed to valproate (monotherapy) or lamotrigine/levetiracetam (composite monotherapy) at the time of conception, by examining AED exposure and health characteristics of the offspring and their mothers. Exploratory objectives 5. To describe the putative risk factors and frequency of NDD, including ASD, as well as CM in offspring paternally exposed to valproate (in combination with other AEDs excluding lamotrigine/levetiracetam) and lamotrigine or levetiracetam (in combination with other AEDs, excluding valproate) at the time of conception. 6. To describe the risk factors and frequency of NDD, including ASD, as well as CM in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception. 7. To investigate the risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception in Sweden. 8. To describe the frequency of CM by target body system organ class in live and non-live offspring paternally exposed to valproate (monotherapy), and to lamotrigine or/ levetiracetam (composite monotherapy) treatment at the time of conception.

Title	A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorders as well as congenital abnormalities in offspring – a population-based retrospective study
Country(-ies) of study	Denmark, Sweden, and Norway

2. Final assessment conclusions and actions

First round of assessment

On **19 January 2023**, the MAH provided the final study report (version 1.0) for the 'post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders, (NDD) including autism spectrum disorders (ASD), as well as congenital malformations (CM) in offspring – a population-based retrospective study', listed as category 1 study in the RMP.

An updated protocol version 6.0 (the main updates of this document concerning the inclusion criteria for data extraction in Sweden, the exclusion criteria in all countries, the study time period, some clarifications on confounders/risk factors selection and on the sensitivity analyses number 2, 6 and 8 and inclusion of a new sensitivity analysis, number 11; the milestones dates were also updated) and an updated SAP version 2.0 (its main updates are linked to the proposed protocol updates) were also submitted.

On **28 March 2023**, due to issues in the statistical programs identified by the MAH, an addendum to the final study report was submitted (version 1.1).

The aim of this retrospective cohort study using databases from Denmark (DK), Sweden (SE) and Norway (NO) was to examine the association between paternal exposure to valproate at conception and the risk of NDD, including ASD (primary objective), as well as congenital malformations (CM, composite of minor and major; secondary objective) in the offspring. Both descriptive and comparative cohorts were established. In the comparative cohorts, paternal exposure to valproate was compared to paternal exposure to lamotrigine or levetiracetam, which are considered first-line treatment.

At the plenary meeting held on **10-12 May 2023**, the PRAC discussed the results of the PASS final study report version 1.1 as submitted by the MAH before being informed by the MAH that the Norwegian dataset was incorrect, leading to potential bias and misleading results and conclusions. The below results and considerations reflect the PRAC's understanding at the time of the first round of assessment, based on the data that were later found to be partially incorrect. The results and PRAC considerations on the corrected dataset can be found under the "Third round of assessment", starting from page 13.

Cohort characteristics

- For the primary objective, the minimum sample size was achieved at country level in all 3 countries. For the secondary objective, the minimum sample size was not achieved at country level in Denmark and Norway. Further clarification regarding the exclusion criteria used in the secondary outcome cohort for comparative analysis was requested.
- Offspring demographic and clinical characteristics were generally similar across countries and exposure groups, with an expected distribution of the gestational age, ratio of males to females and offspring weight, in primary as well as secondary outcome cohort.

- In both the primary and secondary outcome cohort, more offspring in the lamotrigine/levetiracetam group were conceived in the latest year of the study time period compared to those in the valproate group in all 3 countries. This suggests a decreasing trend in valproate use in recent years and might introduce a bias when calculating incidence proportion of NDD, since the group with longer follow-up has higher chance to experience the event.
- Demographic (e.g. age) characteristics of mothers and fathers were generally comparable across the exposure groups and countries, both in the primary and secondary outcome cohort.
- In the primary outcome cohort, both in mothers and fathers, clinical comorbidities were reported somewhat more frequently in the lamotrigine/levetiracetam group than in the valproate group, although the type and pattern of reported comorbidities (i.e. which comorbidities were most or least reported) were comparable. Similarly, exposure to concomitant medications was generally higher in mothers and fathers exposed to lamotrigine/levetiracetam compared to valproate, although the proportion reported were generally within the same range.
- In the secondary outcome cohort, no major differences in paternal and maternal characteristics were observed between offspring exposed to valproate and offspring exposed to lamotrigine/levetiracetam.

Primary outcome: NDD (including ASD)

- For the overall study period (0-12 years), the cumulative incidence proportions (unadjusted) were consistently higher in the valproate group compared to the lamotrigine/levetiracetam group (DK 6.61% [4.92, 8.30] valproate vs 3.67% [2.61, 4.73] lamotrigine/levetiracetam; SE 5.37% [3.95, 6.79] vs 3.51% [2.57, 4.44], NO 6.72% [4.78, 8.66] vs 3.99% [2.96, 5.02]).
- Risk ratios of the cumulative incidence proportions were pooled across countries in a meta-analysis. For the overall study period (0-12 years), the risk of NDD including ASD was significantly higher in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam (0-12 years RR=1.67, 95% CI: 1.34, 2.08; $p < 0.0001$).
- Across the 3 countries, the crude cumulative incidence rate of NDD among offspring paternally exposed to valproate was higher than that among offspring exposed to lamotrigine/levetiracetam, but with overlapping confidence intervals (DK 7.2 [5.4, 9.3] per 1000 PY valproate vs 5.6 [4.0, 7.5] per 1000 PY lamotrigine/levetiracetam; SE 8.0 [6.0, 10.5] vs 6.9 [5.2, 9.1]; NO 9.6 [6.9, 12.9] vs 6.4 [4.8, 8.3]) for the overall study period.
- For the overall study period, results of a meta-analysis showed higher cumulative incidence rate of NDD, including ASD, in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam (0-12 years RR=1.32, 95% CI: 1.05, 1.66; $p = 0.0162$).
- In the PS-weighted model, the observed hazard ratios (HR) were higher than in the crude model and showed a 30-50% increased risk for NDD, including ASD, in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam (DK 1.34 [0.79, 2.25]; SE 1.54 [0.95, 2.51]; NO 1.52 [0.93, 2.49]). Confidence intervals included 1, but in all countries, point estimates point in the same direction, and the lower limit of the confidence interval approach 1 in both Sweden and Norway. After pooling the PS-adjusted HRs, a higher risk of NDD, including ASD, among offspring from fathers exposed to

valproate in comparison to lamotrigine/levetiracetam group) was observed (HR 1.47, 95% CI: 1.10-1.96).

- When using a more narrow NDD composite endpoint (excluding several movement/tic disorders), adjusted analyses showed a stronger association between paternal exposure to valproate and the occurrence of NDD in all 3 countries compared to that observed in the main analysis (DK HR 1.59 95%CI [0.89, 2.86]; SE 1.70 [1.02, 2.81]; NO 1.65 [0.99, 2.76]).
- A sensitivity analysis using only ASD as outcome showed a higher risk of ASD for valproate compared to lamotrigine/levetiracetam in Sweden (HR: 2.68, 95% CI: 1.17, 6.12), but not in Denmark (HR: 0.76, 95% CI: 0.30, 1.89) or Norway (HR:1.45 ,95% CI: 0.50, 4.19) in Norway.
- Regarding potential risk factors/confounders:
 - Offspring male sex was identified as a risk factors for NDD in both countries, with more NDD events reported in male offspring compared to female offspring.
 - Age, smoking during pregnancy, and concomitant medications associated with valproate-indicated psychiatric disorders (bipolar disorder, mania, migraine) during pregnancy were identified as maternal characteristics that increased risk of NDD in both Denmark and Sweden. Affective disorder and use of polypharmacy before the last menstrual period date plus 2 weeks (LMP2), or during pregnancy, were also associated with the outcome in Denmark. In Norway, only maternal affective disorder was associated with NDD (including ASD).
 - Year of offspring conception was a paternal characteristic associated with both exposure (valproate or lamotrigine/levetiracetam) and NDD outcome in both countries. Paternal polypharmacy index was associated with both exposure and outcome only in Sweden.

Secondary outcome: Congenital malformations (CM)

- CM outcome was a composite of major and minor CM. In Denmark, congenital malformation was reported in 12.5% of offspring (9% valproate vs 14% lamotrigine/levetiracetam), in Norway CM was reported in 16% of offspring overall (17% vs 15%), and in Sweden in 10.5% (10.4% vs 10.5%) of offspring overall (live births only). In Denmark, minor CM was more commonly reported than major CM in both exposure groups. In Norway and Sweden (live births only), the occurrence of minor and major CM was evenly distributed and similarly comparable in both exposure groups. The prevalence of major CM in pregnancies in the general population has been estimated at 3.7% of pregnancies among live births (up to 1 year of age) or stillbirths. Offspring from mothers or fathers exposed to drugs with known teratogenic activity/foetal toxicity were not excluded from the secondary outcome cohort for descriptive analyses in the current study.
- When considering the overall study period (0-12) year, the risk (cumulative incidence proportion) of congenital malformations was lower in valproate exposed offspring compared to lamotrigine/levetiracetam exposed offspring in Denmark (VPA 9.3%, [95% CI 6.9%,11.7%] vs lamotrigine/levetiracetam (14.1% [12.1,16.2])), whereas it was higher in Norway (16.6% [13.7, 19.5] vs 15.1, [13.2, 17.0]), with overlapping CIs. When considering the cumulative incidence proportions in shorter periods of time (i.e. 1-year strata between 0-12 years), in both exposure groups, the cumulative incidence proportion was highest in the 0-1 year strata (5.3% [3.4, 7.2] vs 9.1% [7.4, 10.8]; NO 9.5% [7.2, 11.7] vs 9.1% [7.6, 10.6]).

- Results of a pooled meta-analysis did not show a difference in risk of CM in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam (OR 0.79, 95% CI: 0.49, 1.29, $p=0.3503$). Results in the individual countries of Norway and Denmark showed diverging results (DK OR 0.61 [95% CI: 0.36, 1.06] NO OR 1.00 [95% CI: 0.62, 1.61]). The exploratory analysis in live births from Sweden also did not show a difference in the risk of CM between offspring exposed to valproate compared to offspring exposed to lamotrigine/levetiracetam.
- No difference in the risk of CM was observed when comparing different clusters of exposure (high and low dose). The results of the main analysis were confirmed in the sensitivity analyses performed to assess the robustness of the results.
- No risk factors or confounders were identified for the CM outcome. The only characteristic associated with exposure was year of offspring conception, with earlier years of conception being more frequent in the valproate exposed group compared to the lamotrigine/levetiracetam exposed group.

For the primary outcome (NDD, including ASD), overall, the meta-analysed cumulative incidence proportion, cumulative incidence rate as well as the adjusted Cox proportional hazard models, showed a significantly increased risk of NDD (including ASD) in the offspring paternally exposed to valproate, compared to offspring paternally exposed to lamotrigine/levetiracetam. A consistent trend for an increased risk had already been observed in the data from the 3 countries separately, with hazard ratios (HS) in the same direction but not significantly increased. Across the 3 countries the effect estimates were somewhat higher in high exposure clusters compared to low exposure clusters, but no significant differences were observed between different clusters of exposure. Pooling the data of all countries in meta-analyses and adjusted for time and confounders showed a significantly increased risk. Results stratified by cluster of exposure were not meta-analysed.

The association with NDD becomes stronger when a more narrow case definition was used, including major NDD (including ASD) in all 3 countries. Also, in these analyses, using more restricted outcomes, a consistent pattern of higher point estimates in groups with higher intensity exposure (higher doses and prolonged treatment trajectories) to valproate was observed, although not significant.

For the secondary outcome (CM), neither the results of a pooled meta-analysis, nor the results of comparative analyses in the individual countries separately showed a difference in the risk of CM in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam.

For both the primary and secondary outcome, the results of the main analyses were confirmed in sensitivity analyses performed to assess the robustness of the results.

On **12 May 2023**, before being informed that the Norwegian dataset was incorrect and therefore based on analyses that were later updated (please see "Third round of assessment", from page 13), the PRAC concluded that:

- The results of the PASS to evaluate the paternal exposure to valproate and risk of NDD, including ASD, as well as congenital malformations in the offspring, suggested an increased risk of NDD, including ASD, but no difference in risk of CM, in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam.
- These findings added to the already known risks to offspring exposed to valproate in utero. Maternal exposure to valproate during pregnancy is associated with increased risk of both CM and NDD in the offspring.

- In this PASS on paternal exposure, the suggested absolute risk of NDD, including ASD, after paternal exposure was noted of lower magnitude than the risk for NDD after maternal exposure during pregnancy (30-40% of offspring with NDD after maternal exposure [and 11% CM] vs 5-8% in the current PASS).

Notwithstanding the above, on **12 May 2023**, the PRAC also concluded there were still outstanding issues regarding the study results, required to be solved for full interpretation of these results.

The most important issues that required further clarification before final conclusions of the study results could be drawn were results stratified by indication, meta-analyses of the sensitivity analyses, additional sensitivity analyses in former users, additional sensitivity analyses in which only 'probable' NDD cases were included, analyses that took into account the distribution of events during the period of follow-up, including further discussion regarding specificity and sensitivity of NDD diagnosis, by type and by age bands, and whether the median follow-up time in all exposure groups was sufficient to diagnose NDD other than ASD.

In addition, as several recent publications regarding the effect of valproic acid on epigenetic changes had become available, further discussion of non-clinical literature was deemed necessary.

The PRAC also considered that responses to these outstanding issues might impact the full recommendations to be implemented. In addition, it was proposed to request external stakeholder/expert input regarding the impact of the final study results of the paternal PASS, as well as the most appropriate (updated) risk minimisation measures (RMM) (routine and additional) as triggered by the study results, for both healthcare professional (HCP) and patients.

Therefore, on **12 May 2023**, the PRAC agreed that final recommendations were pending, awaiting the responses to a request for supplementary information (RSI) and external stakeholder/expert input.

New information received from the MAH in May-June 2023.

On **25 May 2023**, the MAH informed EMA and the PRAC (Rapporteur) that part of the Norwegian data was incorrect, leading to potential bias and misleading results and conclusions. The MAH further stated that corrected Norwegian study results were expected to be available in Q4 2023.

On **6 June 2023** the MAH also informed that, following detection of the Norwegian data issue, a complete extensive quality check investigation of the data had been conducted and had revealed a new quality issue in the Danish dataset, bringing additional limitations to the results generated so far. The impact of these data quality issues was unknown at that point in time.

In a letter dated **23 June 2023** it was eventually clarified that the data quality issues in the Danish dataset was resolved and it was confirmed that this issue had no impact on the final study results. The corrected Norwegian data remained outstanding and were expected to be available in Q4 2023.

During the plenary meeting held on **3-6 July 2023**, the PRAC noted that no conclusions could be made on the study until the corrected Norwegian data was made available, as it was indicated that the identified issues could lead to potential bias and misleading results and conclusions, and the impact of the issues was yet unknown.

Second round of assessment

As part of the second round of assessment, the main issues addressed in the MAH's responses (submitted on 12 July 2023) to the PRAC's RSI agreed on 12 May 2023 concerned the following:

- 1) Further discussion of preclinical literature regarding the effect of valproic acid on epigenetic changes;
- 2) Further clarification regarding the exclusion criteria used in the secondary outcome cohort for comparative analyses;
- 3) A discussion regarding the impact of missing data on socioeconomic status on the study results;
- 4) Corrections/further clarifications of minor inconsistencies noted in the final study report.

The PRAC noted that, regarding the additional discussion on preclinical literature related to possible epigenetic changes of male germ cells and possible consequence of these changes on future offspring risk of NDD and behavioral changes, most literature did not specifically involve epigenetic changes in germ cells or sperm or transferability to offspring, and mainly provided additional insight on epigenetic changes in vitro or direct exposure to offspring during pregnancy. Only 1 study (**Sakai et al, 2023**⁴) specifically investigated the possibility of paternally transferred epigenetic changes to offspring and possible resulting behavioral changes in mice. However, the PRAC agreed with the MAH that study limitations (non-appropriate methods for behavioral tests, lenient statistical methods) preclude a definite statement. Overall, the PRAC also agreed that available literature is not robust enough to draw conclusions regarding paternally transferred epigenetic changes to offspring at this time. A non-clinical study to evaluate valproate-induced epigenetic changes, as requested by the PRAC (Category 1) in the framework of the referral procedure under article 31 of Directive 2001/83/EC completed in 2018⁵, has been initiated by Sanofi (the originator MAH). The first report from this study was expected in Q4 2023. A final study report for the pivotal epigenetic study is expected in 2025. It was anticipated that this study will provide more robust information on the possibility of paternally transferred valproate epigenetic mediated changes to the offspring. Regarding the responses to the other outstanding issues that were addressed in the consortium response of 12 July 2023, these supported the conclusions drawn in the first assessment round.

As previously outlined, as triggered by the errors in the Norwegian database, incorrect data from 2 study years resulted in a 4-year data gap (to ensure 24 months lookback period) in the availability of diagnostic codes. According to the MAH this had introduced a systemic misclassification of paternal confounders and risk factors, as well as errors in the identification of NDD events, due to incorrect values of variables (exclusion criteria, comorbidities, NDD events). Based on information provided in May 2023, as a result of this misclassification, the MAH expected that around 35% of offspring in the valproate group and 23% in the lamotrigine/levetiracetam would be excluded in the clean data sets from Norway. However, no access to individual data was available at that moment and characteristics of the remaining offspring and number of events in each group would only be known after availability of the corrected Norwegian data. Thus, at the time of the PRAC second round of assessment, the full extent and direction of the NO errors on the paternal PASS final study results was unknown.

Overall, the data that became available in the second round of assessment supported the conclusions made in the first round: the results of the PASS to evaluate the paternal exposure to valproate and risk of NDD (including ASD), as well as congenital malformations in offspring, suggested an increased risk of NDD (including ASD), but no difference in risk of CM in the offspring paternally exposed to valproate compared to the offspring paternally exposed to lamotrigine/levetiracetam. However, there were still outstanding requests for additional analyses that the PRAC considered needed to gain more insight into

⁴ Sakai K, Hara K, Tanemura K (2023) Testicular histone hyperacetylation in mice by valproic acid administration affects the next generation by changes in sperm DNA methylation. PLoS ONE 18(3): e0282898. <https://doi.org/10.1371/journal.pone.0282898>

⁵ Valproate referral 2018 (http://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-prac-recommends-new-measures-avoid-valproate-exposure-pregnancy_en.pdf)

the robustness of the study results. In addition, it became clear that the consortium would be able to provide these additional analyses requested by the PRAC on 12 May 2023 (e.g. analyses that took into account the distribution of events during the period of follow-up, including further discussion regarding specificity and sensitivity of NDD diagnosis, by type and by age bands) only in the long term (e.g. in 2025).

Third round of assessment

On **20 October 2023**, the MAH submitted the corrected Norwegian dataset and updated meta-analyses based on the corrected dataset (including updated results of the meta analysed risk estimate across the 3 countries). An updated protocol version 7.0 (dated 2 October 2023) was also submitted in view of the corrections to the Norwegian dataset. In addition, taking into account the corrected results of the PASS, the MAH submitted proposals for risk minimisation strategies.

As regards the data of the PASS, the MAH described the issues in the Norwegian dataset and how they had been addressed. For the Norwegian dataset, instead of 1 January 2006, the study period started on 1 January 2010, to ensure a sufficient lookback period of 24 months before LMP2 to obtain diagnostic codes from the Norwegian patient registry. Since the end of the study period did not change (31 December 2019 for Norway) this also resulted in a shorter study time period, as well as a shorter maximum follow-up period, for the children from birth to maximum 10 years instead of 12 years. In Denmark and Sweden the maximum follow-up period remained up to 12 years after birth. These changes were adequately incorporated in the study protocol version 7.0 (dated 2 October 2023), which was acceptable. These changes were taken into account in the updated analyses presented below.

In addition, the MAH provided further details on the previously identified and already resolved data quality issue in the Danish dataset, for which it had been confirmed, on 23 June 2023, that this issue had no impact on the final study results. In this dataset, a shorter lookback period for the parents of 37 children (between 3 and 11 months before Last Menstrual Period Date Plus 2 Weeks [LMP2] instead of 12 months) had been applied. Further investigation showed that this mistake in data quality did not result in the exclusion of children. Therefore, the Danish results were confirmed as not impacted and the initial results were considered final.

Corrected Norwegian dataset and updated meta-analyses

Neurodevelopmental disorders (NDD)

In the corrected Norwegian comparative primary outcome cohort (NDD), the number of children decreased from 1943 to 1416. Although the minimum sample size to observe a HR of 2.00 with 5% significance and 80% power was calculated to be 1178, the 589 per exposure group was not reached for Norway, since the valproate group consisted of 398 children and the lamotrigine/levetiracetam group of 1018 children. Of note, for Sweden and Denmark the 589 children per treatment group was reached.

The corrected Norwegian results did not result in major changes in risk estimates. For Norway the crude HR for NDD, including ASD, was 1.60 (0.81, 3.15) and the PS-weighted adjusted HR for NDD, including ASD, was 1.76 (0.83-3.71).

Considering the corrected Norwegian data, a consistent trend for an increased risk of NDD (including ASD) for valproate compared to lamotrigine/levetiracetam group was observed in the data from all 3 countries separately (DK, SE, NO), with hazard ratios (HRs) in the same direction but not significantly increased.

Pooling the data of all countries in a meta-analysis and adjusted for time and confounders, the PS-weighted adjusted HR for NDD was statistically significantly higher for valproate compared to lamotrigine/levetiracetam group, with aHR 1.50 (1.09, 2.07) (please see table 1 below).

The study was underpowered to investigate NDD subtypes.

Table 1: Meta-analysis of the adjusted hazard ratios obtained from the PS-weighted Cox regression model; primary outcome NDD including ASD

NDD*	Denmark	Sweden	Norway	Meta-analysis Pooled HR
N Valproate	678	841	325	
N	38	47	13	
N lamotrigine/levetiracetam	1118	1334	910	
n	36	34	21	
valproate vs lamotrigine/levetiracetam	1.34 (0.79, 2.25)	1.54 (0.95, 2.51)	1.76 (0.83, 3.71)	1.50 (1.09, 2.076)

NDD*: neurodevelopmental disorders

Legend: Hazard Ratio of the outcome between the 2 exposure groups (valproate versus lamotrigine/levetiracetam composite monotherapy) were presented for each country separately and combined (meta-analysis). 95% CI: 95% confidence intervals.

The MAH provided the following additional results. When using a more narrow NDD composite endpoint (excluding several movement/tic disorders), adjusted analyses showed a stronger association between paternal exposure to valproate and the occurrence of NDD compared to that observed in the main analysis, in the three countries separately, as well as the pooled data (meta-analysis aHR 1.69) (1.20-2.39). Meta-analysis of sensitivity analysis 2 (outcome limited to ASD only) could not be provided by the MAH since the corrected Norwegian dataset did not allow comparative analysis for the outcome ASD. The aHRs observed in Sweden (2.70 [1.19 – 6.17]) and Denmark (0.76 [0.30 – 1.89]) differed substantially. When pooling the aHR of Sweden and Denmark (as done by the assessor using Rothman episheet), the pooled aHR was 1.52 (0.83 – 2.81).

A Cox Proportional Hazard adjusted regression model was used and the meta-analysis showed a slightly lower and non-significant aHR 1.25 (0.95 -1.66) compared to the pooled aHR of the PS-weighted analysis [1.50 (1.09 -2.076)].

This comparison showed that the results and observed aHRs depended on the type of model used and how confounding and risk factors were considered. The PS-weighted model was preferred as more covariates were considered compared to the Cox Proportional Hazard adjusted regression model, in which clearly less covariates were considered in all countries and the selection of covariates was quite strict (i.e. only when associated both with the exposure and the outcome).

The pooled results of sensitivity analysis 1 (extended risk window of paternal exposure) (6 months) showed an aHR of 1.37 (1.00 – 1.89). Of note, fathers with valproate use during the spermatogenic risk window (3 months before conception) were not excluded from this analysis. A potential risk of NDD with valproate use outside the spermatogenic risk window cannot be excluded and this was reflected in the proposed PI wordings. An additional analysis in former users was requested to further study this.

In conclusion, a consistent trend for an increased risk for NDD (including ASD) for valproate compared to lamotrigine/levetiracetam group was observed in the data from all 3 countries separately, with hazard ratios (HRs) in the same direction but not significantly increased. When pooling the data, an increased risk for NDD was observed in children of fathers who used valproate in the 3 months before conception compared to lamotrigine/levetiracetam use in fathers during the same period. Considering the limitations of the study results, including potential confounding by indication and differences in follow-up time between exposure groups, ultimately, the risk was still considered a potential risk (i.e. causality was not established).

Congenital malformations

In the corrected Norwegian comparative secondary outcome cohort, the number of children decreased from 705 (262 valproate and 443 lamotrigine/levetiracetam) to 513 (169 valproate and 344 lamotrigine/levetiracetam). The minimum sample size to observe an OR of 2.5 with 5% significance and 80% power was calculated to be 826 (413 per exposure group), which was not reached for Norway and neither for Denmark. Results were meta-analysed for Denmark and Norway, but not for Sweden, as only live births were included in Sweden.

For Norway, the crude Odds Ratio (OR) for CM was 1.06 (95% CI 0.62, 1.82). Moderate to severe heterogeneity was observed between country-specific estimates (Denmark and Norway) in the crude logistic regression models ($I^2=0.5$, 95% CI: Not available, $p=0.1590$). No difference in the risk for CM was observed among offspring from fathers exposed to the valproate group compared to the lamotrigine/levetiracetam group in the meta-analysis of crude OR (OR 0.81, 95% CI: 0.48, 1.36, $p=0.4216$). For Norway the PS-weighted logistic regression model did not converge due to a quasi-complete separation, exacerbated by the low event numbers. Therefore, the PS-weighted adjusted OR for Norway and the pooled PS-weighted adjusted OR could not be estimated. For Sweden, exploratory analysis in live births only resulted in adjusted OR 0.92 (0.59, 1.44).

In conclusion, it was confirmed that no increased risk for CM was observed in children of fathers who used valproate in the 3 months before conception compared to lamotrigine/levetiracetam use in fathers during the same period.

Strengths and limitations of the PASS

Among the strengths of this PASS there were the analyses of population-based data sources with infant-parent (mother and father) linkage from three countries. An adequate number of offspring was included for the primary outcome (composite NDD); however, the study was underpowered to investigate NDD subtypes. There was an active comparator group with similar indications. Adjustment for confounders (PS weighing) could be made; however, not all confounders could be (completely) adjusted for (e.g. lifestyle factors, OTC medications). In addition, there was high missingness of information regarding indication.

The potential for confounding by indication was discussed. The patient group treated with valproate might differ from the patient group treated with lamotrigine/levetiracetam if there would be differences in AED prescription for different types of epilepsy and bipolar disorders, or its severity. In the current study stratified data per indication (epilepsy and bipolar disorder) were not provided and the severity and type of epilepsy (Juvenile Myoclonic Epilepsy, for instance) was not taken into account. There is a link between severe epilepsy and intellectual disability and other NDD; however, it should be noted that history of parental (both mothers and fathers) NDD was used as an exclusion criterion in the current study. Offspring with epilepsy/use of AED were also excluded from the comparative analysis. No information regarding type or severity of epilepsy was currently available from the paternal PASS.

There was no literature suggesting that certain types of epilepsy are linked to higher risk of NDD in offspring.

With regard to differences in follow-up time and licensing of valproate versus comparators, there was a difference in mean follow-up time between exposure groups, with longer follow-up time in the valproate group compared to offspring in the lamotrigine/levetiracetam group. The mean follow-up per offspring was 9.2 years for the valproate group and 6.6 for the lamotrigine/levetiracetam group in Denmark, 6.7 and 5.1 respectively in Sweden, 5.0 and 4.8 respectively in Norway (based on corrected Norwegian data). Thus, the offspring in the valproate group may have had a higher chance of being diagnosed with NDD due to longer follow-up. This may particularly be the case for NDD diagnosed later in childhood: 4 years follow-up was available for 86% in the valproate group compared to 74% of the lamotrigine group; 8-years follow-up was available for 54% in the valproate group, but only for 29% of the lamotrigine/levetiracetam group.

Additional analyses

Additional analyses for full interpretation of the PASS study results have been requested in the first round of the assessment. These included sub-group analyses per indication, analysis per calendar year of conception, analysis focusing of probable NDD cases only, former valproate user analysis and analyses to account for different follow up time between treatment groups.

The MAH considered that the sample sizes of such analyses would be too small to allow for analyses with sufficient power (for subgroup analyses and sensitivity analyses that require stratification) to add to the results already submitted. Therefore, it was argued by the MAH that these additional analyses would not resolve the study limitations and were not expected to result in new RMM.

Although the PRAC considered that the largest body of evidence from the PASS was already available, and acknowledging that the requested additional analyses with subgroup analyses and stratification would likely be based on small numbers of events, the PRAC remained of the position that the additional analyses could add to the interpretation of the results, as it would (for example) be possible to identify certain trends. To increase the power of the study, the PRAC recommended to not exclude children from parents with a history of NDD or CM from the cohort but instead control for the risk factor "parents with a history of NDD or CM" in the analysis. In its response dated **21 December 2023**, the MAH agreed to perform the additional (new) analyses.

Therefore, the MAH should provide a protocol within 6 months after finalisation of the current procedure to detail the additional analyses as part of a new category 1 PASS with appropriate milestones.

Discussion of other relevant data considered in the assessment

Only 2 other studies specifically reported on the association between paternal exposure to AEDs at time of conception and offspring risk of neurodevelopmental disorders.

The study by **Tomson et al (2020)**⁶ used nation-wide Swedish registries, similar to the Swedish data sources used in the current study, to investigate the association between paternal use of AEDs and adverse NDD outcomes (ASD, ADHD, intellectual disability) and major CM.

The study cohort included all singleton live births at >22 weeks completed gestational weeks in the period 2006-2016. The study only included fathers exposed to AEDs with a diagnosis of epilepsy.

⁶ Tomson T, Muraca G, Razaz N. Paternal exposure to antiepileptic drugs and offspring outcomes: a nationwide population-based cohort study in Sweden. *J Neurol Neurosurg Psychiatry*. 2020 Sep;91(9):907-913. doi: 10.1136/jnnp-2020-323028. Epub 2020 Jul 10. PMID: 32651245.

The final sample included 1,144,795 births to 741,726 fathers without epilepsy and 4,544 births to 2,955 fathers with epilepsy. Of these, 2,087 (45.9%) were born to fathers with epilepsy, who had dispensed an AED during the conception period. Carbamazepine (33.8%), valproic acid (27.6%) and lamotrigine (19.6%) were the most commonly used AEDs. Compared with children of fathers without epilepsy, children of fathers with epilepsy had higher rates of autism, ADHD and intellectual disability.

After adjusting for potential confounders, children born to fathers with epilepsy had 30% increased risk of autism, and 60% higher risk of ADHD and intellectual disability, compared to fathers without epilepsy. Offspring of fathers exposed to AEDs did not show an increased risk of adverse outcomes, compared with offspring of fathers not exposed to AEDs, neither for congenital malformation nor for NDD. Similarly, in the propensity-score adjusted analyses, no association was observed between AED exposure during conception and any of the outcomes. However, when restricting analyses to offspring born to fathers with epilepsy who used either valproate or carbamazepine in monotherapy, higher adjusted hazard ratios (aHRs [95% CI]) were observed for offspring exposed to valproate monotherapy (versus unexposed father with epilepsy) than in offspring exposed to carbamazepine (vs unexposed father with epilepsy) for ASD (VPA 1.4 [0.6,3.1]; CBZ 0.9 [0.4,1.9]), ADHD (VPA 1.4 [0.7,2.8]; CBZ 0.9 [0.4,1.9]), and intellectual disability (VPA 1.6 [0.5,5.1], CBZ 0.6 [0.1,2.9]), but all confidence intervals overlapped and included 1.

The study might be underpowered to detect an increased risk as there seems to be 576 children with paternal valproate exposure included (based on 27.6% of the total). The main finding of the study by Tomson et al (2020) was that offspring from fathers with epilepsy are at increased risk of NDD outcomes, compared to fathers without epilepsy, and this risk was not further increased in offspring paternally exposed versus unexposed to AEDs.

Veiby et al (2013)⁷ investigated whether exposure to AEDs affects early child development. Development in children of fathers with epilepsy was included as secondary objective. Different aspects of child development (motor development, language, social skills, autistic traits) were reported by the mothers at 18 months and 36 months using items from a standardized screening tool.

The study included 653 children of fathers with self-reported epilepsy. Regarding the risk for adverse development scores, data from 363 children with paternal epilepsy (n=216 unexposed to AEDs; n=147 exposed) were available at 18 months, and data from 282 children with paternal epilepsy (n=173 unexposed to AEDs; N=110 exposed) at 36 months. Compared to a reference group of children of parents who did not have epilepsy, children of fathers with epilepsy had higher risk of a positive screening on autistic traits and poor social skills if the father used AEDs compared to the reference group at 18 months, but not at 36 months. The article only reported paternal AED use, but did not specify which AEDs the fathers were exposed to.

The study by Veiby et al (2013) had several limitations, including small sample size, potential selection bias, use of self-reported measures of child development instead of clinical diagnosis, and follow-up limited to 36 months, and did not specifically look at valproate. Considering these limitations, this publication was not considered to add any relevant information regarding the association between exposure to AEDs and the risk of NDD.

The study by Tomson et al (2020) was more comparable to the current PASS, using population-based data sources and long follow-up time. However, important differences between the study by Tomson et al (2020) and the paternal PASS were that the study by Tomson et al (2020) used:

⁷ Veiby G, Daltveit AK, Schjølberg S, Stoltenberg C, Øyen AS, Vollset SE, Engelsen BA, Gilhus NE. Exposure to antiepileptic drugs in utero and child development: a prospective population-based study. *Epilepsia*. 2013 Aug;54(8):1462-72. doi: 10.1111/epi.12226. Epub 2013 Jul 19. PMID: 23865818; PMCID: PMC3766256.

- 1) A more narrow NDD definition (limited to ASD, ADHD, intellectual disability);
- 2) A more restricted patient population (only fathers with epilepsy indication were included);
- 3) A comparison between offspring paternally exposed to AED versus unexposed to AED, but no comparison between different AED exposures.

To conclude, only limited information regarding the association between paternal exposure to AEDs (valproate) and risk of NDD, including ASD, was available from literature.

Following the stakeholder meeting held on 16 November 2023, professor Jakob Christensen, representative of Epilepsiforeningen, a Danish patient organization for epilepsy, shared the confidential draft manuscript entitled "*Paternal use of valproate during spermatogenesis and risk of offspring congenital malformations and neurodevelopmental disorders – a Danish cohort study*".

At the time of authoring this AR, the authors were planning to submit the manuscript to a peer-reviewed journal for publication⁸. The data evaluated by the PRAC were preliminary information and the final analyses were published after the finalisation of this assessment report.

The study did not replicate the trend of an increased risk of NDD in children of fathers who used valproate in the 3 months before conception, as observed in the Danish results from the PASS.

The available results (main analysis) of the study by Christensen et al did not suggest an increased risk of NDD in children with paternal valproate exposure in the 3 months before conception compared to unexposed children (general population), with crude HR of 1.60 (1.31 – 1.97) and adjusted HR of 1.11 (0.90 – 1.37). When restricting the analysis to children of fathers with epilepsy, the adjusted HR was 1.16 (0.92 – 1.46). When comparing to lamotrigine exposure, an aHR of 1.00 (0.71 – 1.41) was observed. The aHR was 0.92 (0.62 – 1.36) for children of fathers who used valproate in 3 months before conception compared to children of fathers who filled prescription for valproate two years prior to the exposure period, but not during the exposure period.

Although the authors used data from a comparable data source and study period, they applied different methodologies compared to the MAH's consortium PASS, with regard to the inclusion and exclusion criteria, comparator cohorts, definitions used for NDD, type of analysis applied, confounders and risk factors considered. Clearly different inclusion and exclusion criteria resulted in different and larger cohorts in the study of Christensen et al compared to the PASS of the MAH's consortium.

The main comparator group used by Christensen et al, i.e. unexposed children, was not considered appropriate. Christensen et al aimed to rule out confounding by indication; however, in the views of the PRAC, the conducted analyses did not sufficiently address this concern.

In addition, the fathers included in both restricted analysis (epilepsy only) and active comparator analysis (lamotrigine) were not restricted to monotherapy, information on type of epilepsy of the fathers was not available and any potential differences in this regard between the treatment groups could introduce confounding by indication.

Important risk factors that may be associated with occurrence of NDD in children but were not considered by Christensen et al included the following (of note – these risk factors were included in the PASS conducted by the MAH's consortium):

- Maternal: obesity, smoking, alcohol abuse, rubella, CMV (Cytomegalovirus), diabetes;

⁸ Christensen J. et al, Valproate Use During Spermatogenesis and Risk to Offspring, JAMA Netw Open. 2024;7(6):e2414709. doi:10.1001/jamanetworkopen.2024.14709

- For maternal and paternal: substance abuse, medications associated with valproate-indicated psychiatric conditions, medications associated with neuropsychiatric adverse effects.

Whether the study was sufficiently powered to detect differences between the different treatment groups remained unaddressed by Christensen et al.

Also the duration of follow-up time per treatment group was not presented in the draft manuscript; differences in duration of follow-up between groups could impact the observed HRs in the study.

Based on the limited information provided on the study of Christensen et al in the draft manuscript a potential risk of NDD in children of fathers that used valproate in the three months before conception cannot be ruled out.

A review of **preclinical data including literature**, also provided by the MAH, showed that valproate may induce epigenetic changes. However, most of the preclinical literature related to possible epigenetic changes of male germ cells, and possible consequence of these changes on future offspring risk of NDD and behavioural changes, did not specifically involve epigenetic changes in germ cells or sperm or transferability to offspring, and mainly provided additional insight on epigenetic changes in vitro or direct exposure to offspring during pregnancy.

Only one study (**Sakai et al, 2023⁹**) specifically investigated the possibility of paternally transferred epigenetic changes to offspring and possible resulting behavioural changes in mice. Study limitations (non-appropriate methods for behavioural tests, lenient statistical methods) preclude a definite statement. Overall, the available literature is not robust enough to draw conclusions regarding paternally transferred epigenetic changes to offspring at this time. A non-clinical study to evaluate valproate-induced epigenetic changes, as requested by the PRAC (Cat 1) in the framework of the referral procedure under article 31 of Directive 2001/83/EC completed in 2018, has been initiated by the originator MAH. The first report from this study was expected in Q4 2023. The final study report is expected in 2025. It is anticipated that this study will provide more robust information on the possibility of paternally transferred valproate epigenetic mediated changes to the offspring.

Input from external stakeholders and experts involved in the treatment of male patients with valproate was obtained, to collect their views on the proposed routine and additional RMM, their impact in routine clinical practice, and to determine the most appropriate RM strategy, during the meetings held on **16 November** and **4 December 2023**, respectively.

Overall, experts agreed that the strength of the evidence for NDD with paternal valproate exposure was rather low, given different uncertainties (i.e. uncertain potential mechanism and unknown risk outside the exposure window) and study limitations.

However, as outlined in both meetings, there was an overall agreement on the need to inform HCPs and patients about the results of the retrospective cohort study conducted in the Nordic countries by the MAH. As triggered by the seriousness of the potential increased risk of NDD (including ASD) noted in children born to men treated with valproate, it was considered that a precautionary approach would be justified, despite paucity of data and study limitations, and while waiting for additional analyses to gain further insights on the robustness of current information. At the same time, it was deemed necessary to contextualise available data, and ensure that balanced information would be disseminated to HCPs and patients.

⁹ Sakai K, Hara K, Tanemura K (2023) Testicular histone hyperacetylation in mice by valproic acid administration affects the next generation by changes in sperm DNA methylation. PLoS ONE 18(3): e0282898. <https://doi.org/10.1371/journal.pone.0282898>

Furthermore, the risk to impact and dilute the message already disseminated for WCBP and pregnant women should be avoided, as in this case there is a much higher degree of certainty. All participants fully supported the importance for HCPs to discuss effective contraception with patients.

As also outlined by clinical experts during the scientific advisory group (SAG) neurology, switching from valproate treatment is very difficult to implement. The decision about switching treatment should ultimately be left to the patient, after careful discussion with his prescriber on the benefits and risks of each available therapeutic option.

With regard to the patient card, supported by a considerable number of participants (although a need to complement it with other RMM, e.g. patient or HCPs guide, was also considered), it was overall agreed to update this very impactful and (one of the) most powerful RMM with a view toward ensuring that new information targeting males is proportionate (to the magnitude and strength of the evidence for this risk) and that it does not affect or dilute the important message for WCBP, already outlined via this educational tool for females. In addition, it was overall agreed that restricting initiation and supervision of valproate prescription for male patients to specialists experienced in the management of epilepsy or bipolar disorder would be sensible, safe and ensure consistency of treatment(s) across EU MSs, although it was recognised that, in some clinical settings, practical implementation would be difficult (i.e. due to major capacity issues); therefore, it was concluded that flexibility should be applied.

Following input from stakeholders and experts, the PRAC considered that the need to annually review all male patients is not risk proportionate in view of the magnitude and strength of the evidence for the risk. The need for periodic review can be decided by the prescribers and the advice to regularly review male patients, as appropriate, was considered sufficient. In addition, considering the uncertainties and compared to the much higher risks observed with in utero exposure, the monitoring advices included in PI and educational materials, as proposed below, were considered adequate and proportionate and therefore sufficient.

Scientific conclusions and grounds for variation to the terms of the marketing authorisation(s)

Having considered the results of the PASS final report, imposed to the MAH's of medicinal product(s) containing valproate and related active substances in the European Union (EU), in the framework of the Article 31 referral completed in 2018¹⁰, together with non-clinical, literature data to date, the input of external stakeholders (including representative of patients and HCP organisations) and clinical experts who attended at the SAG neurology (enriched with psychiatry expertise), as agreed during the plenary meeting held on **8-11 January 2024**, the PRAC scientific conclusions are as follows.

The results of the population-based, retrospective cohort study using databases from Denmark (DK), Sweden (SE) and Norway (NO), conducted to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders (NDD), including autism spectrum disorders (ASD), as well as congenital malformations (CM) in the offspring, suggested an increased risk of NDD, including ASD, but no difference in the risk of congenital malformations in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine or levetiracetam. A trend for an increased risk of NDD (including ASD), although not significant in the three individual countries, was apparent in the data from NO, SE and DK, and the combined data from these three countries showed a borderline statistically significant increased risk. However, taking into consideration the study limitations, including potential confounding by indication and differences in follow-up time between exposure

¹⁰Valproate referral 2018
(http://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-prac-recommends-new-measures-avoid-valproate-exposure-pregnancy_en.pdf)

groups, together with (limited) information from other sources, and the input of external stakeholders and clinical experts, the risk was considered by PRAC as potential (i.e. causality has not been established).

Considering the seriousness of the NDDs (including ASD) and their life-long impact on children and families, the PRAC also concluded that the study findings, including their uncertainties, should be communicated to patients and healthcare professionals (HCP) and confirmed that current available data were sufficient to justify applying precautionary, risk proportionate, measures, also in light of the confirmed and higher risk for children following *in utero* exposure to valproate. The input obtained from clinical experts and stakeholders also supported the PRAC's conclusion on the request to the MAH to address the uncertainty of this potential risk, via (new) additional analyses (including subgroup analyses and stratification), as part of a new category 1 PASS with appropriate milestones.

In light of all the above, with regard to male patients, the PRAC recommended to **update the product information** of medicinal products containing valproate and related substances to include that / with:

- It is recommended that valproate is initiated and supervised by a specialist experienced in the management of epilepsy <or> bipolar disorder <or> migraine>. Specialists are generally best aware of prescribing conditions and they are best placed to (re-)evaluate the need for initiating or continuing treatment with valproate or the need to switch to other medication, in case of a wish for fathering a child.
- The need for a regular review by a specialist to evaluate whether valproate is (still) the most suitable treatment and to remind the male patient about the potential risk for NDD (including ASD) with valproate when used during conception and talk about whether the male patient wishes to conceive a child. The need and frequency of such review can be decided by the patient and HCP, considering the patient's need and individual circumstances.
- Information on the potential risk of NDD in the offspring born to fathers using valproate around the conception period, including the recommendation for prescribers to inform patients on the potential risk, discuss the need to consider effective contraception in male patients using valproate (and their female partner), advice male patients to consult their specialist when they are planning to conceive a child and before discontinuing contraception, and to consider the possibility of treatment alternatives in case the male patient using valproate is planning to conceive a child. Male patients should also be advised to not donate sperm while on valproate treatment, and for at least 3 months after treatment discontinuation.
- Educational materials are made available for healthcare professionals and patients. A patient guide should be provided to male patients using valproate.

The PRAC also recommended the following **additional risk minimisation measures**:

- To update the existing HCP guide with a dedicated section on male patients, to inform HCPs about the potential risk of NDD (including ASD) following paternal exposure to valproate and the advices to provide to male patients and their female partners. An updated English 'core version of the HCP guide' with a dedicated section on use of valproate in male patients is agreed by the committee, to complement the current version, focussed on the pregnancy prevention program for girls and women of childbearing potential.
- To update the valproate patient card with information on the potential risk of NDD after paternal exposure to valproate. This card, attached to the outer packaging, ensures distribution of

information to all patients each time valproate is dispensed. In addition, it facilitates pharmacists to remind patients about risks associated with the product without the need to distribute materials themselves.

- A new, dedicated guide for male patients to inform and facilitate a discussion of the risks. As only limited information could be included in the existing patient card, PRAC considered critical that patients are well informed about the potential risk to the offspring when valproate is used around the time of conception and advised on how to minimize this risk. The patient guide should explain the available evidence, uncertainties about the risk, and detail considerations for valproate use in male patients. As the key messages to be addressed in this patient educational material (EM) for males differ from the key messages addressed in the material for females, a separate guide for male patients was deemed necessary by PRAC.

The PRAC recommended distribution of a **DHPC** to inform HCPs about the potential risk of valproate in male patients, the need to inform current male valproate users about the potential risk and the need to consider a treatment review in these male patients, the proposed recommendations, and PI updates.

All MAHs should submit an updated RMP, within 3 months after completion of procedure EMEA-H-N-PSR-J-0043, to reflect that the paternal PASS was completed, the results of this study and all routine and additional RMM agreed by the PRAC in the current procedure are reflected accordingly. The new category 1 PASS, as recommended above, should also be included in the document.

Further actions for the MAHs:

- The MAHs are strongly encouraged to publish the results of this PASS in a scientific journal: sharing the study results would be helpful and relevant for future research.
- With regard to the additional analyses, a study protocol should be provided for PRAC review and approval within 6 months after finalisation of the current procedure. The additional analyses should be performed as part of a new category 1 PASS, addressing the following questions:

Question 1

To increase the power of the study, the PRAC recommends to not exclude children from parents with a history of neurodevelopmental disorders (NDD) or congenital malformations (CM) from the cohort but instead to control for the risk factor “parents with a history of NDD or CM” in the analysis. This approach may increase the power of the additional analyses including subgroup and stratified analyses. The results of the main analysis for this approach should also be provided, in order to allow comparison and interpretation.

Question 2

In the construction of the PS models, the MAH reports that variables enter the model based on their univariate association with the outcome of interest. The advantage of using a PS is that one is not restricted in the number of covariates that are put into the model. Besides that, there may be important interactions between covariates that play a role, which will be left out when variables only enter the model based on their univariate associations with the outcome. This is not the preferred method to use; therefore, the main analyses for the primary (NDD including autism spectrum disorders - ASD) and secondary outcome (CM) should be rerun in all databases without this preselection of variables (i.e. all identified risk factors for the outcome - all variables that affect the outcome of interest regardless whether they are determinants of treatment - [from literature] should be put in the PS model at the same time). To minimize the effort, it would be enough to restrict this to PS model 1. Afterwards, the balance should be assessed and the main results should be recalculated, and pooled together.

Question 3

To gain further insight regarding the distribution of different types of epilepsy among the treatment groups, the MAH should provide an overview of the distribution of different ICD-10 subcodes for epilepsy (i.e. G40.0 – G40.9 and G40.A, G40.B) in all treatment groups (valproate, lamotrigine, levetiracetam, lamotrigine/levetiracetam) and for all countries.

Question 4

Considering the potential for confounding by indication, the MAH should present the results for the primary outcome (cumulative incidence proportions, cumulative incidence rates, and effect estimates) stratified for epilepsy versus other indications (bipolar disorder/unknown).

Question 5

The MAH should provide an additional analysis in 'former users', i.e. to compare children of fathers **ever** exposed to valproate **with at least 3 consecutive prescriptions** up to 3 months prior to conception (**not during** 3 months prior to conception) with children of fathers ever exposed to levetiracetam/lamotrigine use but not during 3 months prior to conception. This could provide more information regarding potential effects of valproate outside the spermatogenic risk window and possible reversibility of effects.

Question 6

With the aim to gain more information regarding the potential confounding by indication, the MAH should provide the main analysis but compare to a new comparator group (i.e. to compare children born to fathers who used valproate 3 months before conception with children whose fathers used valproate up to 1 year after conception and never used valproate before conception).

Question 7

In the main analysis used for the primary outcome, all cases with at least 1 ICD-10 code of NDD were included. The MAH should include an additional sensitivity analysis for the primary outcome in which only 'probable' cases are included by applying the following definition "if multiple diagnostic codes for the same respective disorder" (please see L Straub et al Validity of claims-based algorithms to identify neurodevelopmental disorders in children 2021. Pharmacoepidemiology and drug safety).

Question 8

- a. Although the PS-weighted models were adjusted for follow-up time, it is acknowledged that a single average hazard ratio (HR) does not take into account distribution of events during the period of follow-up, which was longer in the valproate group compared to the lamotrigine/levetiracetam exposed group. According to the MAH, the feasibility of constructing adjusted Kaplan-Meier curves is questionable due to the low number of events observed across the 3 countries. However, as noted by the MAH when discussing sensitivity analysis 2 (outcome limited to ASD only), several other methods could be used to provide further information. For the composite endpoint NDD including ASD, approximately 100 events have been observed per country across exposure groups. Thus, some stratification or analyses taking into account follow-up time could have been presented. For example, in addition to the overall HR (currently provided for 0-12 years) the MAH should present average HRs across different periods of follow-up time (e.g. 2 years, 5-6 years, 7-8 years, overall). Similarly, as noted by the MAH in their discussion, there may be several time points that may be clinically relevant for diagnosis of NDD including ASD (<2 years, 4-5 years, 7-8 years, overall) and the MAH discussed the option of performing restricted mean survival analysis (RMST), but no results of such analyses have been provided. Therefore, the MAH should provide an additional discussion regarding the feasibility to further investigate analyses adjusted for/taking into account follow-up time, and present the results of such analyses when feasible.

- b. The MAH should perform an analysis stratified on calendar year of birth in suitable categories, (e.g. 2 or 3 years) per database and pooled for the three databases, including:
 - i. Median follow-up time per exposure group per calendar year of birth (or suitable periods in calendar time) per database and pooled for the three databases.
 - ii. Median age at time of NDD diagnosis (i.e. second diagnostic code for NDD in time) per exposure group per calendar year of birth (or suitable periods in calendar time) per database and pooled for the three databases.
 - iii. HR for NDD in offspring with valproate paternal exposure at conception per calendar year of birth (or suitable periods in calendar time) per database and pooled for the three databases.

Question 9

To gain further insight in the distribution of diagnoses across follow-up time, the MAH should provide for each country, what percentage of NDD (including ASD) has been diagnosed at the mean follow-up time in the valproate group, and also with which follow-up time 60-80-100% of all NDD incl ASD could be diagnosed, and what percentage of the comparator group would have a minimum follow-up time up to that point. If feasible, this should also be done for the narrow composite NDD including ASD endpoint (sensitivity analysis 11) and ASD only endpoint (sensitivity analysis 2). Pending these group sizes, stratification of results by minimum follow-up time may also provide more insight into the potential impact of differences in follow-up time between the valproate and lamotrigine/levetiracetam group. The MAH should also perform restricted analyses in treatment cohorts with a similar time of follow up and a similar chance of being diagnosed with the event of interest, e.g. by starting follow-up time from 2010 onwards (i.e., when lamotrigine/levetiracetam treatment became commonly used in the clinical practice).

Question 10

A composite outcome (major + minor CM) was used for the secondary outcome. The MAH should also provide cumulative incidence proportions and effect estimates for major CM only. The outcome major congenital malformations should cover all offspring (live and non-live offspring) with at least one ICD-10 code for a major congenital malformation, meaning that an offspring with both major and minor congenital malformations should be considered in the outcome "major congenital malformation". The EUROCAT classification might be used to identify the major congenital malformations
[Full Guide 1 4 version 28 DEC2018.pdf \(europa.eu\)](#).

Further actions for National Competent Authorities (NCAs):

To enhance awareness in clinical practice, NCAs might consider additional tools (including relevant journals) and tailored initiatives at national level to foster dissemination of information on the potential risk of NDD in children of fathers treated with valproate and the advice for HCP and patients.

3. Final Recommendations

Based on the PRAC review of the PASS final study report, including the corrigendum version 1.0 (with updated meta-analysis based on the corrected Norwegian dataset) and addendum version 2.0 to the final study version 1.1, the MAH responses to the outstanding requests for information, and the input from the stakeholders' and the scientific advisory group (SAG neurology enriched with psychiatry expertise) meetings and Member States comments, as discussed during the plenary meetings held on 10-12 May 2023, 5-8 June 2023, 3-6 July 2023, 25-28 September 2023, 23-26 October 2023 and 8-11 January 2024, the PRAC considered that:

☒ the risk-benefit balance of medicinal products containing the active substance valproate concerned by the PASS final report (including Corrigendum version 1.0 and addendum version 2.0 to the final study report version 1.1) remains unchanged but recommends that the terms of the marketing authorisation(s) should be varied as follows:

The following changes to the product information of medicinal products containing the active substance valproate are recommended, in SmPC sections 4.2, 4.4 and 4.6, and PIL section 2 and 3 (new text **underlined and in bold**, deleted text in ~~striketrough~~):

Summary of Product characteristics

[...]

4.2 *Posology and method of administration*

Posology

[...]

Female children and women of childbearing potential

<Invented name> must be initiated and supervised by a specialist experienced in the management of epilepsy <or> bipolar disorder or <migraine>. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (sections 4.3 and 4.4).

The benefit and risk should be carefully reconsidered at regular treatment reviews.

Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Males

It is recommended that <Invented name> is initiated and supervised by a specialist experienced in the management of epilepsy <or> bipolar disorder <or migraine> (see sections 4.4 and 4.6).

Patients with renal insufficiency

[...]

Method of administration

[...]

4.4 *Special warnings and precautions for use*

Pregnancy Prevention Programme

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

<Invented name> is contraindicated in the following situations:

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.6).

Treatment of bipolar disorder <and prophylaxis of migraine attacks>

- in pregnancy (see sections 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:

The prescriber must ensure that

- Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy, or bipolar disorders <or migraine>.
- the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her physician in case of pregnancy.
- the patient has received the patient guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

- The prescribers must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Estrogen-containing products

Concomitant use with estrogen-containing products, including estrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing estrogen-containing products.

On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist

The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss the annual risk acknowledgement form, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning.

For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

For the indication bipolar disorder <and> <migraine> if a woman is planning to become pregnant a specialist experienced in the management of bipolar disorder <and> <migraine> must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

In case of pregnancy

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. The patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in <teratology> {to be adapted depending on health care system} for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacist must ensure that

- the patient card is provided with every valproate dispensing and that the patients understand its content.
- the patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide and patient card should be provided to all women of childbearing potential using valproate.

An annual risk acknowledgement form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Use in male patients

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section 4.6).

As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

[...]

4.6 Fertility, pregnancy and lactation

Pregnancy and women of childbearing potential

[...]

Teratogenicity and developmental effects from in utero exposure

Pregnancy Exposure Risk related to valproate

In females, Both valproate monotherapy and valproate polytherapy including other antiepileptics are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate. Valproate was shown to cross the placental barrier both in animal species and in humans (see section 5.2).

In animals: teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

*Congenital malformations **from in utero exposure***

[...]

*Neurodevelopmental disorders **from in utero exposure***

[...]

If a woman plans a pregnancy

[...]

Pregnant women

[...]

Risk in the neonate

[...]

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate is the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Breast-feeding

[...]

Fertility

[...]

Package Leaflet

[...]

2. What you need to know before you <take> <use> X

[...]

Pregnancy, breast-feeding and fertility

Important advice for women

Bipolar disorder <and> <migraine>

- For bipolar disorder <and> <migraine>, you must not use <Invented name> if you are pregnant.

For bipolar disorder <and> <migraine>, if you are a woman able to have a baby, you must not take <Invented name>, unless you use effective method of birth control (contraception) during your entire treatment with <Invented name>. Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further.

Epilepsy

- For epilepsy, you must not use <Invented name> if you are pregnant, unless nothing else works for you.
- For epilepsy, if you are a woman able to have a baby, you must not take <Invented name> unless you use effective method of birth control (contraception) during your entire treatment

with <Invented name>. Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further.

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, including when valproate is used in combination with other medicines to treat epilepsy.
- It can cause serious birth defects and can affect the physical and mental development of the child as it grows after birth.
- The most frequently reported birth defects 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. Because valproate has been used for many years we know that in women who take valproate around 11 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate during pregnancy and there is some evidence that children exposed to valproate during pregnancy are at increased risk of developing Attention Deficit Hyperactivity Disorder (ADHD).
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a baby you must not stop taking your medicine or your method of contraception until you have discussed this with your doctor.
- Some birth control pills (oestrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your doctor about the method of birth control (contraception) that is the most appropriate for you.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact the doctor once your child using valproate experiences menarche.
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use

Please choose and read the situations which apply to you from the situations described below:

- ☐ **I AM STARTING TREATMENT WITH <INVENTED NAME>**
- ☐ **I AM TAKING <INVENTED NAME> AND NOT PLANNING TO HAVE A BABY**
- ☐ **I AM TAKING <INVENTED NAME> AND PLANNING TO HAVE A BABY**
- ☐ **I AM PREGNANT AND I AM TAKING <INVENTED NAME>** Error! Bookmark not defined.

I AM STARTING TREATMENT WITH <invented name>

If this is the first time you have been prescribed <Invented name> your doctor will have explained the risks to an unborn child if you become pregnant. Once you are able to have a baby, you will need to make sure you use an effective method of contraception without interruption throughout your treatment with <Invented name>. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- Pregnancy must be excluded before start of treatment with <Invented name> with the result of a pregnancy test, confirmed by your doctor.
- You must use an effective method of birth control (contraception) during your entire treatment with <Invented name>.

- You must discuss the appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control.
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder or epilepsy <or> <migraine>. During this visit your doctor will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKING <invented name> AND NOT PLANNING TO HAVE A BABY

If you are continuing treatment with <Invented name> but you are not planning to have a baby make sure you are using an effective method of contraception without interruption during your entire treatment with <Invented name>. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- You must use an effective method of birth control (contraception) during your entire treatment with <Invented name>.
- You must discuss contraception (birth control) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control.
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder or epilepsy <or> <migraine>. During this visit your doctor will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKING <invented name> AND PLANNING TO HAVE A BABY

If you are planning to have a baby, first schedule an appointment with your doctor.

Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. Your doctor will refer you to a specialist experienced in the management of bipolar disorder <migraine> or epilepsy, so that alternative treatment options can be evaluated early on. Your specialist can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your specialist may decide to change the dose of <Invented name> or switch you to another medicine, or stop treatment with <Invented name>, a long time before you become pregnant – this is to make sure your illness is stable.

Ask your doctor about taking folic acid when planning to have a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Do not stop taking <Invented name> unless your doctor tells you to.
- Do not stop using your methods of birth control (contraception) before you have talked to your doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced.
- First schedule an appointment with your doctor. During this visit your doctor will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Your doctor will try to switch you to another medicine, or stop treatment with <Invented name> a long time before you become pregnant.
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USING <INVENTED NAME>

Do not stop taking <Invented name>, unless your doctor tells you to as your condition may become worse. Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating.

You will be referred to a specialist experienced in the management of bipolar disorder, or epilepsy, so that alternative treatment options can be evaluated.

In the exceptional circumstances when <Invented name> is the only available treatment option during pregnancy, you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing. You and your partner could receive counselling and support regarding the valproate exposed pregnancy.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.
- Do not stop taking <Invented name> unless your doctor tells you to.
- Make sure you are referred to a specialist experienced in the treatment of epilepsy or bipolar disorder <or> migraine> to evaluate the need for alternative treatment options.
- You must get thorough counselling on the risks of <Invented name> during pregnancy, including teratogenicity (birth defects) and physical and mental development disorders in children.
- Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations.

[This sentence below should be adapted to National requirements]

Make sure you read the patient guide that you will receive from your doctor. Your doctor will discuss the Annual Risk Acknowledgement Form and will ask you to sign it and keep it. You will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.

<If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your <doctor> <or> <pharmacist> for advice before taking this medicine.>

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

A study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known. The study has limitations and therefore it is not clear if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. The study was not large enough to show which particular type of movement and mental developmental disorder children may be at risk of developing.

As a precautionary measure, your doctor will discuss with you:

- **The potential risk in children born to fathers treated with valproate**
- **The need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment**
- **The need to consult your doctor when you are planning to conceive a child and before stopping contraception (birth control)**

- **The possibility of other treatments that can be used to treat your disease, depending on your individual situation**

Do not donate sperm when taking valproate and for 3 months after stopping valproate.

Talk to your doctor if you are thinking about having a baby.

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your doctor. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber. During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Make sure you read the patient guide that you will receive from your doctor. You will also receive a Patient Card from your pharmacist to remind you of the potential risks of valproate.

3. How to take <invented name>

[...]

Female children and women of childbearing potential

<Invented name> treatment must be started and supervised by a doctor specialised in the treatment of <epilepsy> <or> <bipolar disorder> <or> <migraine>.

Male patients

It is recommended that <Invented name> is initiated and supervised by a specialist experienced in the management of epilepsy <or> bipolar disorder <or migraine>- see section 2 Important advice for male patients.

Additional risk minimization measures

The following additional risk minimisation measures are recommended for medicinal products containing the active substance valproate*:

Updated HCP Guide

An updated English 'core version of the HCP guide' with a dedicated section on use of valproate in male patients.

New Patient Guide for male patients

A new English 'core version of the patient guide for male patients' to fully inform male patients about the risk of valproate and the recommended actions.

Updated Patient Card

An updated 'core version' of the patient card*, 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, to reflect information on the potential risk of NDD in children whose fathers have used valproate in the 3 months before conception.

* The patient card is not required for injectable formulations, in line with referral finalised in 2018, see [Valproate - Art 31 referral - EMEA/H-A31/1454 \(europa.eu\)](#).

The updated core version of the patient card is presented below:

Patient Card for Valproate <invented name>

What you must know and do

All girls and women using valproate and who could become pregnant:

- Valproate can seriously harm an unborn child when taken by the mother during pregnancy.
- Always use effective contraception without interruption during the entire duration of treatment with valproate.
- If you think you are pregnant: Schedule an urgent appointment with your doctor.
- Visit your specialist at least each year.

Males using valproate:

- There is a possible risk of movement and mental developmental disorders in children when valproate is taken by the father in the 3 months before conception.
- Discuss this possible risk and the need for effective contraception with your doctor.

----- Other side -----

Patient Card for Valproate <invented name>

What you must know and do

- Valproate is an effective medicine for epilepsy and bipolar disorder <and migraine>.

This applies to all girls and women using valproate who could become pregnant and males using valproate:

- Read the package leaflet carefully before use.
- Never stop taking valproate unless your doctor tells you to as your condition may become worse.
- If you are thinking about having a baby, do not stop using valproate and contraception before you talked to your doctor.
- Ask your doctor to give you the patient guide. {Subject to national implementation:}[<More information about valproate use can be found at <webpage>.]

Keep this card safe so you always know what to do

Final versions of all educational materials should be implemented at national level in agreement with the NCA.

DHPC

A DHPC to inform HCPs about the results of the paternal PASS study, the PI updates and the implementation of aRMM for male patients should be distributed, in accordance with the agreed communication plan.

The DHPC and the DHPC communication plan can be found [here](#).

Risk Management Plan

All MAHs of valproate-containing products in the EU should submit an updated RMP, within 3 months after completion of procedure EMEA-H-N-PSR-J-0043, in order to:

- Reflect that the paternal PASS is completed, the results of this study and all (routine and additional) RMM agreed within procedure EMEA-H-N-PSR-J-0043 are outlined in the document. The new category 1 PASS, as recommended below, should also be included.

Conditions of the marketing authorisation

The marketing authorisation holder(s) (MAHs) shall complete the following condition(s) within the stated timeframe:

The MAHs of medicinal products with substances related to valproate shall conduct a new non-interventional post-authorisation safety study to provide the results of the additional analyses requested in the framework of the assessment of the results of study EUPAS34201, in order to further investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders (including autism) in the offspring. Protocol to be submitted to the PRAC in accordance with Article 107n (1) of Directive 2001/83/EC: The final study report shall be submitted to the PRAC:	Within 6 months of the CMDh position / commission decision. Within 1 year of the endorsement of the study protocol.
The MAHs of medicinal products with substances related to valproate shall develop and submit educational materials according to the agreed core elements. These materials should ensure that prescribers are informed and the patients understand the potential risk associated with paternal exposure to valproate. These should be submitted to the National Competent Authorities:	Within 3 months of the CMDh position / Commission decision.
All MAHs should update their RMP and submit it to the relevant national Competent Authorities through an appropriate procedure. The RMP should reflect: - Neurodevelopmental disorders in children born to fathers treated with valproate before conception as an important potential risk - That category 1 paternal PASS is completed - The new category 1 study in order to further investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders (including autism) in the offspring	Within 3 months of CMDh position / Commission decision.

- The additional risk minimization measures related to valproate use in male patients: - o Patient guide for male patients - o Updated core version of HCP guide - o Updated core version of patient card	
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4. Other considerations

☒ The recommendations proposed by the PRAC 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.