Medicines & Healthcare products Regulatory Agency

Paternal exposure to valproate and risk of neurodevelopmental disorders and congenital malformations in offspring

Review of results from a Scandinavian post-authorisation safety study (PASS)

Public Assessment Report

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Contents

1. Plain Language Summary

Key messages:

Valproate (as sodium valproate, valproate semisodium, or valproic acid; brand names Epilim, Depakote, Convulex, Episenta, Epival, Syonell, Belvo and Dyzantil) is approved in the UK to treat epilepsy and bipolar disorder. It is also sometimes used outside of the licence (‘off label’) to treat other conditions.

The results of a retrospective observational study indicates a possible association between valproate use by men around the time of conception and an increased risk of neurodevelopmental disorders in their children, when compared to men prescribed lamotrigine or levetiracetam.

Men who may father a child should be informed of this potential risk at initiation and at their next treatment review.

As a precautionary measure, it is now recommended that male patients and their female partner should use effective contraception during valproate use and for at least 3 months after stopping valproate. Healthcare professionals should offer male patients a discussion of this potential risk, either during their next scheduled review or as a priority in any male patients who are planning to father a child in the next year. The discussion should also cover the impact on their current treatment, and other treatment options available.

No-one should stop valproate without advice from their healthcare professional.

Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) regulates medicines, medical devices and blood components for transfusion in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. The Commission on Human Medicines (CHM) advises government ministers and the licensing authority on the safety, efficacy and quality of medicines.

This report presents the review of the results of a study on the potential risk to children born to men who took valproate in the 3 months before conception, and the steps that the MHRA are taking to implement new safety measures in consultation with the clinical community and other stakeholders.

More information about this medicine

Valproate is a medicine used in the management of epilepsy and in bipolar disorder. Epilepsy is a medical condition that affects the brain generally leading to a tendency to have seizures. There are many different types of epilepsy, which can have different causes. People with bipolar disorder experience periods of depression (feeling very low and lethargic) and mania (feeling very high and overactive), and often a mixture of these. The high and low phases of bipolar disorder often interfere with everyday life and there are options for treating bipolar disorder that can help with minimising these.

Due to the known risks of valproate in pregnancy, a number of measures have been taken to reduce the risk of a developing baby being exposed to this medicine. In 2018 the valproate Pregnancy Prevention Programme was introduced following a review by the MHRA and across Europe. See Drug Safety Update from April 2018 for more information.

During the 2018 review, a number of concerns were also considered about risks in other patient groups, not only women of childbearing potential, and these included the potential risks to babies born to fathers who take valproate (paternal risks), as well as the possible side effects of valproate being passed down through more than one generation (intergenerational or transgenerational effects). European studies were started to provide further data on paternal risks and any intergenerational or transgenerational effects of valproate. More information on the 2018 review is available in the summary from the European Medicines Agency.

The MHRA and the CHM have kept the safety of valproate in male patients under review. Concerns in male patients include the effect valproate can have on fertility, which can make it difficult to father a child, and studies in animals which have shown valproate to have toxic effects on the developing testicles. The MHRA published the review of valproate safety data and expert advice on management of risks in 2023.

In January 2024, the way that medicines containing valproate can be prescribed changed. Valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. Patients and healthcare professionals must discuss the risks as well as the benefits of treatment and complete a risk acknowledgement form. Further information can be found in the Drug Safety Update from January 2024.

Reasons for the latest review and information considered

One of the studies that started following the 2018 European review was completed and submitted to the MHRA and other regulators in 2023 by the marketing authorisation holders. This study looked at electronic medical records in Norway, Denmark and Sweden and

compared children born to men prescribed valproate with those prescribed two other medicines for epilepsy, lamotrigine and levetiracetam. The study looked at neurodevelopmental disorders (mental and movement related development disorders) and congenital malformations (abnormalities that develop in a baby during pregnancy) in the children.

The latest review considers in detail the design and results of that study and other data submitted by the marketing authorisation holders relevant to the question of transmission of harm from valproate via the father to his children.

The MHRA reviewed the risks and considered options on how best to minimise harm to the UK public. The review is presented in this report, alongside the advice of the CHM and how the MHRA took on their advice.

How the CHM reached their conclusions

The CHM considered the MHRA review of the study and additional data and the advice of the Pharmacovigilance Expert Advisory Group at their meeting in February 2024. The CHM was asked to advise on the strength of evidence for an association between fathers using valproate and the risk of neurodevelopmental disorders and congenital malformations in the child and whether there were other data sources that could help answer the question.

Conclusions of the review

The CHM considered the results of the study which showed that around 5 out of 100 children had a neurodevelopmental disorder when born to fathers treated with valproate compared with around 3 out of 100 when born to fathers treated with lamotrigine or levetiracetam. The study did not find an increased risk of congenital malformations (birth defects) with valproate compared to lamotrigine or levetiracetam.

The CHM noted the limitations of the study and concluded that whilst the study did not prove that valproate caused neurodevelopmental disorders in the children of fathers taking valproate when the child was conceived, it equally did not disprove causality.

The CHM therefore concluded that as a precaution, the results of the study should be added to the Summary of Product Characteristics for healthcare professionals and the Patient Information Leaflet, and that advice should be issued to healthcare professionals and patients.

Advice from CHM

The CHM advised the following measures on the basis of the study:

Men and their female partners should both use effective birth control while taking valproate and for at least 3 months after stopping.

Men should not donate sperm while taking valproate and for at least 3 months after stopping.

Men who are taking valproate and planning to father a child in the next year should discuss the risk of neurodevelopmental disorders and treatment options with their prescriber.

Next steps

If you are a patient on valproate, please discuss any concerns you have with your healthcare professional. No one should stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may become worse without treatment, which can be harmful.

We have issued an article in Drug Safety Update to inform healthcare professionals of the results of the new study and the advice to provide to male patients taking valproate. We have also issued a release on the MHRA website to provide further details of our advice.

We are updating the Summary of Product Characteristics and Patient Information Leaflet in line with the advice of the CHM and working with patients and experts to develop further communications to help male patients on valproate to make fully informed decisions about their treatment.

2. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines, medical devices and blood components for transfusion in the UK. The MHRA is responsible for making sure these products meet acceptable standards for safety, quality and efficacy. The Commission on Human Medicines (CHM) advises the government about medicines safety. The CHM is independent – it is not part of the government or the pharmaceutical industry.

In our safety Public Assessment Reports, we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

Public Assessment Reports relating to previous reviews of valproate were published by the European Medicines Agency in October 2014 and February 2018, and by MHRA in November 2023.

This report presents the MHRA's review of a Post Authorisation Safety Study (PASS) commissioned by the European Medicines Agency (EMA) in 2018, which reports an increased risk of neurodevelopmental disorders in children born to fathers taking valproate three months prior to and at the time of conception, and expert advice on the management of risks, as advised on by the CHM and its Pharmacovigilance Expert Advisory Group (PEAG). Changes have been made to the ordering and wording used in the original assessment report to aid readability and presentation.

A glossary is provided for an explanation of the terms used in this report.

The information and analyses contained in this report reflect evidence that was available at the time of the completion of the review in February 2024. The MHRA will continue to monitor the safety of valproate closely and will seek the advice of the CHM as required, however the information in this report will not be actively updated with new data or studies.

3. Background

3.1 Pharmacological properties

Valproic acid was synthesised as a derivative of valeric acid. It was mainly used as a solvent for organic compounds until the 1960s, when it was discovered to have anticonvulsant properties.

The active ingredients in the authorised medicines are either sodium valproate, valproic acid or valproate semisodium. Valproate semisodium, is a stable coordination compound comprised of sodium valproate and valproic acid in a 1 to 1 molar relationship. It is also known as divalproex sodium. The term valproate is used throughout this report to cover all of these active ingredients.

The most likely mode of action for valproate is thought to be potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the synthesis or metabolism of GABA. 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. Valproate also acts on calcium channels.

3.2 Authorisation and monitoring of valproate in the UK

The first application for valproate was received by the marketing authority which at the time was the Department for Health and Social Security (DHSS), in 1971, and considered by the Committee of Safety of Medicines (CSM). In January 1972, the CSM Sub-Committee on Toxicity and Clinical Trials reported that clinical studies of valproate did not show adequate evidence of safety and efficacy, and further toxicological and teratological data was required. After requesting further clinical data, in May the same year, they concluded that they were unable to advise granting the licence, due to inadequate data on toxicology and teratology. Specifically, they raised concerns about this data “in view of the expected long term administration of the drug”. The following month, the Sub-Committee reported that they had received sufficient data to grant a conditional licence for a year, limiting valproate use to hospitals and other specialist centres for epilepsy, provided all patients were monitored for therapeutic efficacy and safety, and the results reported to the licensing authority.

Since licensing, due to the evolving evidence of the risks of valproate in pregnancy, a number of measures have been taken to reduce the risk of a developing baby being exposed to this medicine. In 2018 the valproate Pregnancy Prevention Programme was introduced following a review by the MHRA and across Europe.

During the 2018 review, a number of concerns were also considered about risks in other patient groups, not only women of childbearing potential, and these included the potential risks to babies born to fathers who take valproate (paternal risks), as well as the possible side effects of valproate being passed down through more than one generation (intergenerational or transgenerational effects). European studies were started to provide further data on paternal risks and any intergenerational or transgenerational effects of valproate.

3.3 Post-authorisation Safety Study on Paternal Transmission of Risk with Valproate

In early 2023, MHRA received the results of a study, which had been commissioned by the European Medicines Agency, on outcomes in children whose fathers took valproate in the 3 months prior to conception. However, errors were subsequently identified in the original data which required reanalysis. Following the reanalysis, the final revised results of the PASS study were submitted to regulators in October 2023.

Regulatory authorities in Singapore issued updated product information and advice for males to use contraception in March 2023, and New Zealand issued communications in May 2023 based on the previous submission of the study which were both subsequently updated in in response to the reanalysis.

The EMA's Pharmacovigilance Risk Assessment Committee re-considered the revised results of the PASS study at their January 2024 meeting and recommended precautionary measures for males taking valproate. The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed the PRAC position and MAHs were requested to update SmPCs and PILs in the EU accordingly.

This Public Assessment Report presents the MHRA's review of the revised results of the PASS study on potential paternal transmission of risk with valproate, and the advice of the Commission on Human Medicines and Pharmacovigilance Expert Advisory Group. It also presents the actions of the MHRA following this advice, including working with manufacturers to update the SmPCs and PILs in the UK and with the healthcare system to support the safe implementation of the new measures.

4. Description and results of the PASS study

In brief, the PASS was designed to evaluate the risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD), and congenital malformations (CM), in offspring following paternal exposure to valproate in the 3 months prior to conception, compared to paternal exposure to lamotrigine or levetiracetam. The retrospective study has been conducted using national population registries in Denmark (DK), Sweden (SE), and Norway (NO). The primary finding of the study is that, after pooling non-significant propensity score weighted Cox model hazard ratio estimates from the three separate country-specific analyses, a statistically significant higher risk of NDD, including ASD, among offspring from fathers exposed to valproate in the three months prior to conception in comparison to those exposed to lamotrigine/levetiracetam was observed (HR 1.50, 95% CI: 1.09, 2.07; p=0.0138). The hazard ratios within individual country analyses were consistently but non-significantly greater than 1. No increased risk of congenital malformations was observed.

4.1 Study objectives

The aim of this retrospective cohort study was to examine the associations between paternal exposure to valproate at conception and the risks of NDD, including ASD, as well as congenital malformations in offspring. The primary objective was to investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception.

Secondary and exploratory objectives considered the risk of congenital malformations as well as exploring potential risk factors for NDD and considering alternative study designs and sensitivity analyses.

4.2 Study design

This was a multi-country, population-based, retrospective cohort study using data from national registries in Denmark, Sweden, and Norway. A cohort of offspring paternally exposed to valproate was compared to a cohort of offspring paternally exposed to lamotrigine/levetiracetam, at the time of conception, to investigate the risk of NDD, including ASD, as the primary outcome of interest and the risk of CM (as a composite of major and/or minor CM) as a secondary outcome. The study design for the primary objective is shown in Figure 1.

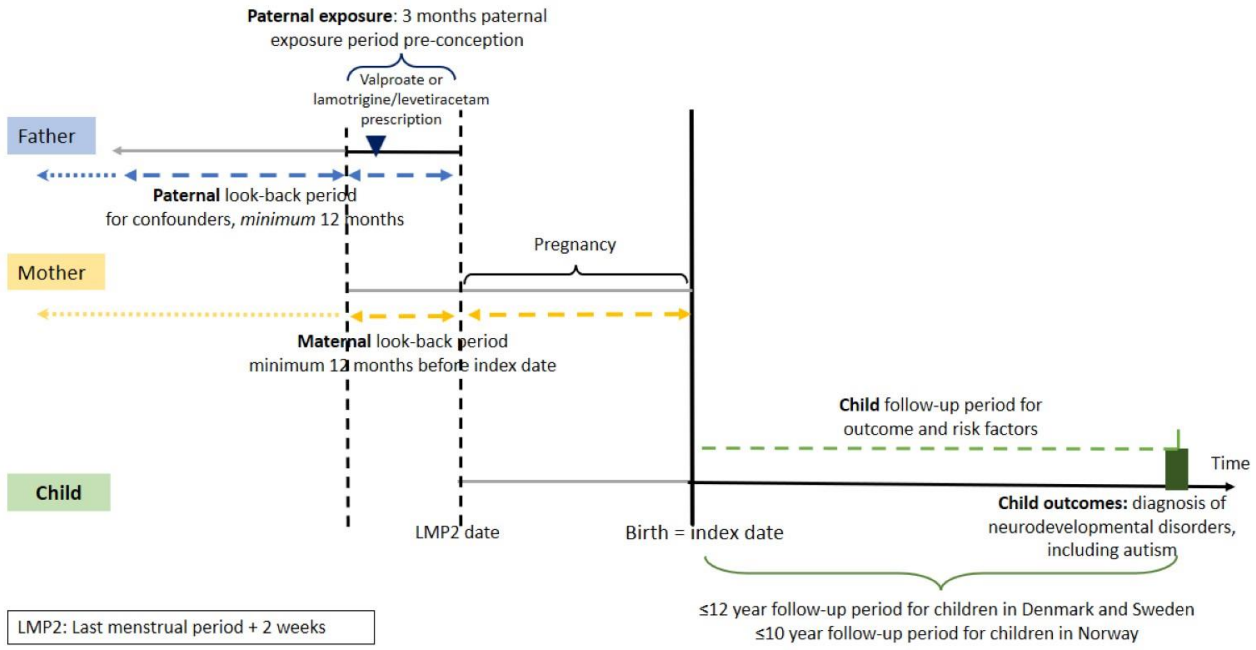

Figure 1: Overview of the family linkage, Neurodevelopmental Disorders (NDD) including Autism Spectrum Disorders (ASD) as presented in the PASS report

4.3 Outcome definition

The definition of NDD used in the study is from the Diagnostic and Statistical Manual of Mental Disorders – 5 (DSM-V) "a group of conditions with onset in the developmental period identified using ICD-10 codes. The disorders typically manifest early in development, often before the child enters grade school, and are characterised by developmental deficits that produce impairments of personal, social, academic, or occupational functioning. The range of developmental deficits varies from very specific limitations of learning or control of executive functions to global impairments of social skills or intelligence."

NDDs comprise:

- Intellectual Disabilities (IDs)
- Communication Disorders
- Autism Spectrum Disorder (ASD)
- Attention-Deficit/Hyperactivity Disorder (ADHD)
- Specific Learning Disorders

- Motor disorders (MDs) such as developmental coordination disorder, stereotypic movement disorder, and tic disorders
- Other NDDs

The prevalence of these disorders in the general population as reported in the MAH safety evaluation report, when known, is provided below:

- IDs: approximately 1% in an overall general population, and prevalence rates vary by age
- ASD: about 1% of the population across U.S. and non-U.S. countries, with similar estimates in child and adult samples
- ADHD: about 5% of children and about 2.5% of adults in most cultures
- Specific learning disorders: 5%–15% among school-age children across the academic domains of reading, writing, and mathematics, and across different languages and cultures. Prevalence in adults is unknown but appears to be approximately 4%.
- MDs: Developmental coordination disorder: 5%–6% in children ages 5–11 years. Simple stereotypic movements (for example, rocking) are common in young typically developing children. Complex stereotypic movements are much less common (occurring in approximately 3%–4%). Tics are common in childhood but transient in most cases.

Autism alone, and a narrow definition of NDD, were investigated in two separate sensitivity analyses (see Table 2).

The data are insufficient to evaluate the exact sub-type and severity of adverse outcomes or determine if all the identified learning and developmental disorders are sustained long term.

4.4 Setting

The study period began on 1 January 1997 (1 April 2004 for the secondary outcome) in Denmark, 1 January 2007 in Sweden and 1 January 2010 in Norway, based on the availability of information from national registries. The study time period ended on 31 December 2018 for Denmark and 31 December 2019 for both Sweden and Norway.

4.5 Subjects and study size

Pregnancies were included if they met all the following inclusion criteria:

- Singleton pregnancies, with known pregnancy-length of at least 12 weeks within the study time period
- Pregnancies linked to both mother and father within the study time period

- Father with a continuous enrolment in the database for ≥12 months prior to linked mother at the date of the last menstrual period plus 2 weeks (LMP2)
- Father with at least one antiepileptic drug (AED) in the data available

Pregnancies were excluded if they met any of the following exclusion criteria:

- Adopted children
- Pregnancy associated with in vitro fertilisation (IVF)
- Pregnancies with missing gestational age and/or missing maternal LMP2 (for these pregnancies it will not be possible to identify the exposure window for the study)

Different cohorts were constructed using additional inclusion/exclusion criteria for analysis of individual study objectives**.** and are briefly summarised below.

Additional inclusion criteria for the primary outcome (NDD including ADD):

- Singleton born alive within the study period (i.e. the birth of only one child during a single delivery)
- Mother with a continuous enrolment for ≥12 months prior to child birthdate

Additional exclusion criteria for the primary outcome (NDD including ASD):

- Offspring whose parent(s) have a history of CM or NDD (according to available records)

Additional inclusion criteria for the secondary outcome (CM):

- Mother with a continuous enrolment of 12 months prior to index date (12^{th} week of gestation in Norway, 22^{nd} in Denmark, offspring birth date in Sweden).

Additional exclusion criteria for the secondary outcome (CM):

- Offspring whose parent(s) have a history of CM or NDD (according to available records)

For the primary outcome, NDD including ASD, to observe a hazard ratio (HR) of 2.00 with 5% significance and 80% power, a sample size of 1,178 offspring within the family linked unit was needed across all 3 countries. This required a minimum of 589 offspring within a family linked unit with paternal exposure to valproate (monotherapy) and a minimum of 589 offspring within a family linked unit with paternal exposure to lamotrigine/levetiracetam (composite monotherapy).

For the secondary outcome, CM, assuming to observe an odds ratio (OR) of 2.5 with 5% significance and 80% power, sample size of 826 offspring within the family linked unit was

needed across all 3 countries. This required a minimum of 413 offspring within a family linked unit with paternal exposure to valproate (monotherapy) and a minimum of 413 offspring within a family linked unit with paternal exposure to lamotrigine/levetiracetam (composite monotherapy).

4.6 Variables and Data Sources

The primary outcome of interest was NDD, including ASD, and the secondary outcome of interest was a composite of CM (major and/or minor), in offspring up to 12 years of age for both outcomes, based on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnostic codes.

The primary exposure of interest was paternal use of valproate during the spermatogenic risk window prior to conception of the offspring. Date of conception was defined by the first day of the last menstrual period plus 2 weeks (LMP2) date of the mother within the linked family unit. Exposure information was derived from prescription data, as recorded in the National Prescription Registries for each country (from 1995 in Denmark, 2005 in Sweden and 2008 in Norway). Country-specific cohorts of eligible linked family units were then identified.

The data sources used to retrieve this information were national registries in Denmark, Sweden and Norway:

- Denmark: Danish civil registration system, Register of medicinal product statistics, National patient registry, Cause of death register, Medical birth registry, The in vitro fertilization register
- Sweden: Multigenerational register, Cause of death register, National prescription registry, National patient registry, Medical birth registry
- Norway: Central person register, Norwegian prescription database, Norwegian patient registry, Medical birth registry, Cause of death register

4.7 Statistical analyses

The comparative analysis for the primary objective compared paternal exposure (3 months prior to conception) to valproate monotherapy (group ‘valproate’) to paternal exposure to lamotrigine or levetiracetam monotherapy (group ‘lamotrigine/levetiracetam’). Crude and propensity score (PS) weighted Cox proportional hazards (PH) regression models were performed to investigate the risk of NDD including ASD in those in the `valproate’ group to those in the `lamotrigine/levetiracetam’ group. PSs estimated using logistic regression, random forest models, and logistic regression informed by random forest were considered, with the best model on visual comparison used to apply inverse probability of treatment weights. A broad range of risk factors and potential confounders were considered (Table 1).

Table 1: Potential risk factors for NDD as presented in table 4 of the PASS report

Mother	Father	Offspring
Age Obesity (12 month look back from LMP2) Smoking (12 month look back from LMP2 and during pregnancy (DP) Substance abuse (12 month look back from LMP2 and DP) Alcohol abuse (12 month look back from LMP2 and DP) Schizophrenia, schizotypal and delusional disorders (ever) Affective Disorder (ever) Neurotic Disorder (ever) Rubella exposure (DP) CMV (DP) Diabetes (ever) & Gestational Diabetes (DP) Any concomitant medications associated with valproate-indicated psychiatric conditions (12 month look back from LMP2 and DP) Any concomitant medications associated with neuropsychiatric adverse effects (12 month look back from LMP2 and DP)	Substance abuse (12 month look back from LMP2) Affective Disorders (excluding bipolar and mania) (ever) Schizophrenia, schizotypal and delusional disorders (ever) Neurotic Disorder (ever) Any concomitant medications associated with valproate-indicated psychiatric conditions (12 month look back from LMP2) Any concomitant medications associated with neuropsychiatric adverse effects (12 month look back from LMP2)	Sex Fetal Alcohol Syndrome Fragile X Syndrome Congenital CMV Congenital Rubella Lejeune/cri du chat syndrome Tuberous sclerosis

Data were analysed at within-country level then pooled with meta-analytic techniques. In the primary analysis, exposure was expressed as a dichotomous variable: exposure to valproate in monotherapy vs. exposure to lamotrigine/levetiracetam in monotherapy. However, for one of the secondary analyses, paternal person-time exposed to valproate or lamotrigine/levetiracetam was classified, to take into account intensity of drug exposure during the 3 months preconception risk window using the longitudinal K-means clustering algorithm. Exposure data were individually transformed into the number of WHO Defined Daily Doses (DDDs) dispensed during every 14 day interval within the 3 months exposure period. The

longitudinal K-means clustering algorithm was then applied to create K clusters with homogenous trajectories, as empirically driven by the data. In the secondary analysis an additional PS-weighted Cox PH model was estimated and adjusted by exposure clusters. A wide range of sensitivity analyses were conducted and are outlined in Table 2.

Table 2: Description of sensitivity analyses conducted

Sensitivity analysis	Title	Description	Relevant outcome
1	Variation of time window	An extended risk window of paternal AED exposure of 6 months prior to LMP2 was investigated to determine whether valproate exposure outside of the spermatogenic cycle may have an effect.	NDD
2	ASD as the primary outcome	The risk of ASD alone was evaluated in the primary outcome cohort.	NDD
3	Low birth weight/<8m gestation offspring excluded	Preterm birth and low birth weight were postulated as possible mediators of the relationship between paternal valproate exposure and NDD, so this SA excluded relevant offspring to explore the impact of doing so.	NDD
4	Broad definition of CM	There was likely underdiagnosis of CM in spontaneous abortion and stillbirth. In this sensitivity analysis, a broader definition of CM was used to capture additional cases. The definition included live births with CM diagnosis; spontaneous abortions/stillbirths with CM recorded diagnosis/reason for death; spontaneous abortions/stillbirths without an ICD-10 code for the diagnosis/reason for death.	CM
5	Separation of the comparator group	The study exposure and comparator groups have different indications and were licensed at different times. This means there may be systematic differences in the populations treated with these medications. This SA separated the combined lamotrigine/levetiracetam comparator groups by medication.	NDD & CM

6	Multivariate analysis without PS weighting	In this SA, the multivariate analysis was repeated without PS weighting. Confounders were included, and potential risk factors if they were associated with the exposure and the outcome in univariate analysis.	NDD & CM
7	Effect of paternal valproate exposure on NDD in offspring with epilepsy/post-natal exposure to AED	The neurodevelopmental effects of post-natal AED exposure and/or epilepsy diagnosis on risk of NDD were poorly understood. This SA included relevant offspring and incorporated offspring epilepsy diagnosis/AED exposure as time-varying covariates in the models.	NDD
8	Validation of Defined Daily Dose (DDD) assumptions	This SA compared the ratio of estimated treatment durations (expected) and time between prescriptions (observed) to determine whether use of the WHO DDD was a good approximation of reality. These descriptive analyses were performed for each study medication and for patients with and without a diagnosis of epilepsy.	N/A, descriptive analysis
9	Narrow definition of CM (live births only)	This SA repeated the CM analyses using live births only in Denmark and Norway, to align with data availability in Sweden.	CM
10	Cumulative exposure considered	In this SA, cumulative exposure to the study medications in the 3-month window prior to LMP2 was evaluated. The exposure was calculated as a continuous measure of 'number of days covered' (NDD). This measure was divided into tertiles of low, medium and high use for inclusion in the models. The analyses for NDD included a Cox PH model including the continuous measure of cumulative exposure and the interaction between exposure group and cumulative measure; within-treatment-group analysis to study any dose-response relationship using tertiles of treatment; within-treatment-group Cox PH model to compare tertiles of exposure and the outcome. For CM, the same analyses were performed using logistic rather than Cox models.	NDD & CM
11	Narrow definition of NDD	This SA employed a narrower case definition of NDD.	NDD

4.8 Results

Primary objective

The comparative analysis of the primary outcome cohort included 1,950 offspring (respectively, 793 paternally exposed to valproate and 1,157 to lamotrigine/levetiracetam) in Denmark, 2,355 offspring (respectively, 930 and 1,425) in Sweden, and 1,416 offspring (respectively, 398 and 1,018) in Norway. The overall absolute risk of NDD associated with paternal exposure to valproate was 4.4% and for lamotrigine/levetiracetam was 2.9% from the results of the crude model.

The overall absolute risk of NDD associated with paternal exposure to valproate was 5.2% and for lamotrigine/levetiracetam was 2.7% from the results of the PS-weighted model. The results of the crude and PS-weighted adjusted Cox models within individual countries, and pooled analyses, are presented in Table 3.

Heterogeneity between the country-specific estimates was tested using Chi-square with 95% CI and the I^2 statistic. No heterogeneity was observed in the crude or adjusted Cox models. When the results from the three countries were combined in a meta-analysis, a statistically significantly higher risk of NDD (including ASD) was observed among offspring from fathers exposed to valproate in comparison to offspring from fathers exposed to lamotrigine/levetiracetam.

Table 3: Results for the primary objective, showing risk of NDD (including ASD) associated with paternal exposure to valproate vs. lamotrigine/levetiracetam.

	Country	Corrected results	
		By country	Pooled (N=5,721)
Risk of NDD (crude Cox model)	Denmark	HR: 0.94, 95% CI: 0.60, 1.46	HR: 1.13 (95% CI: 0.85-1.49)
	Norway	HR: 1.60, 95% CI: 0.81, 3.15	
	Sweden	HR: 1.16, 95% CI: 0.76, 1.76	
Risk of NDD (PS-weighted Cox model)	Denmark	HR: 1.34, 95% CI: 0.79, 2.25	HR: 1.50 (95% CI: 1.09-2.07)
	Norway	HR: 1.76, 95% CI: 0.83, 3.71	
	Sweden	HR: 1.54, 95% CI: 0.95, 2.51	

Sensitivity analyses (relating to NDD)

Results from sensitivity analyses 1, 2, 3, 5, 6, 7 and 11 are presented in Table 4. In Denmark, the results of the sensitivity analyses did not statistically differ from the main results. In Norway, a number of the sensitivity analyses couldn't be conducted fully due to low event counts. Where they were undertaken, no differences from the main results were found. In the Swedish data, higher risk among paternally valproate exposed offspring was observed in sensitivity analysis 11, exploring a narrow definition of NDD (HR 1.70, 95% CI: 1.02-3.96) and sensitivity analyses 2, looking at ASD only (HR: 2.70, 95% CI: [1.19, 6.17]).

Findings from sensitivity analysis 10 are presented in Table 5 and describe analyses of cumulative exposure. The models could not be run in Norway due to low event counts. In Denmark and Sweden, Cox models testing the mean paternal exposure of valproate vs. lamotrigine/levetiracetam did not find any difference in risk of NDD. When comparing high and medium vs. low exposure within the valproate group no difference was observed in either country.

Table 4: Sensitivity analyses relating to NDD

Sensitivity Analysis	Description	N	HR (95% CI) estimates		HR estimates by cluster of exposure		
			Crude HR (95% CI)	Adjusted HR	Cluster A	Cluster B	Cluster C
Denmark							
Sensitivity analysis 1	Extended risk window of paternal valproate exposure (6 months)	2,049	0.86 (0.56, 1.32)	1.13 (0.68, 1.89)	1.51 (0.79, 2.87)	0.80 (0.35, 1.84)	
Sensitivity analysis 2	ASD only as a primary outcome	1,786		0.76 (0.30, 1.89)			
Sensitivity analysis 3	Exclusion of offspring with low birth weight or born prior to 8th months	1,931	0.93 (0.59, 1.46)	1.36 (0.82, 2.27)	1.50 (0.80, 2.84)	1.19 (0.53, 2.69)	
Sensitivity analysis 5a	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	2,137	0.98 (0.62, 1.54)	1.51 (0.90, 2.53)	1.57 (0.81, 3.04)	1.42 (0.63, 3.20)	
Sensitivity analysis 5b	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	906	* estimated HR not interpretable	0.59 (0.18, 1.95)	0.70 (0.16, 3.06)	0.43 (0.06, 3.30)	
Sensitivity analysis 6	Comparison of PS-weighted model with covariate adjustment model	2,355	-	1.22 (0.77, 1.92)	-	-	

Sensitivity analysis 7	Effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy	1,987	1.03 (0.68,1.57)	1.41 (0.84, 2.38)	1.42 (0.75, 2.67)	1.38 (0.59, 3.22)	
Sensitivity analysis 11	Narrow definition of NDD	1,950	0.98 (0.61, 1.55)	1.59 (0.89, 2.86)	1.60 (0.75, 3.41)	1.55 (0.64, 3.78)	
Norway							
Sensitivity analysis 1	Extended risk window of paternal valproate exposure (6 months)	1,479	NA[1]	1.86 (0.87, 3.99)	1.83 (0.66, 5.04)	1.91 (0.60, 6.13)	
Sensitivity analysis 2	ASD only as a primary outcome	1,416		[2]			
Sensitivity analysis 3	Exclusion of offspring with low birth weight or born prior to 8th months	1,403	NA[1]	1.84 (0.87, 3.88)	1.85 (0.74, 4.61)	1.78 (0.47, 6.69)	
Sensitivity analysis 5a	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	1,261	NA[1]	1.68 (0.77, 3.67)	1.77 (0.68, 4.63)	1.50 (0.58, 3.89)	
Sensitivity analysis 5b	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	553	NA[3]	1.75 (0.40, 7.73)	1.46 (0.32, 6.72	NA[4]	
Sensitivity analysis 6	Comparison of PS-weighted model with covariate adjustment model	1,416	-	1.60 (0.81, 3.15)[1]	-	-	
Sensitivity analysis 7	Effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs	1,436	NA[5]	1.92 (0.97, 3.81)	NA[5]	NA[5]	

	after birth, and/or diagnosed with epilepsy						
Sensitivity analysis 11	Narrow definition of NDD	1,415	1.63 (0.80, 3.32) [6]	1.87 (0.86, 4.08)	1.82 (0.69, 4.83)	1.85 (0.49, 6.94)	
Sweden							
Sensitivity analysis 1	Extended risk window of paternal valproate exposure (6 months)	2,504	1.13 (0.74, 1.71)	1.43 (0.89, 2.31)	1.93 (1.03, 3.64)	0.89 (0.43, 1.844)	
Sensitivity analysis 2	ASD only as a primary outcome	2,182		2.70 (1.19, 6.17)			
Sensitivity analysis 3	Exclusion of offspring with low birth weight or born prior to 8th months	2,335	1.19 (0.78, 1.81)	1.48 (0.91, 2.42)	1.50 (0.74, 3.02)	1.42 (0.55, 3.69)	1.50 (0.58, 3.89)
Sensitivity analysis 5a	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	2,137	1.31 (0.84, 2.04)	1.65 (0.98, 2.77)	2.27 (1.02, 5.05)	1.07 (0.41, 2.78)	1.58 (0.59, 4.27)
Sensitivity analysis 5b	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	1,140	-	0.67 (0.20, 2.24)	0.40 (0.12, 1.32)	-	-
Sensitivity analysis 6	Comparison of PS-weighted model with covariate adjustment model	2,355	-	1.17 (0.77, 1.78)	-	-	-
Sensitivity analysis 7	Effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy	2,399	1.04 (0.70, 1.54)	1.34 (0.84, 2.11)	1.54 (0.79, 3.01)	1.05 (0.43, 2.55)	

Sensitivity analysis 11	Narrow definition of NDD	2,355	1.26 (0.82, 1.93)	1.70 (1.02, 2.81)	1.92 (0.93, 3.96)	1.86 (0.67, 5.15)	

[1] Results presented are from the PS-adjusted model

[2] Influential subjects were identified using the dfbetas and excluded (N = 15). The N = 15 excluded offspring included all NDD, including ASD events in the valproate group. The exclusion of these events led to an invalid crude HR (95% CI) estimate.

[3] Event count too small to run models

[4] Due to the sample size, the estimated HR was not interpretable (>100,000). Crude and adjusted models do not always use the same population leading to differences in the sample size and number of events in the models

[5] Effect estimation for NDD using crude Cox regression model and propensity score weighted Cox regression model adjusted for K-means exposure cluster could not be produced due to the low number of events (less than 30 and 50 events, respectively).

[6] Out of the total N = 1415 offspring, N = 14 influential subjects were identified using the dfbetas and excluded, resulting in a sample size of N = 1401 offspring. The N = 14 excluded offspring included all NDD, including ASD events in the valproate group. The exclusion of these events led to an invalid crude HR (95% CI) estimate. The crude model was rerun without considering the dfbetas criterion, which represents a deviation from the protocol, and the findings were reported.

Table 5: Results from sensitivity analysis 10 looking at cumulative exposure

		Valproate	Lamotrigine/levetiracetam
	Cumulative exposure: N (%)		
Denmark	Low	268 (33.80)	385 (33.28)
	Medium	259 (32.66)	387 (33.45)
	High	266 (33.54)	385 (33.28)
	Mean (SD)	53.14 (21.79)	54.51 (26.01)
		HR (95% CI)	HR (95% CI)
	Cox model of valproate vs. lamo/lev at mean cumulative exposure	0.58 (0.31-1.08)	
	Cox model of valproate & lamotrigine comparing tertiles of cumulative exp.		Lamotrigine
	Low	Ref.	Ref.
	Medium	0.00 (0.00, 0.00) P<0.0001	
	High	1.17 (0.59, 2.33) P=0.6453	<20 events so result not generated
		Valproate	Lamotrigine/levetiracetam

Norway	**Low**	**129 (32.41)**	**340 (33.40)**
	Medium	95 (23.87)	69 (6.78)
	High	174 (43.72)	609 (59.82)
	Mean (SD)	64.75 (23.67)	69.55 (22.57)
		HR (95% CI)	HR (95% CI)
	Cox model of valproate vs. lamo/lev at mean cumulative exposure	Not produced due to low event count	
	Cox model of valproate & lamotrigine comparing tertiles of cumulative exp.		Lamotrigine
	Low	Ref.	Ref.
	Medium	Not produced due to low event count	
	High	Not produced due to low event count	
		Valproate	Lamotrigine/levetiracetam
Sweden	Low	300 (32.26)	477 (33.47)
	Medium	322 (34.62)	34.62 (468 (32.84)
	High	308 (33.12)	33.68 (33.68)
	Mean (SD)	50.25 (22.85)	49.64 (34.93)
		HR (95% CI)	HR (95% CI)
	Cox model of valproate vs. lamo/lev at mean cumulative exposure	1.17 (0.62, 2.18) P not reported	
	Cox model of valproate & lamotrigine comparing tertiles of cumulative exp.		Lamotrigine
	Low	Ref.	Ref.

	Medium	0.11 (0.03, 0.46) P=0.0025	1.00, P=0.9854
	High	1.01 (0.52, 1.95) P=0.9813	No events in this group, therefore HR was not interpretable

Secondary objective

The comparative analysis of the secondary outcome cohort included offspring from two countries only (see Table 6). Data from Sweden were not included in this analysis because they did not have information on spontaneous abortions or stillbirths available. The cohort for this analysis included 648 offspring (respectively, 259 paternally exposed to valproate and 389 to lamotrigine/levetiracetam) in Denmark, and 513 offspring (respectively, 169 and 344) in Norway. The results of the crude and PS-weighted adjusted logistic regression models within individual countries, and pooled analyses, are presented in Table 5.

Heterogeneity was observed between the country-specific estimates from the crude model (I^2=0.5, 95% CI not available, p=0.1590), but no difference in risk of CM was observed in among offspring from the two groups based on meta-analysis of the crude model results.

In Norway, the PS-weighted logistic regression model did not converge. Therefore, it was not possible to produce a country-specific estimate for risk of CM using an adjusted model for Norway; nor was it possible to undertake a meta-analysis of pooled results for this outcome.

Table 6: Results for the secondary objective, showing risk of CM associated with paternal exposure to valproate vs. lamotrigine/levetiracetam.

	Country	Corrected results	
		By country	**Pooled (N=5,721)**
Risk of CM (crude logistic model)	Denmark	OR: 0.62 (95% CI: 0.37, 1.04)	OR: 0.81, 95% CI: 0.48, 1.36)
	Norway	OR: 1.06 (95% CI: 0.62, 1.82)	
	Sweden	-	
Risk of CM (PS-weighted Cox model)	Denmark	OR: 0.61 (95% CI: 0.36, 1.06)	-
	Norway	non-convergence due to low event count	
	Sweden	-	

Sensitivity analyses (relating to CM)

Results of the sensitivity analyses relating to the secondary outcome are presented in Table

7. In both Denmark and Norway it was not possible to run sensitivity analysis 6 as no patients with CM remained after removal of outliers. For sensitivity analysis 10, only descriptive analyses of the cumulative exposure were performed. Again, it was not possible run models due to low event counts. For the other sensitivity analyses performed, the results were aligned with the main results of the study. In Norway, while sensitivity analysis 5a (pairwise comparison with lamotrigine) showed a non-significant decrease in risk associated with paternal exposure to valproate similar to the main result (OR of valproate and lamotrigine 0.86, 95% CI: 0.46, 1.59), sensitivity analysis 5b (pairwise comparison with levetiracetam) showed a non-significant increase (OR of valproate and levetiracetam 1.60, 95% CI: 0.57, 4.52).

Table 7: Sensitivity analyses relating to CM

Sensitivity Analysis	Description	N	HR (95% CI) estimates		HR estimates by cluster of exposure	
Denmark			**Crude HR (95% CI)**	**Adjusted HR**	**Cluster A**	**Cluster B**
Sensitivity analysis 4	Handling of missing CM diagnosis	648	0.62 (0.37, 1.04)	0.61 (0.36, 1.06)	0.68 (0.31, 1.48)	0.54 (0.26, 1.12)
Sensitivity analysis 5a	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	581	0.62 (0.36, 1.06)	0.61 (0.35, 1.07)	0.65 (0.29, 1.45)	0.54 (0.26, 1.16)
Sensitivity analysis 5b	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	326	0.62 (0.27, 1.42)	0.64 (0.27, 1.52)		
Sensitivity analysis 6	Comparison of PS-weighted model with covariate adjustment model	NA[2]		NA[2]	NA[2]	NA[2]
Sensitivity analysis 9	Narrow case definition		0.61 (0.34, 1.06)	0.61 (0.34, 1.06)	0.69 (0.32, 1.49)	0.51 (0.24, 1.10)
Norway						
Sensitivity analysis 4	Handling of missing CM diagnosis	513	1.06 (0.62, 1.82)	0.76 (0.40, 1.44)	0.58 (0.14, 2.29)	0.83 (0.40, 1.73)
Sensitivity analysis 5a	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	446	1.02 (0.58, 1.79)	0.86 (0.46, 1.59)	0.50 (0.14, 1.78)	1.03 (0.51, 2.11)
Sensitivity analysis 5b	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	236	1.23 (0.52, 2.89)	1.60 (0.57, 4.52)	NA[1]	NA[1]

Sensitivity analysis 6	Comparison of PS-weighted model with covariate adjustment model		NA[2]	NA[2]	NA[2]	NA[2]
Sensitivity analysis 9	Narrow case definition	513	1.06 (0.62, 1.82)	0.76 (0.40, 1.44)	0.58 (0.14, 2.29)	0.83 (0.40, 1.73)

[1] The logistic regression model did not converge. The odds ratios of valproate across K-means cluster were not shown
[2] After removal of outliers there were no cases of CM remaining. Thus, it was not possible to perform logistic regression.

Summary of study authors' discussion and conclusions

The authors report a statistically significantly increased risk of NDD including ASD associated with paternal exposure to valproate compared with paternal exposure to lamotrigine/levetiracetam at the time of conception when pooling country-specific adjusted risk estimate into a meta-analysis (PS-weighted adjusted HR: 1.5, 95% CI:1.1, 2.1; I2=0.0%). The authors conclude that due to the observational nature of this study, no causal relationship can be established, nor the biological or the pharmacological mechanisms to explain the relationship.

The nature of the NDD and specific subtypes (ASD, intellectual disabilities, attention deficit hyperactivity disorder) were not assessed because the study was powered to investigate NDD as a composite outcome. However, sensitivity analyses focusing on a narrow definition of NDD showed that the risk estimates varied in strength, and significance compared to those from the main analysis, and these variations were not consistent across the three countries. For example, with sensitivity analysis 2 focusing on ASD as primary outcome, the association reversed toward a non-significant reduced risk with the paternal exposure to valproate in Denmark, while the risk almost doubled and became significant in Sweden.

The study authors noted that differences in the length of follow-up were observed between countries. In Denmark and Sweden, where offspring were followed from birth to 12 years of age, follow-up was shorter in Sweden, with 23.3% of the offspring in the lamotrigine/levetiracetam group followed-up more than 8 years versus 41.8% in the valproate group; it was longer in Denmark, with 40.2% lamotrigine/levetiracetam group followed-up more than 8 years versus 74.3% in the valproate group. The authors suggest this may explain the lower rate of ASD captured in the lamotrigine/levetiracetam group in Sweden compared to Denmark and may highlight the impact of the follow-up duration on the results. These sensitivity analyses relied on lower number of events and estimates may be more prone to instability and lower reliability, so they call for caution in the interpretation of the study results. The authors note that offspring paternally exposed to valproate were systematically more frequently conceived in the earlier years of inclusion than those exposed to lamotrigine/levetiracetam, although this variation was minor in Norway. As a result, offspring paternally exposed to valproate had on average a longer follow-up time and a higher probability of presenting NDD, including ASD diagnoses. Considering that the risk of being diagnosed with NDD including ASD is not constant across ages but rather detected at later ages when children start school (from 5 or 6 years old), the authors suggest this may have biased the risk estimates generated from Cox regression models.

The authors noted that in line with previously published studies, results from crude pooled OR suggested no increased risk of CM associated with the paternal exposure to valproate compared to the paternal exposure to lamotrigine/levetiracetam in the 3 months preconception period, consistent across Denmark and Norway (pooled OR: 0.81, 95% CI: 0.48, 1.36; I^2=49.6%). However, they acknowledge these findings should be interpreted with caution since they are crude data that have not been adjusted for other variables and may reflect the observed heterogeneity. The presence of such heterogeneity may be due to only two estimates pooled in the meta-analysis. Non-convergence of adjusted logistic regression models precluded the pooled PS-weighted adjusted OR to be estimated.

The authors also acknowledged some methodological limitations. The study used secondary data that was not collected primarily for research purposes. Therefore data on certain parameters was not available, such as some known risk factors and/or causal factors (for example, genetic abnormalities, congenital infectious diseases, paternal condition severity that required AED use, lifestyle factors) and could not be controlled for in the analysis. These factors were assumed to be balanced between the two paternal exposure groups, but this assumption could not be verified, and unmeasured confounding may bias the risk estimates. Of particular concern is the type of epilepsy, which may not be balanced between the two paternal exposure groups; valproate is the treatment of choice (or first-line drug) for male patients with idiopathic generalized epilepsy (NICE, 2022), a type of epilepsy which could be associated with NDD and is known to have a genetic basis and as such can be found in several members of the same family (Devinsky, 2024).

This study found an increased risk of NDD, including ASD, with paternal exposure to valproate compared to lamotrigine/levetiracetam at the time of conception. Due to methodological limitations, especially the difference in follow-up time between the two paternal exposure groups which may impact the interpretation of the results, these findings regarding risk of NDD should be interpreted with caution. While the study did not find any difference in risks of CM between the 2 paternal exposure groups, findings were based on crude estimates which were potentially biased and also affected by moderate-to-substantial heterogeneity, thus these findings should also be interpreted with caution.

5. Other data submitted by the Marketing Authorisation Holder

5.1 The mechanism of transmission of harm via the father

The mechanism of transmission of harm via the father was investigated through consideration of data relating to genetic changes in the paternal germ cell, epigenetic changes in paternal germ cells or exposure of the fetus via seminal fluid.

Genotoxicity in paternal germ cell

The MAH has provided a report which summarises the genetic in vitro/vivo toxicology studies conducted by Sanofi or the previous valproate MAH, Abbott, for valproate between 1977 and 1988 . Additional in vitro studies, further assessing the intrinsic mutagenic and clastogenic potential of valproate as requested by the PRAC within the 2018 referral procedure were conducted in 2019. These studies were aligned with ICH S2 and OECD protocols and were GLP (Good Laboratory Practice) compliant.

All initial studies were negative, and, in the 2019 studies, valproate did not induce mutation either in 5 histidine-requiring bacterial strains (Ames test) nor at the tk locus of L5178Y mouse lymphoma cells under the experimental conditions of these studies. The MAH states that some studies (Fucic and others, 2010, Ahmad and others, 2013, Abdella and others, 2014, Khan and others, 2011) from the literature (micronucleus test, chromosome aberration test and Comet assay) suggested that valproate could slightly increase DNA (including sperm DNA) and chromosome damage in mice.

Whether sperm cells with slight chromosomal damage could still be used to fertilize an ovum and lead to a viable zygote, which would thus contain genetic changes, is unknown.

Limitations exist in the published literature (for example, non-GLP-compliance, non-clinically relevant route of administration and absence of toxicokinetic information), which should be considered when translating the clinical relevance of the findings.

To note, available data have previously been considered and adopted in section 5.3 of the SmPC of valproate containing medicines:

> *“Valproate was neither mutagenic in bacteria, nor in the mouse lymphoma assay in vitro and did not induce DNA repair in primary rat hepatocyte cultures. In vivo, however, contradictory results were obtained at teratogenic doses depending on the route of administration. After oral administration, the predominant route of administration in humans, valproate did not induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate increased DNA strand-breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanges in patients with epilepsy exposed to valproate as compared to untreated healthy subjects have been reported in published studies.*
>
> *However, conflicting results were obtained when comparing data in patients with epilepsy treated with valproate with those in untreated patients with epilepsy. The clinical relevance of these DNA/chromosome findings is unknown.”*

It is generally assumed that genotoxic findings observed in somatic cells will also apply to germ line cells, hence the provision of contraceptive guidance wording as a result of findings from the battery of regulatory genotoxicity studies using somatic cells. Regulatory guidance (ICH S2) for the assessment of genotoxic risk requires both in vitro and in vivo assessment to GLP-compliant standards.

No GLP-compliant in vivo studies to current regulatory standards have been performed and in vivo data which does exist (historical MAH and literature data) has limitations. However, as previously requested by PRAC, the MAH conducted two further GLP-compliant in vitro studies to assess both mutagenic and clastogenic potential, results of which the MAH states suggest no genotoxic risk. By today’s regulatory standards, a GLP-compliant in vivo study would have to be conducted, however, it was considered by PRAC that an additional study would be unlikely to provide additional relevant information.

In summary, genetic damage to paternal germ cell DNA could theoretically be transmitted as mutations to the subsequent generation. However, tests for gene mutations have been negative and thus suggest that this type of transmission is unlikely to occur. Clastogenicity is expected to lead to cell death or reduced fertility and thus unlikely to transmit effects to the offspring. The 2019 GLP-compliant in vitro study suggests valproate is not clastogenic. It

should also be noted that conventional nonclinical carcinogenicity studies indicated that valproate was not carcinogenic, which supports a lack of genotoxic potential for valproate. In considering the totality of the available evidence and limitations that exist, the weight of evidence suggests that valproate is unlikely to be genotoxic, however, a further GLP-compliant vivo study could provide further clarity (for example., OECD 483 – Mammalian Spermatogonial Chromosomal Aberration Test).

5.2 Epigenetic data

Epigenetic changes induced in male germ cells have been suggested as a potential mechanism by which abnormalities could be transmitted to the offspring, for instance by modifying gene expression. A potential route of changing gene expression is inhibition of histone deacetylase enzyme (HDAC) involved in remodelling of chromatin and regulation of DNA methylation. Publications suggest that valproate is capable of inducing altered DNA methylation (Houtepen and others, 2016) by acting as a HDAC inhibitor (Phiel and others, 2001, Kubota and others, 2012). An epigenetic investigative programme has started and an study to evaluate valproate-induced epigenetic changes of paternal germ cells is due to start in 2024.

The MAH report presents one publication (Ibi and others, 2019) which has evaluated in mice the effect of paternal valproate exposure on behaviour and epigenetic markers in offspring. This paper provides some evidence of behavioural changes in F1 generation through paternal valproate exposure as well as impact of valproate on histone acetylation in F0 adult testis (concluded by the authors as indication of changes in epigenome of male germ cells) and female F1 brains; though the causal relationship as well as the underlying mechanisms are not characterized in this paper.

Different subsets of animals were evaluated for behavioural testing and epigenetic changes, likely with the intention to avoid confounding results (i.e., influence of behavioural testing on epigenetic marks), however, no correlation between behavioural changes and epigenetic changes at the individual level in F1s could be performed. In F1 males, behavioural effects consisted of deficits in object cognitive memory and social interactions while no changes in histone acetylation was observed in brain. In females, changes in histone acetylation were observed in several brain areas (prefrontal cortex and hippocampus) while behavioural alterations were limited to deficits in sensorimotor gating (prepulse inhibition (PPI) deficit) and deficit in object cognitive memory.

Limitations in the study design exist which include non-clinically relevant route of administration (i.p), absence of toxicokinetic information, and clarity regarding animal

numbers. As stated by the author, sex-based differences in both brain histone acetylation and behaviour exist in the F1 generation. The author postulates that sex hormone differences could be a contributary factor in the sex-based differences observed and that further studies are required to elucidate. An update to the valproate SmPC was completed in 2020 to reflect this data. The CHM's Epigenetics Expert Working Group is examining in detail the risk of epigenetic effects with valproate.

5.3 Exposure to the fetus via semen

The MAH's report states that the MAH considers fetal exposure to valproate via semen to be a negligible risk but relies on evidence from the published literature to support this conclusion rather than directly generated evidence.

The PRAC report published in 2018 summarised the available data and concluded that the exposure to valproate via seminal fluid is significantly lower (i.e., 25,000 times) than following direct treatment of pregnant women and unlikely to cause adverse effects by itself. This conclusion was based on the literature rather than specific evidence from the MAH.

Valproate transfer into seminal fluid was investigated (Swanson and others, 1978). In this study, one subject was administered single, oral 500 mg valproate doses on four separate occasions, with at least one week between successive doses and a second subject was administered one single, oral 500 mg valproate dose. Valproate was then quantified in seminal fluid and plasma over time using a gas-liquid chromatographic assay. Following single oral 500 mg doses of valproate, valproate concentrations in semen were low compared with concentrations in concurrent plasma samples. The semen:plasma drug concentration ratio for both subjects ranged from 0.058 to 0.091. Therefore, valproate transfer into seminal fluid was minimal under these conditions. The highest valproate concentration determined in semen was 3.26 µg/mL at 4.3 hours after dosing (range for both subjects: 0.53 to 3.26 µg/mL).

Valproate vaginal dose and systemic exposure, when a male partner is exposed to valproate, can be estimated (Banholzer and others, 2012), by including several conservative assumptions: Seminal fluid volume is 6 mL; vaginal absorption is 100%; and pharmacokinetic linearity, i.e., a direct linear relationship between dose and systemic exposure. Using the highest valproate concentration in seminal fluid (3.26 µg/mL), a vaginal (or in utero) dose of valproate can be calculated as: 3.26 µg/mL x 6 mL seminal fluid = 19.56 µg. Following a single, oral 500 mg valproate dose, systemic exposure (area under the curve) in women was reported to be 917.9 mg.h/L (Ibarra and others, 2013). As the oral bioavailability of valproate is considered to be 100% (Gugler and others, 1980) a direct correlation can be made between valproate oral and vaginal administration, resulting in a projected AUC of 0.0367 mg.h/L

following a vaginal dose of 19.56 µg. Using the data reported and assumptions in combination with the pharmacokinetic characteristics of valproate, the estimated systemic exposure to valproate via the vaginal route when a male partner is exposed to valproate is estimated to be approximately 25,000-fold less than that of a single 500 mg oral dose in women. It is noted that male patients would be receiving valproate as a multiple-dose treatment regimen, and systemic exposure at steady-state would be higher than that following a single 500 mg dose used for the above exercise; however, the same principles would apply although absolute concentrations would probably be higher.

The PRAC concluded that there are very limited available data on the transmission of valproate via seminal fluid. The above exercise has attempted to use these data from only one male subject to estimate direct in utero exposure and maternal systemic exposure. As a proportion of dose, the amount of valproate present in the semen appears to be very low (≤10%). When considering direct in utero exposure, for example, during fertilisation or embryonic development, thresholds for toxic effects are unknown. However, effects from maternal systemic exposure can probably be considered negligible.

5.4 Spontaneous reports relating to paternal exposure to valproate - MAH Database

A total of 80 cases referring to exposure to valproate via the child's father (paternal exposure) were identified in the MAH database up to 30 June 2023. Among these 80 cases, 8 cases were excluded from the current analysis because: 6 cases also involved in utero exposure to valproate via the treated mother; one case of autism also involved potential exposure to valproate via a grandmother and one case of tremor concerned the patient's father (2020SA001367) and not the child exposed to valproate via her father.

Among the 72 cases involving children exposed to valproate solely via the father, 6 cases concerned children presenting with NDDs, i.e., ASD (n = 1), "genotoxicity" without any further details, learning disorder, disturbance in social behaviour and fine motor delay (n = 1), learning disorder (n = 1), developmental delay, speech disorder developmental and learning disorder (n = 1), dyslexia (n = 1) and 'multidyslexia disorder' (n=1).

Among these 6 cases, valproate treatment was prescribed for epilepsy in 4 cases, for bipolar disorder in one case and for an unknown indication in the remaining case. In 5 cases, valproate was given as monotherapy based on available data, while in the 6th case, valproate was administered concomitantly with lamotrigine. The time of exposure to valproate was reported as, or estimated to be, before and during the conception in 2 cases. In the other 4

cases, the time of exposure was unspecified, and it could not be excluded that the “exposure” occurred only before or after conception.

No karyotype and hereditary investigations were reported in any of these 6 cases. Information on any medicines or other substances potentially bearing teratogenic properties that were taken by the pregnant mothers or to which they could have been exposed is lacking in these cases. Similarly, personal and family medical history of the fathers and of the mothers are not available.

Overall, very limited information are provided and no relevant conclusions can be made about NDDs based on these cases of paternal exposure.

The remaining 66 cases involving children exposed to valproate via the father were not associated with NDDs and further details were not provided by the MAH.

5.5 Literature review

The results from a nation-wide population-based study of the Swedish registries (Tomson and others, 2020) in offspring born to fathers without and with epilepsy (n=1,144,795 and n=4544, respectively), and in the latter with and without AEDs (n=2087 and n=2457, respectively) showed no significant increased risks of major congenital malformations, ADHD, ASD, and ID in offspring born to fathers with epilepsy exposed to AEDs compared to those in offspring born to fathers with epilepsy unexposed to AEDs (after adjustment).

Similarly, no significant increased risks were found when comparing the specific valproate group to the unexposed group. Notably, higher risks of ADHD, ASD, and ID in offspring born to fathers with epilepsy compared to those born to fathers without epilepsy were observed.

An additional publication aimed at investigating the risk of NDD in offspring paternally exposed to any AED, compared to unexposed children using a prospective Norwegian cohort (Veiby and others, 2013) (the MoBa cohort, constituting approximately 18% of all births in Norway), including all children born to mothers included in the MoBa cohort. NDD outcome was not based on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) coding algorithm but was prospectively assessed using scales to evaluate gross and fine motor skills, personal-social skills, autism, and autistics traits with mandatory visits up to 36 months.

The study showed a significant association between paternal exposure and occurrence of disorders of personal-social skills, autisms and autistic traits at 18 months of age when

compared to unexposed children. However, there was no statistically significant association at 36 months. The authors concluded that there was no NDD risk in offspring associated with AED paternal exposure, believing the results at 36 months to be more reliable than the clinical evaluation at 18 months. This study was assessed during the EU procedure in 2018.

6. Discussion

6.1 EU commissioned PASS

The primary finding of the study is that, after pooling non-significant propensity score weighted Cox model hazard ratio estimates from the three separate country-specific analyses, a statistically significantly higher risk of NDD, including autism spectrum disorder, among offspring from fathers exposed to valproate in the three months prior to conception in comparison to those exposed to lamotrigine/levetiracetam was observed (HR 1.50, 95% CI: 1.09, 2.07; p=0.0138). The same hazard ratios within individual country analyses were consistently but non-significantly greater than 1.

The study did not find any difference in risks of CM between the two paternal exposure groups. These findings were predominantly based on crude estimates, which are potentially confounded and also affected by moderate to substantial heterogeneity. The results for the CM outcome are difficult to interpret given they are unadjusted. As a result, the study limitations discussed below mostly relate to the results for the NDD outcome but, where relevant, limitations for the CM outcome have been highlighted.

6.2 Confounding

Potential residual confounding is considered to be the major limitation affecting the results and interpretation of this study. Several issues related to confounding were considered and are discussed below.

Propensity score models

Risk factors considered for inclusion in the propensity score models are shown in Table 1 and were considered to be appropriate. Variables were selected for inclusion in the propensity score models on the basis of their univariate association with the outcome. After delivery of the interim report this approach was queried by PRAC, and a request made for the models to include all identified risk factors for the outcome based on the literature. The consortium of MAH's agreed with PRAC's suggested approach but responded that updated analyses would need to be conducted under a new protocol. No comprehensive list of known risk factors was presented in the PASS or associated documentation, although the consortium highlighted that some risk factors would likely be highly missing so it wouldn't be possible to include them in models. The approach used to generate the propensity scores in the final version of the study

is therefore not ideal and may have led to the exclusion of potential confounders from the models (also highlighted by PRAC).

Choice of comparator and paternal indication for use

Offspring with fathers exposed to levetiracetam and lamotrigine were selected as the comparator group. These drugs are not associated with an increased risk of NDD, low birth weight for gestational age or congenital malformations from in-utero exposure via the mother and so this choice of comparator is reasonable from a safety perspective (Dreier and others, 2023). However, potential differences causing confounding by specific indication related to paternal epilepsy subtype remain and are discussed below.

From an efficacy perspective, the comparator may not be comparable with valproate in terms of the subtypes or severity of epilepsy for which they are prescribed. Valproate is often used in epilepsy patients where other treatments have proved ineffective (MHRA, 2021), resulting in possible confounding by indication.

Furthermore, precise data on indications for medications were not available in all the data sources used in the study. The indication was estimated based on searching the entire medical history for each father up to the estimated date of conception (LMP2 date) to identify diagnosis records of epilepsy and bipolar disorder/mania. In case more than one diagnosis was found, then priority was given to epilepsy followed by bipolar disorder/mania. If none of these diagnoses were found in the medical history, the indication was considered “other/unknown”. Indication was therefore considered a proxy and was not accounted for in the comparative analyses, compounding the likely effect of confounding by indication.

Paternal and maternal risk factors

Paternal linkage to the offspring might be misclassified when the registered father is not the biological father of the child, thus resulting in misclassification of paternal risk factors. It isn’t known what proportion of the cohort could be affected but is likely to be small and non-differential between the paternal exposure groups.

There was no information available on the subtype of epilepsy in the fathers, which is particularly relevant for epilepsies with a genetic predisposition (for example, idiopathic generalised epilepsy) and which could be associated with an increased risk of an NDD. Whilst fathers with a diagnosis of an NDD in their medical history were excluded from the comparative analysis, those with undiagnosed NDD would have remained. On average, the

valproate exposed offspring were more likely to be conceived in the earlier years of the study. Given trends in diagnosis of NDD it's possible this could result in differential levels of undiagnosed NDD between the exposure groups, leading to residual confounding. The study authors adjusted for year of conception to try and account for this, but without further information it is not possible to comment on how this may have impacted the results.

Maternal folic acid supplementation prior to and during early pregnancy is known for its role in the prevention of CMs, in particular neural tube defects and congenital heart defects. Data was not available on maternal folic acid supplementation in this study and is therefore a key potential confounder for the CM outcome. It is considered likely to be non-differential between the exposure groups. Some studies have suggested that the protective effects of folic acid may also extend to NDDs, including ASDs (Gao and others, 2016). A systematic review and meta-analysis (Hoek and others, 2020) has suggested an association between paternal folate status and sperm quality, fertility, congenital malformations and placental weight. The association between low folate intake and an increased risk of congenital malformations was, however, only based on one human study in this systematic review. In the current study, paternal folate status was not measured or adjusted for, so there is the potential for confounding, but given the paucity of studies evaluating associations between paternal folate status and congenital malformations, further studies are required to confirm this association. However, it is noted that maternal folate did not significantly alter IQ at age 6 years in a prospective cohort of children maternally exposed to valproate although there was an impact in those exposed to lamotrigine or phenytoin (Meador and others, 2013).

There was missing data on socioeconomic status, which is likely to be non-differential between the exposure groups and could potentially dilute the observed association. Other risk factors not adjusted for include genetic abnormalities and congenital infectious diseases which are also likely to be non-differential between the exposure groups.

Offspring risk factors

Offspring exposed to AEDs and/or diagnosed with epilepsy after birth were described but excluded from the comparative analyses for the primary outcome. Epilepsy and bipolar disorders are strong risk factors for NDD, therefore offspring with epilepsy or receiving AEDs are already at an increased risk of NDD independent of paternal AED exposure. The approach taken in the study is deemed appropriate.

6.3 Exposure

Exposure information was derived from medicine dispensation data as recorded in the National Prescription Registries for each of the three countries. Exposure to the AED was assumed to start on the dispensation date and is likely to be more reliable than if exposure was based on prescribing data, which assumes that the medicine was dispensed on the same day the prescription was issued.

Paternal exposure to AEDs was defined using a risk window of 3 months prior to the estimated date of conception. Given the sperm cycle is around 2-3 months, this window should capture all relevant exposures.

The date of conception could have been incorrectly estimated. With regards to the AEDs, the exposure window of 3 months prior to conception used may have been conservative and exposed fathers at the time of conception could have been misclassified as unexposed.

There was an attempt to investigate a dose-response relationship by estimating cumulative exposure in the three-month period prior to the LMP2 date (estimated date of conception). This was done by stratifying the cumulative exposure into tertiles based on number of days exposed (low, medium and high exposure), but the corresponding daily doses were not specified for each tertile. As a result, it is not possible to evaluate how the tertiles correspond to daily doses prescribed in the UK and any corresponding dose-response relationship.

6.4 Outcomes

The study used broad outcomes of NDD and CM in offspring. With regards to NDDs, individual NDDs were not evaluated, aside from the sensitivity analysis on ASD, as the study was designed and powered to investigate NDD as a composite outcome. Some of the ICD- 10 codes included were non-specific and so it isn’t clear how well these NDDs were classified especially across the three countries due to potential differences in diagnostic criteria. It is also likely the diagnosis of some non-specific NDDs could be delayed, for example, if mild in their manifestation, or underdiagnosed or misclassified.

Sensitivity analyses focusing on a narrow definition of NDD showed that the risk estimates varied in strength and significance compared to those from the main analysis, and these variations were not consistent across the 3 countries. For example, with sensitivity analysis 2 focusing on ASD as primary outcome, the association reversed toward a non-significant reduced risk with the paternal exposure to valproate in Denmark, while the risk almost doubled and became significant with this exposure in Sweden.

Differences in the length of follow-up were observed between countries and between exposure groups. In Denmark and Sweden, where offspring were followed from birth to 12 years of age, follow-up was shorter in Sweden; 23.3% of the offspring in the lamotrigine/levetiracetam group were followed-up in Sweden for more than 8 years versus 41.8% in the valproate group compared with in Denmark, 40.2% lamotrigine/levetiracetam group followed-up more than 8 years versus 74.3% in the valproate group. This may explain the lower rate of ASD captured in the lamotrigine/levetiracetam group in Sweden compared to Denmark and may highlight the impact of the follow-up duration on the results. These sensitivity analyses relied on a lower number of events and estimates and will be more prone to instability and lower reliability. Offspring paternally exposed to valproate were systematically more frequently conceived in the earlier years of inclusion than those exposed to lamotrigine/levetiracetam, although this variation was minor in Norway. As a result, offspring paternally exposed to valproate had on average a longer follow-up time and a higher probability of presenting NDD, including ASD diagnoses. Considering that the risk of being diagnosed with NDD including ASD is not constant across ages but rather detected at later ages when children start school (i.e., from 5 or 6 years old), this may have biased the risk estimates generated from Cox regression models.

With regards to CMs, information about spontaneous abortions and stillbirths were not available in Sweden, for Denmark before the 22nd week of pregnancy and for Norway before the 12th week of pregnancy. Diagnoses of CM leading to spontaneous abortion and elective terminations of pregnancies which occurred before these weeks of gestation were, therefore, undetectable and not included as outcomes. This may have led to a selection of cases and to a survivor bias as the distribution of type of CM and severity is likely to be different.

6.5 Meta-analysis methodology

As the results were pooled in a meta-analysis, the analyses are subject to several limitations.

In some analyses, the I^2 statistic was low suggesting low heterogeneity, however confidence intervals were quite wide, suggesting uncertainty in those results. This was compounded by the meta-analyses being limited to three sets of results for the primary outcome (DE, SE and NO) and two sets of results for the secondary outcome (DE and NO). The pooled results for the secondary outcome showed significant heterogeneity (I2=49.6%) and risk estimates in opposite directions for DE (OR = 0.62, 95% CI: 0.37, 1.04) and NO (OR = 1.06, 95% CI: 0.62, 1.82), which make the results difficult to interpret.

The country-specific results, from which the pooled results were derived, may be subject to residual confounding because of differences in the availability of covariates and strength of the associations between exposures and outcomes. This will then affect the degree of adjustment for potential confounding.

6.6 Generalisability

The PASS was conducted in three countries in Northern Europe, SE, NO and DK. The chosen data sources cover the entire population of the countries, as well longitudinal data of patients. The data sources have been used in many other pharmacoepidemiological research studies. The databases selected were the only available databases with children linked to their fathers based on nationwide registries. A high rate of paternal offspring linked data is available in those registries, 97.5% in DK, 97% in NO and 90% in SE.

The study excluded twins, parents with a history of NDD/CM regardless of outcome studied and mothers with a history of epilepsy. Given all of these are risk factors for NDD and CM in offspring, it was deemed appropriate to make these exclusions in order to try to tease out the drug effect of paternal AED exposure on outcomes in offspring.

6.7 Other Data

The biological mechanism for the transmission of the risk of NDD from the father to the child could relate to genetic or epigenetic changes in the sperm DNA. The risk related to exposure via semen has been estimated during the EU Referral in 2018. The conclusions were that the estimated level of valproate in maternal plasma following exposure via seminal fluid is 25,000 times less than concentrations that would be present in maternal plasma after a standard dose of valproate. Hence transmission of harm to the offspring from exposure to valproate through the seminal fluid is considered unlikely. Specific data have not been provided by the MAH.

There is a lack of data on the specific impact of valproate on sperm DNA provided by the MAH. The current SmPC has information related to genotoxicity which is conflicting and states that whilst in vitro somatic cell studies do not show evidence of DNA repair in rat hepatocytes, there is some evidence of increased DNA strand-breaks and chromosomal damage in rodents (which includes sperm DNA). In addition, increase sister-chromatid exchanges in patients with epilepsy exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, recent regulatory-compliant in vitro studies performed by the MAH at the request of PRAC, have suggested that valproate is neither mutagenic nor clastogenic.

There are published literature discussing the possibility of the HDAC inhibitory properties of valproate and that this may be a mechanism for epigenetic change in the sperm but this

requires confirmation. The epigenetic studies in the male germ cell are underway in Europe with the final report due in 2025. An Expert Working Group of the CHM is considering evidence as to whether valproate is an HDAC inhibitor and the potential for HDAC inhibition at clinically relevant exposures.

The spontaneous adverse drug reports of NDDs following paternal exposure to valproate lack the necessary detail for a causal association assessment. The literature studies have not shown an increased risk of harm to the child following paternal exposure. The results of this retrospective observational study are the first to show the association.

6.8 Opportunities for further epidemiological studies

The linked data sources used in the current study covered the entire population of the countries as well as longitudinal follow-up patients. There are very limited opportunities worldwide to explore the association between paternal exposures and offspring outcomes because paternal health records are rarely linked to their children.

In order to replicate this study in another database, the data source would need to record sufficiently large patient exposure to valproate and the comparator. The current study was powered to detect a hazard ratio of 2.0 for the primary outcome with 5% significance and 80% power equating to a minimum of 589 offspring within a family linked unit with paternal exposure to valproate (monotherapy) and a minimum of 589 offspring within a family linked unit with paternal exposure to lamotrigine/levetiracetam (composite therapy). The individual country-specific cohorts were larger than this and a small association was found following pooling of the results in a meta-analysis. A future study would therefore need to be as large as the current one.

The UK Clinical Practice Research Datalink (CPRD) is likely to suffer from similar limitations as the current study with regards to missing data on indication for AED use, NDDs, CMs and important confounders. Importantly, the CPRD does not currently provide linkage of the father to the child through the primary care record, although one study recently attempted to develop a mother-father-child triad linkage within CPRD to explore the clinical characteristics of children affected by intimate partner violence (Syed and others, 2023). Developing and validating this linkage would be resource-intensive and require funding to develop an appropriate methodology.

The US insurance claims databases may permit linkage of parents to their children if the parents' insurance plan applies to the whole household. However, patient follow-up time in these databases is likely to be lower than in the Scandinavian databases and registries.

Again, there is also likely to be missing data on indication important confounders. It is also understood that valproate is much less commonly used in the US compared to the newer anti-seizure medication.

The NEAD study, which provided the pivotal evidence on the magnitude and extent of sustained neurodevelopmental disorders in children exposed to valproate through their mothers was a prospective resource intensive cohort study. Replicating such a study to explore a potential paternal risk would be very challenging both in terms of cohort identification and the number of patients needed to explore a lower magnitude of risk.

7. CHM advice

On the basis of the evidence provided, the CHM and the PEAG were asked to advise on the strength of evidence for an association between paternal valproate use and the risk of NDDs and CMs in the child and whether there are alternative data sources which would provide further opportunities to study this research question. A range of regulatory options were presented to the CHM by the MHRA for their advice.

The PEAG considered in detail the design of the study and advised that the study sample sizes were large enough to detect a Hazard Ratio of 2, and pooling of the data from individual countries had resulted in narrowing of the confidence intervals and a statistically significant result. Given this, alongside limitations in the data, the evidence base can be considered modest. The study author conclusions were appropriate, in that the study design could not demonstrate causality.

The PEAG advised that the composite primary outcome grouped a range of distinct neurodevelopmental outcomes, which creates “noise” and leads to a lack of sensitivity. The average age of diagnosis of the neurodevelopmental disorders in Scandinavia is 6-7 years, meaning many children in the study would not have had long enough follow-up to present/be diagnosed. There was a lack of findings from analyses aiming to explore a dose-response relationship.

The PEAG discussed that confounding by indication was likely to be an issue due to valproate and lamotrigine/levetiracetam being used to treat different indications and subtypes of epilepsy. It is also likely that there are genetic differences between the exposure groups because of these differences.

The PEAG commented that the differences in length of follow-up between the exposure groups had not been fully accounted for in the study. As an older drug, there may have been higher rates of undiagnosed mental health and neurodevelopmental disorders in fathers taking valproate versus lamotrigine and levetiracetam.

The PEAG advised that the study analysis could be strengthened with further analyses. Suggested analyses included quantitative bias analysis; modelling to test assumptions about the impact of missing confounders; and use of a negative control for outcome or exposure.

Use of a historic control group who had used valproate in the past (at least 6 months prior) was suggested as an alternative control group. OpenSafely was suggested as a future data source.

The PEAG suggested that a prospective study would be a suitable next step to enhance the evidence base. This would allow improved choice of outcomes (for example, IQ) and per protocol, blinded outcome assessment. The PEAG commented that work into the feasibility of a prospective study looking at paternal valproate use was underway in Manchester and that Seagull in Liverpool could possibly provide useful birth cohort data.

The PEAG agreed that layering of evidence is required to improve the evidence base, with use of different data sources and methodologies, as opposed to repeating a similar database study given the data limitations.

The PEAG commented that the PASS study results must be seen in the context of available preclinical data on valproate exposures, which raise concerns about effects of valproate on spermatozoa and behavioural changes in the offspring. The PEAG agreed that the data on effects of valproate on the testes are a concern and that the totality of data should be taken into account when reaching a consensus on communications to patients.

The PEAG advised that the overall approach should be a balance between sharing information and regulatory action. They noted the potential risk for unintended consequences from regulatory action and the need to monitor the impact of any regulatory action.

The CHM considered the advice of the PEAG and proposals for updates to the valproate licence and additional risk minimisation materials and discussed the need for shared responsibility of all healthcare providers in the healthcare system to ensure male patients are made aware of the new information.

The CHM advised that general practitioners issuing repeat prescriptions and community pharmacists should be involved in regular medication reviews and that prescribing systems such as EMIS could help reinforce the messaging.

The advice of the CHM was sought on proposals for the valproate SmPC and PIL and additional risk minimisation materials including adding the results of the study to the male risk acknowledgement form, developing a separate patient guide for male patients and whether the existing patient card should remain specific to the Pregnancy Prevention Programme and maternal risks or include risks to male patients. The advice of the CHM was sought on any appropriate methods for communicating the risks to male patients.

SmPC and PIL updates

Results of the PASS

The CHM advised that the study results should be included in the product information and that reference to uncertain causality should not be included. The CHM advised that whilst this study doesn't prove causality of valproate causing NDDs Iin the children of fathers who were taking valproate when the child was conceived, it equally does not disprove causality. Therefore the advice in the SmPC should reflect the totality of information available including that on testicular toxicity, male infertility and the ongoing work of the epigenetics expert working group and avoid using confusing causality statements for healthcare professionals and patients.

Contraception advice

The CHM advised that as a precaution, there should be a clear recommendation for the male patient and their partner to use contraception.

Advice for sperm donation.

The CHM advised that the product information should be updated to include advice on avoidance of sperm donation during treatment and for 3 months after stopping valproate.

Advice for regular review of male patients

The CHM advised that regular review of male patients by prescribers should be included in the valproate product information, in line with current good medical practice.

Advice for planning to conceive

The CHM advised that the product information should include a recommendation for men planning to conceive to discuss the risk of neurodevelopmental disorders and consider other treatments with their prescriber.

Additional risk minimisation materials

Risk acknowledgement form for male patients starting valproate

The CHM advised that the male risk acknowledgement form should be updated with the PASS results, contraception advice and the need to avoid sperm donation while being treated with valproate.

Male Patient Guide

The CHM noted that a separate male patient guide, would be helpful and that the information should be developed through engagement with relevant stakeholders including patients, patient organisations and charities to ensure balanced messaging, particularly as valproate can cause male infertility and also now requires the use of effective contraception by male patients and their female partners.

Communication

The CHM advised that careful updates to the risk minimisation materials will be required and that these should be developed over the coming months, in collaboration with stakeholders including patient groups, charities and professional bodies.

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9. Glossary of terms

Antiepileptic drug or AED

A drug used to treat epilepsy, mainly by controlling or managing the occurrence of seizures in a patient with epilepsy. Also called anti-seizure medicine or epilepsy medicine.

Anti-seizure medication or ASM

A drug used to treat epilepsy, mainly by controlling or managing the occurrence of seizures in a patient with epilepsy. This term may be more commonly used in UK clinical practice than antiepileptic drug.

Autism spectrum disorder

Autism is a lifelong developmental disability which affects how people communicate and interact with the world. Autism is a spectrum condition and affects people in different ways.

Bipolar disorder

Bipolar disorder is a mental health condition that affects moods and can make them swing from one extreme to another. It used to be known as manic depression. People with bipolar disorder have episodes of depression (feeling very low and lethargic) and mania (feeling very high and overactive). Unlike simple mood swings, each extreme episode of bipolar disorder can last for several weeks (or even longer).

Cleft lip or palate

A cleft is a gap or split in the upper lip or roof of the mouth (palate). Cleft lip and palate can each occur alone or together. It is the most common facial birth defect in the UK affecting around 1 in every 700 babies.

Clinical data or clinical studies

Data on the effects of medicines that come from studies of people taking the medicines. This includes data from clinical trials and epidemiological studies.

Cohort study

In a cohort study, a group of individuals exposed to a risk factor and a group who are unexposed to the risk factor are followed over time (often years) to determine the occurrence of disease. The incidence of disease in the exposed group is compared with the incidence of disease in the unexposed group.

Commission on Human Medicines

The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products.

Confidence interval

A statistical range of numbers with a specific probability that a particular value lies within this range. Confidence intervals (CI) are used to assess the true difference in risk between two groups, and usually accompany ratio values such as odds ratios, hazard ratios and ‘observed versus expected’ ratios. A 95% CI suggests that there is a 95% chance that the real difference between two groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant.

Confounds/confounding/confounded

Where people who receive a medicine are also more likely to have a particular risk factor then they may be more likely to develop a medical condition because of this risk factor and not because of the medicine. This can affect the results of epidemiological studies.

Congenital

A medical condition that is acquired by the fetus during pregnancy and is present at birth.

Congenital Malformations

A physical defect present in a baby at birth that can involve many different parts of the body, including the brain, heart, lungs, liver, bones, and intestinal tract.

Contra-indicated/Contraindication

When a drug should not be used in a specific situation, condition or group of people because it may be harmful to the person.

Defect

A fault or imperfection in the body.

Developmental Delay

Where a child had not gained the developmental skills expected of them, compared to others of the same age. Delays may occur in the areas of motor function, speech language, cognition, play and social skills.

Diagnostic and Statistical Manual of Mental Disorders or DSM

A classification of mental disorders and associated criteria for their diagnosis produced by the American Psychiatric Association.

Epidemiological studies

Studies which assess trends in the occurrence, distribution or control of diseases or medical conditions in defined populations.

Epigenetic / Epigenetic factors

Epigenetics are how your behaviours and environment can cause changes that affect the way your genes work (your genetics)

Epilepsy

A brain condition characterised by fits or seizures.

Generalised seizures

A generalised seizure starts when all areas of the brain are affected by an abnormal electrical impulse and happen without warning. There are different types of generalised seizures, including: absence seizures (petit mal seizures), myoclonic seizures, and clonic seizures. The person will be unconscious (except in myoclonic seizures), even if just for a few seconds and afterwards will not remember what happened during the seizure.

Good Laboratory Practice

A set of rules and criteria intended to assure the quality and integrity of non-clinical laboratory studies.

Healthcare databases

Healthcare databases are systems into which healthcare providers routinely enter clinical and laboratory data during usual practice as a record of the patient's care.

Incidence

The occurrence of new cases of a disease or condition in a population over a specified time period.

Indication

The disease or condition, or manifestation or symptoms thereof, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

In-utero

The time that the fetus is in the uterus of the pregnant female.

Major congenital malformations

Physical defects present in a baby at birth that have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention.

Marketing authorisation holder

The company or other legal entity that has the authorisation to market a medicine in the UK.

Meta-analysis

A meta-analysis is a statistical analysis that combines the results of multiple scientific studies.

Monotherapy

The treatment of a disease or condition with a single medicine.

Motor skills

Motor skills are movements and actions of the muscles to perform a specific task. Fine motor skills refer to small movements in the hands, wrists, fingers, feet, toes, lips and tongue.

Gross motor skills involve motor development of muscles that enable babies to hold up their heads, sit and crawl, and eventually walk, run, jump and skip.

Myoclonic seizures

Myoclonic means ‘muscle jerk’. Myoclonic seizures are brief but can happen in clusters (many happening close together in time), and often happen shortly after waking. They are classified as generalised seizures because the person is likely to have other seizures as well as myoclonic seizures.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Their role is to improve outcomes for people using the NHS and other public health social care services. They also provide clinical guidance on how to manage specific conditions in England.

Neonate

Newborn infant.

Neural

Relating to a nerve or the nervous system.

Neural tube defects

Neural tube defects are birth defects of the brain, spine, or spinal cord. The neural tube is the structure that eventually develops into the baby’s brain and spinal cord. The neural tube starts to form in early pregnancy and closes about 4 weeks after conception. Spina bifida is a type of neural tube defect. In spina bifida, part of the neural tube does not develop or close properly, leading to defects in the spinal cord and bones of the spine (vertebrae).

Neurodevelopment

A general term used to encompass the development of the nervous system.

Neurodevelopmental disorders and delay

A group of disorders in which the development of the central nervous system is disturbed. The disorders can affect emotion, learning ability, self-control and memory. They can also manifest as conditions such as attention deficit hyperactivity disorder or autism spectrum disorder.

Neurogenic

Effects or conditions giving rise to or arising from the nerves or the nervous system.

Neurons

Nerve cells that send information to each other by releasing chemicals, known as neurotransmitters, across junctions known as synapses.

Non-clinical studies

In drug development, preclinical development, also named preclinical studies and non- clinical studies, is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data are collected. Used interchangeably with the term ‘pre-clinical studies’ within this report.

Patient Information Leaflet

Every medicine pack includes a patient information leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics (SPCs) which are a description of a medicinal product’s properties and the conditions attached to its use.

Partial seizures

See focal seizures.

Pervasive developmental disorders

A group of disorders characterized by delays in the development of socialization and communication skills. Parents may note symptoms as early as infancy, although the typical age of onset is before 3 years of age.

Pregnancy Prevention Programme

A Pregnancy Prevention Programme is a set of measures that are intended to minimise the risk for the both the women and the unborn baby associated with the use of a medicine in women of childbearing age and during pregnancy.

Pregnancy Registry

A study that collects health information from women who take prescription medicines or vaccines when they are pregnant. Information is also collected on the newborn baby.

Prenatal

Before birth, during or relating to pregnancy.

Prospective cohort study

A prospective study asks a specific study question (usually about how a particular exposure affects an outcome), recruits appropriate participants, and looks at the exposures and outcomes of interest in these people over the following months or years.

Retrospective study

A study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls). A retrospective study looks backwards and examines the medical and lifestyle histories of the people in each group to learn what factors may be associated with a disease or condition that is established at the start of the study.

Risk factor

A substance or activity that increases the likelihood of someone developing an illness or medical condition.

Risk Ratio/Relative Risk

A risk ratio (RR), also called relative risk, compares the risk of a health event (disease, injury, risk factor, or death) among one group with the risk among another group.

Seizure

Uncontrolled electrical activity in the brain that produces fits or convulsions of the body.

Spontaneous abortion

Is the loss of a pregnancy naturally before 20 weeks of gestation.

Summary of Product Characteristics (SmPC)

Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at: https://www.gov.uk/guidance/find-product-information-about-medicines

Systematic review

A review of the published scientific literature that aims to find as much as possible of the research relevant to a particular research question and based on appraisal of the research summarises the main findings (qualitative or quantitative).

Teratogen/ teratogenic

A teratogen is an agent that can disrupt the anatomical development of the embryo resulting in a birth defect.

Tonic clonic seizures

The type of epileptic seizure most people recognise. There are two phases to these seizures. In the first phase the ‘tonic’ phase the person will lose consciousness and won’t be aware of what is happening, their muscles will go stiff and so they may fall (if standing) and also bite their tongue. In the second phase the ‘clonic’ phase their limbs will jerk quickly and rhythmically and they may lose control of their bladder and/or bowels. They are likely to feel confused or sleepy afterwards and take a while to recover fully.

Transgenerational effects

Transgenerational effects are effects than can pass from a mother or father through successive generations of a family, such as to children or grandchildren.

Trimester

One of the three 3-month periods that a human 9-month pregnancy can be divided into.