Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Advisory Committee on Medicines Minutes
Item 3.01

Sodium valproate and use in pregnancy

Sponsors: Sanofi-Aventis Australia Pty Ltd and multiple generic sponsors

April 2024

Contents

Medicine details

Details	
Product names:	EPILIM (Sanofi-Aventis Australia Pty Ltd) There are also multiple generic brands by AFT Pharmaceuticals Pty Ltd, Alphapharm Pty Ltd, Apotex Pty Ltd, Juno Pharmaceuticals Pty Ltd and Wockhardt Bio Pty Ltd.
Active ingredient:	sodium valproate
Approved strengths and dose forms:	Tablets (100 mg) Enteric-coated tablets (200 mg and 500 mg) Syrup (200 mg per 5 mL) Powder for injection (400 mg) Solution for injection (300 mg/3 mL; 400 mg/4mL; 1000 mg/10 mL)
Current indications:	Epilepsy: Primary generalised epilepsy (petit mal absences, various forms of myoclonic epilepsy and tonic-clonic grand mal seizures). Partial (focal) epilepsy either alone or as adjuvant therapy. Mania: For the treatment of mania where other therapy has proved inadequate or is inappropriate.
Off-label uses include:	Migraine prevention; Neuropathic pain; 'Mood stabilisation'; Status epilepticus; Status migrainosus; Cyclic vomiting

Documents submitted for ACM consideration

The ACM considered the following documentation for this post-market request for advice:

A1 Delegate's Summary and Request for ACM Advice
A1a TGA – MSSI Signal Analysis – date
A1b UK MHRA – Public Assessment Report – November 2023
M5 TGA – Clinical evaluation report

Delegate's Overview

Delegate's summary of issues

The Delegate identified the following in their request for ACM advice.

The UK's Medical & Healthcare products Regulatory Agency (MHRA) has introduced new safety measures to reduce the known harms of valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the emerging data on the risk of harms in male patients.

In the UK from January 2024, valproate must not be started in new patients (male or female) younger than 55 years, unless 2 specialists independently consider and document that there is no other effective or tolerated treatment, or unless there are compelling reasons that the reproductive risks do not apply. All UK female patients of childbearing potential and girls who are currently taking valproate will be reviewed at their next annual specialist review, using a revised valproate Annual Risk Acknowledgement Form, which will include the need for a second opinion's signature if the patient is to continue with valproate. A similar system will be introduced later in 2024 for male patients currently taking valproate.

In Australia, valproate is included in Use in Pregnancy Category D.[1] (Note: The TGA did not propose, and the ACM did not suggest, a change to Category X).

Sodium valproate and use in pregnancy and women of child-bearing age was discussed by the ACM in June 2018 (meeting 9). At the time it was recommended that prescribers be educated on the risk of sodium valproate use in pregnancy. The ACM did not support the introduction of a pregnancy prevention program in Australia at that time.

Sanofi-Aventis has recently sought to update the Epilim Product Information on the risk of neurodevelopmental disorders (NDD) in children born to males being treated with valproate, including autism spectrum disorders (ASD) after paternal exposure to valproate and additional nonclinical information relating to testicular function.

The TGA's Clinical Evaluation Report references a retrospective observational study on electronic medical records in 3 Nordic countries that indicates an increased risk of NDDs in children (from 0 to 11 years old) born to men treated with valproate at the time of or in the 3 months prior to conception compared to those treated with lamotrigine or levetiracetam.

Delegate's preliminary position

The Delegate intends to agree to the PI changes requested by Sanofi.

Given the extensive information about risk in pregnancy in the current (and proposed) PI, the only further restrictions that could be added would be for age groups.

Advice sought by Delegate of the Secretary of Department of Health and Aged Care

1. Noting that the MHRA has not proposed a change to the indication within the UK-SmPC (PI equivalent), does the Committee consider there is sufficient evidence to warrant amending the indication and/or prescribing requirements and recommendations of valproate in the Australian PI?

2. Previous advice from PBAC was based on PBS's stance on avoiding gender-based access to valproate. Noting that the latest MHRA prescribing restrictions are applicable to both men and women, does the Committee support the referral of this issue to PBAC for consideration of relevant prescribing amendments?

3. Are there other risk minimisation activities that the TGA could consider for this issue?

[1] Use in Pregnancy Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

4. Regarding the emerging information on the risk of exposure to valproate through paternal exposure, and noting the sponsor-initiated PI update to include the risk of neurodevelopmental disorders in children born to males being treated with valproate/reproductive toxicity in males, does the Committee consider that further risk minimisation measures are currently required in Australia?

ACM discussion

General comments

The ACM noted that the known adverse events from valproate (weight gain, tremor, alopecia) often deter prescribers and patients.

Valproate has paediatric uses, and so patients can transition into reproductive age while on valproate.

The ACM noted recent studies on the effectiveness of valproate for a range of conditions, including reports that showed valproate to be more effective than levetiracetam in juvenile myoclonic epilepsy,[2] and to have protective effects similar to lithium, quetiapine, olanzapine, carbamazepine and lamotrigine in bipolar disorders.[3]

The ACM considered the long-documented history of teratogenicity following maternal valproate: initially spina bifida, then other structural anomalies, and more recently neurobehavioural effects (with and without congenital malformations). Up to 30% of individuals may be affected, and no threshold dose below which no risk exists has been established. Much of these data were available prior to 2018.

The ACM also noted that there is dose-related teratogenicity with lithium and reassuring data with regard to both structural malformations and neurodevelopmental outcomes with lamotrigine.[4]

The ACM noted the ongoing value from already implemented practices supporting appropriate prescribing, education of patients and clinicians, and pharmacovigilance activities.

The ACM noted that despite the uncertainty of effectiveness, folic acid supplementation 4 to 5 mg/daily prior to and in early pregnancy to prevent congenital anomalies continues to be recommended for women on anti-epileptic drugs.

Recent Australian experience

The ACM noted the TGA's view that it is difficult to quantify the number of Australian pregnancies that were exposed to valproate given the potential for overlap between reporting of literature article cases and case reports; the TGA was notionally aware of 109 cases from the period 2019 to 2023 inclusive. There has been no reported Australian case involving paternal exposure to valproate.

The ACM noted unpublished data of falling numbers of inquiries to MotherSafe on the use of valproate in pregnancy as well as cases of paternal exposure.

[2] Zhang Y, Chen J, Ren J, Liu W, Yang T, Zhou D. Clinical features and treatment outcomes of Juvenile myoclonic epilepsy patients. *Epilepsia Open*. 2019 Apr 19;4(2):302-308. doi: 10.1002/epi4.12321.

[3] Yee CS, Vázquez GH, Hawken ER, Biorac A, Tondo L, Baldessarini RJ. Long-Term Treatment of Bipolar Disorder with Valproate: Updated Systematic Review and Meta-analyses. *Harv Rev Psychiatry*. 2021 May-Jun 01;29(3):188-195. doi: 10.1097/HRP.0000000000000292.

[4] Patorno E, Huybrechts KF, Bateman BT, Cohen JM, Desai RJ, Mogun H, Cohen LS, Hernandez-Diaz S. Lithium Use in Pregnancy and the Risk of Cardiac Malformations. *N Engl J Med*. 2017 Jun 8;376(23):2245-2254. doi: 10.1056/NEJMoa1612222.

ACM advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***Noting that the MHRA has not proposed a change to the indication within the UK-SmPC (PI equivalent), does the Committee consider there is sufficient evidence to warrant amending the indication and/or prescribing requirements and recommendations of valproate in the Australian PI?***

The ACM advised that there is insufficient evidence to warrant amending the indication (such as to exclude women of child-bearing age). There has been no real change in the risk profile to infants following maternal exposure since the ACM last reviewed this issue in 2018, and the risk profile to infants following paternal exposure has been insufficiently explored (see Q4).

The ACM suggested that the PI could include prescribing recommendation to encourage consideration of potential impacts on fertility (for both males and females), teratogenic risks, pregnancy prevention and contraceptive advice for all patients in determining whether valproate is the best treatment choice. The ACM noted that the Australian PI currently contains information on these risks in Section 4.4 (a 3 page warning on pregnancy and women of childbearing potential). Any other changes to the PI should make clear study limitations and areas where data are insufficient.

The ACM noted ongoing interest in the role of shared decision-making on the use of valproate.[5]

The ACM noted that the agenda paper did not contain post-2018 data from the Australian Pregnancy Register of Antiepileptic Drugs in Pregnancy (APR), which may show the impact on prescribing trends of the initiatives introduced following the ACM's advice in 2018, for example, pregnancy warning graphic and wording on packaging and educational initiatives undertaken with *Therapeutic Guidelines* and relevant professional colleges.

The ACM noted that the USA prescribing information includes a boxed warning on teratogenicity and that no further changes are currently under consideration in the USA.

2. ***Previous advice from PBAC was based on PBS's stance on avoiding gender-based access to valproate. Noting that the latest MHRA prescribing restrictions are applicable to both men and women, does the Committee support the referral of this issue to PBAC for consideration of relevant prescribing amendments?***

The ACM recalled its 2018 advice that 'consideration could be given to implementing mechanisms [PBS] that could reduce inappropriate prescribing in female patients between 14 and 50 years of age and use for non-seizure related indications. The effect of any actions taken should be reviewed after two years'.[6] This was not implemented as the TGA was informed that the PBS avoids using a patient's sex as a criterion for access to medicines.

The ACM suggested that the PBAC could be asked to consider expanding access to lamotrigine (for bipolar disorder) and levetiracetam, which could reduce the usage of valproate.

3. ***Are there other risk minimisation activities that the TGA could consider for this issue?***

The ACM advised the UK's approach of 2 specialists to independently consider and document the necessity to commence or continue valproate would create a substantial burden in the Australian context for patients and prescribers.

An annual consent process would provide opportunities for improved patient education; such an approach would be feasible and have medicolegal benefits. While this would be outside the scope of

[5] Macfarlane A, Greenhalgh T. Sodium valproate in pregnancy: what are the risks and should we use a shared decision-making approach*? BMC Pregnancy Childbirth*. 2018 Jun 1;18(1):200. doi: 10.1186/s12884-018-1842-x.

[6] ACM meeting statement, Meeting 9, 31 May - 1 June 2018 | Therapeutic Goods Administration (TGA)

the TGA, it could be referred to the relevant specialist colleges as a consideration, to aid clinicians in their patient discussions (rather than as a mandated requirement).

4. Regarding the emerging information on the risk of exposure to valproate through paternal exposure, and noting the sponsor-initiated PI update to include the risk of neurodevelopmental disorders in children born to males being treated with valproate/reproductive toxicity in males, does the Committee consider that further risk minimisation measures are currently required in Australia?

The ACM noted that the data relied on by the MHRA to form its view contained errors and required re-analysis, which was not yet available.[7] Regulatory action beyond continued educational measures would be premature at this time. The proposed PI changes on paternal exposure were based on limited data with acknowledged limitations and causation has not been demonstrated.

Regarding the IQVIA Valproate EU consortium study,[8] the ACM advised that due to methodological limitations, especially the difference in follow-up time between the 2 paternal exposure groups which may impact the interpretation of the results, the findings regarding risk of neurodevelopmental delay should be interpreted with caution. Also, while the study did not find any difference in risks of congenital malformations 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.

Further, the ACM noted the findings by Tomson et al (2020)[9] from a registry-based cohort study of over a million births, including 4,544 births with 2,955 fathers with epilepsy, of whom 45.9% had had dispensed an antiepileptic drug during the conception period. No difference was found in risk of major congenital malformations, autism spectrum disorder, ADHD or intellectual disability with or without conceptional exposure. In the valproate monotherapy subgroup there were slightly higher rates of autism and intellectual disability that did not reach statistical significance.

The basis of choice of paternal age of 55 years was unclear. Paternal age and underlying paternal disease, and epigenetic changes, should be considered in any exploration of biological plausibility and resultant prescribing guidelines or precautionary measures.

Ratified and provided to the Delegate on 22 April 2024.

[7] Valproate-report-review-and-expert-advice.pdf (publishing.service.gov.uk)
[8] Valproate_PASS_Abstract_V2.0_0.pdf (europa.eu)
[9] Tomson T, Muraca G, Razaz N. Paternal exposure to antiepileptic drugs and offspring outcomes: a nationwide population-based cohort study in Sweden. *J Neurol Neurosurg Psychiatry*. 2020 Sep;91(9):907-913. doi: 10.1136/jnnp-2020-323028.

Therapeutic Goods Administration

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Reference/Publication #

Item 3.01 sodium valproate Post-market item

ACM 44

4 AND 5 APRIL 2024

SPEAKER: s22 [redacted]

Submission information

The MHRA has introduced new safety measures to reduce the known harms of valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the emerging data on the risk of harms in male patients.

It is recommended that this issue be reviewed by the Advisory Committee on medicines (ACM) to determine if it is appropriate for Australia to introduce stricter prescribing requirements for this medication. The TGA will need to refer to the PBAC if considering making changes to existing PBS listings.

International regulatory status-MHRA (UK)

From January 2024, 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 unless there are compelling reasons that the reproductive risks do not apply

All female patients of childbearing potential and girls who are currently taking valproate will be reviewed at their next annual specialist review, using a revised valproate Annual Risk Acknowledgement Form, which will include the need for a second opinion's signature if the patient is to continue with valproate.

Similar system will be introduced later in 2024 for male patients currently taking valproate

Follows advice from an independent expert group of the Commission on Human Medicines, with representation from across the healthcare system, that the measures should be introduced in a phased manner to ensure ongoing patient care is not disrupted

Europe

EMA and CMDh endorsed measures to avoid valproate exposure in pregnancy in 2018

Valproate must not be used in girls and women able to have children unless terms of specific **pregnancy prevention programme** followed:-

- Assessment of patient's potential to become pregnant
- Pregnancy tests before starting and during treatment as needed
- Counselling about risks of valproate treatment and need for effective contraception throyghout treatment
- Review of ongoing treatment by a specialist at least annually
- Introduction of a **risk acknowlegment form** that patient and prescribers will go through at each annual review to confirm that appropriate advice has been given and understood

Changes to product information leaflet(package and SmPC for HCP) and packaging including**visual warning with boxed test**

Educational materials and **patient alert card**

EMA

- European Medicines Agency have also released updated guidance on the use of valproate in “people who produce sperm”
- Their advice is that valproate treatment in these patients is initiated and supervised by a specialist, discuss contraceptive options with these patients, recommend they do not donate sperm and that healthcare professionals discuss these potential risks
- They do also highlight that the study had limitations, specifically differences in the types of epilepsy that the medications were used in and follow up times, as such they were unable to determine if there was a direct relation to valproate use

Document 2

International regulatory status-USA

US Product information

5.4 Use in Women of Childbearing Potential Because of the risk to the fetus of decreased IQ and major congenital malformations (including neural tube defects), which may occur very early in pregnancy, valproate should not be administered to a woman of childbearing potential unless the drug is essential to the management of her medical condition. This is especially important when valproate use is considered for a condition not usually associated with permanent injury or death (e.g., migraine). Women should use effective contraception while using valproate. Women who are planning a pregnancy should be counseled regarding the relative risks and benefits of valproate use during pregnancy, and alternative therapeutic options should be considered for these patients

WARNING: LIFE THREATENING ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

- **Hepatotoxicity, including fatalities, usually during first 6 months of treatment. Children under the age of 2 years are at considerably higher risk of fatal hepatotoxicity. Monitor patients closely, and perform liver function tests prior to therapy and at frequent intervals thereafter (5.1)**
- **Teratogenicity, including neural tube defects (5.2)**
- **Pancreatitis, including fatal hemorrhagic cases (5.3)**

At present no changes to current prescribing or warnings

Australia-Current regulatory status and PBS

Issue previously discussed at ACM in 2018

Recommended that prescribers be educated on the risk of sodium valproate use in pregnancy and to undertake risk communications in relation with prescribing

At that stage the introduction of a pregnancy prevention program in Australia was not deemed necessary (unlike Europe)

TGA also considered a suggestion to avoid exposure to sodium valproate during pregnancy and to minimise use in female patients of childbearing age by altering the PBS listing

However TGA was informed that the PBS avoids using a patient's sex as a criteria for access

Thus implementing a more restrictive listing for women than for men was unlikely to be considered appropriate and would be contrary to the usual practices

In addition there was also a concern that if a separate PBS item listing was created for women of childbearing potential, then prescribers would instead use the unrestricted item to reduce administrative burden

Australian valproate exposure data

Case search performed on 15 December 2023 for ‘sodium valproate’ and ‘valproic acid’ and the PTs ‘exposure during pregnancy’, ‘foetal exposure during pregnancy’, ‘maternal exposure during pregnancy’ revealed 109 cases with the following breakdown of recent years

2019: 2 cases

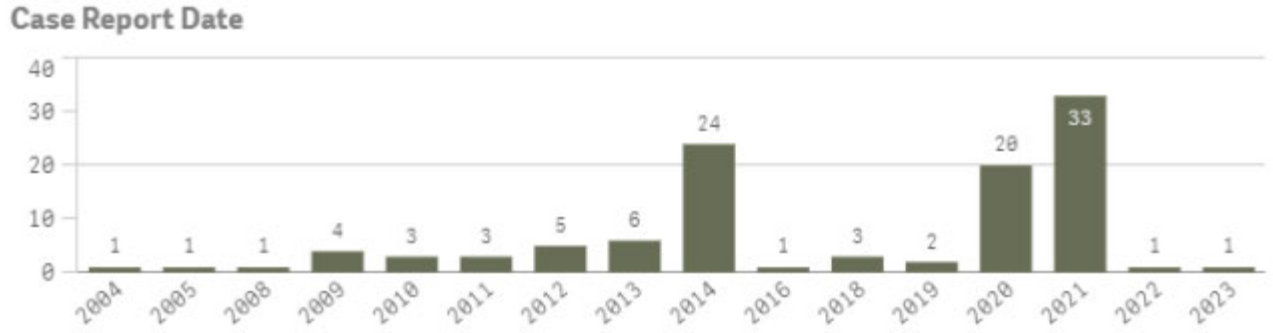
2020: 20 cases

2021: 33 cases

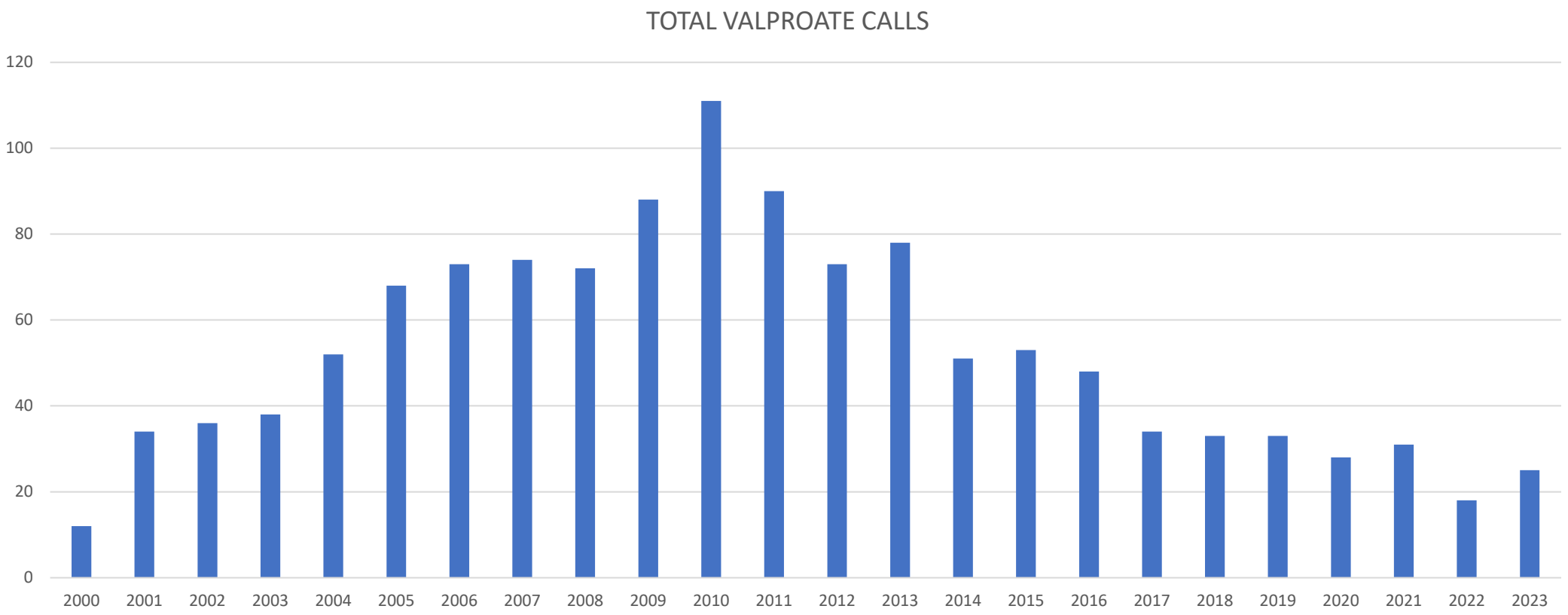
2022: 1 case

2023: 1 case

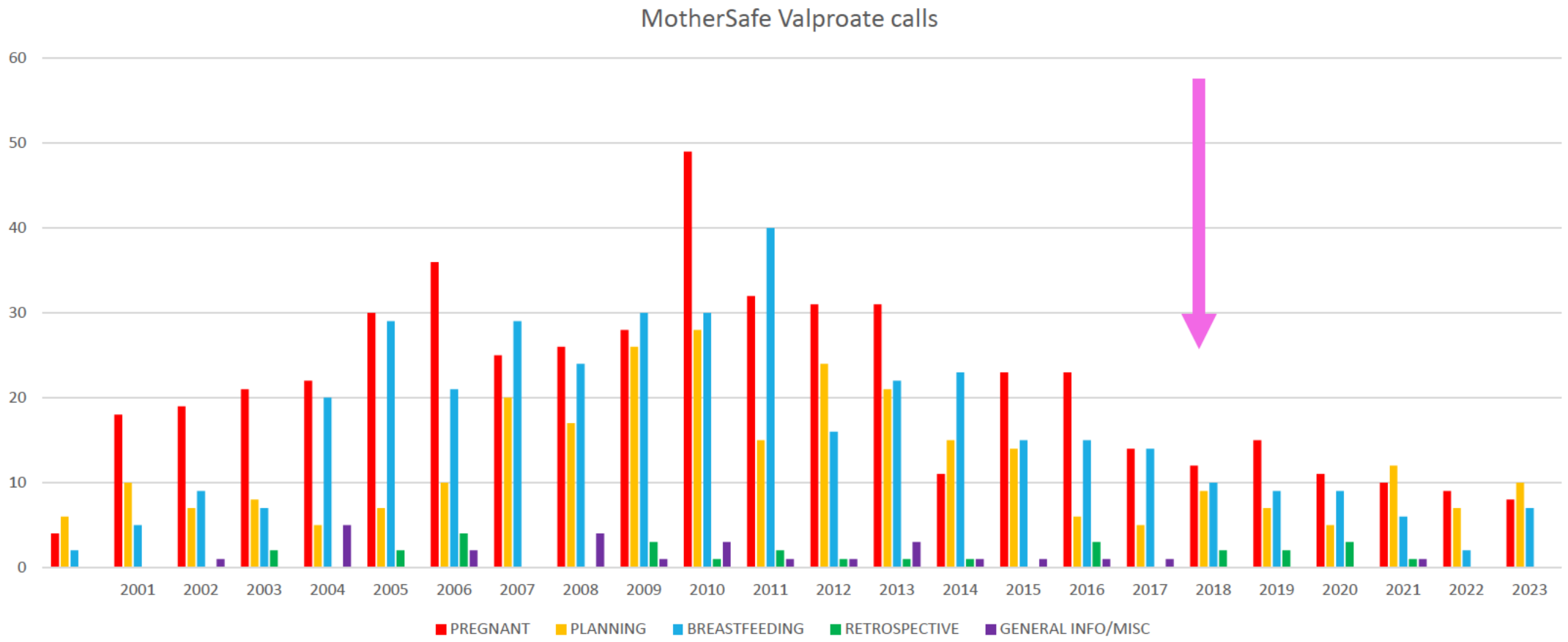
Figure 1: Case reports for ‘sodium valproate’ and ‘valproic acid’ and the PTs ‘exposure during pregnancy’, ‘foetal exposure during pregnancy’, ‘maternal exposure during pregnancy’ by year.



Total valproate calls MotherSafe 2000-2023



Reason for valproate call to MotherSafe



MotherSafe paternal valproate calls 2000-2024

YEAR	CALLER	REASON	OTHER MEDS	DIAGNOSIS
2001	GP	Pregnant	sertraline, olanzapine	?psych
2001	consumer		lamotrigine,clobazam	epilepsy
2004	HCP	pregnant		
2008	consumer	planning		
2008	consumer		escitalopram, temazepam, carbamazepine	
2010	HCP (GC)	pregnant	quetiapine, amisulprode	psych
2010	HCP(GP)	pregnant	risedronate	
2010	consumer	planning	olanzapine	psych
2013	consumer	planning		epilepsy
2013	consumer	planning		epilepsy
2014	consumer	planning	mesalazine , prednisolone (Crohn's)	
2014	HCP(GP)	pregnant		
2015	consumer	planning		bipolar
2016	consumer	planning		epilepsy
2017	consumer	planning		
2017	consumer	planning	lamotrigine, 5mg folic acid	epilepsy
2021	consumer	planning (ref by GC)	candesartan (hypertension) herbals	epilepsy
2022	consumer	planning		
2023	consumer	planning	venlafaxine (neuropathic pain)	bipolar
2023	consumer	planning	venlafaxine	mood disorder
2023	consumer	planning	levetiracetam, perampanel	epilepsy
2023	consumer	planning		epilepsy
2024	HCP(pharmacist)	further info following UK guidelines		
2024	consumer	planning		epilepsy

Valproate indications and use- Australia

Primary generalised epilepsy

- Petit mal absences
- Myoclonic epilepsy
- Tonic-clonic grand mal seizures

Sole or adjuvant therapy in partial (focal) epilepsy

Mania where other therapy has proved inadequate or inappropriate

Widely used in paediatric practice due to its tolerability and benefits in treating variety of seizures including absence, grand mal, juvenile myoclonic seizures

Means many paediatric patients will transition to reproductive age/ adulthood while still taking the medication

Valproate off-label uses

Migraine prophylaxis
Emergency treatment of status epilepticus
Diabetic peripheral neuropathy
Postherpetic neuralgia
Impulsivity, agitation, and aggression
Cyclical vomiting

Valproate mechanism of action

Mode of action not fully established

Anti-epileptic effect attributed to blockage of voltage-gated sodium channels and increased levels of GABA

- Inhibition of degradative enzymes gamma-aminobutyric acid (GABA) transaminase and/or succinic semialdehyde dehydrogenase
- Inhibition of GABA reuptake by neuronal cells

Anti-mania properties thought to be related to effects on GABA

Inhibition of HDAC enzymes which are involved in regulation of gene expression by modifying histone acetylation

Modulation of calcium channels

Wide range of actions related to alterations in ion channels and regulation of gene expression reflected in broad indications to treat various neurological/neuropsychiatric conditions

Australian Therapeutic Guidelines

*Fetal exposure to **sodium valproate** is associated with a high risk of major congenital malformations (neural tube defects have an incidence of 11% in some studies) and neurodevelopmental disorders (30 to 40% estimated incidence).*

Evidence also shows that children of mothers taking sodium valproate during pregnancy have lower intelligence and greater risk of learning difficulties than those exposed to other antiepileptic drugs

These effects are dose-related—at daily doses less than 600 to 800 mg, sodium valproate's teratogenicity and effect on cognition are similar to other antiepileptic drugs. However, a controlled cohort study showed that even at doses less than 800 mg daily, maternal valproate therapy was associated with an increased need for educational intervention

During pregnancy, avoid doses of sodium valproate more than 600 mg daily if possible

Australian therapeutic guidelines- valproate for epilepsy

Females with epilepsy who are planning a pregnancy should consult an expert to discuss the harms and benefits of valproate and its alternatives with the patient.

Valproate is often the only drug that controls genetic (idiopathic) generalised epilepsies, including juvenile myoclonic epilepsy. Because low doses are usually sufficient, valproate therapy can continue in a female with genetic (idiopathic) generalised epilepsy planning a pregnancy, without increasing the risk of teratogenicity and neurodevelopmental adverse effects to an unacceptable level.

If sodium valproate is essential, use 600 mg or less daily if possible.

Juvenile myoclonic epilepsy is a long-lasting condition—withdrawal of sodium valproate in anticipation of pregnancy can be hazardous, because seizures are likely to recur

The harms and benefits of valproate and its alternatives must be discussed with the patient

Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy (JME) is commonest type of genetic generalized epilepsy (GGE), occurring around puberty.

Includes myoclonic seizure (MS), which can occur with

- generalized tonic-clonic seizure (GTCS) in 80%-95% of JME patients
- absence seizure (AS) observed in approximately 1/3 of JME patients

Typical interictal electroencephalogram (EEG) characterized by 3-6 Hz generalized irregular spike-wave or polyspike-wave discharges of frontal predominance with a normal background

Usually associated with normal neurodevelopment

JME and treatment

Most patients with JME have good response to appropriate antiepileptic drugs (AEDs)

However there is a high rate of relapse upon AED withdrawal

Therefore recommended that patients with JME receive long-term AED treatment

Study of 66 JME patients with a mean follow-up time of 44.6 years reported seizure freedom for at least 5 years in 59.1% of patients

- Senf P, et al *Neurology*. 2013;81:2128

Valproate (VPA) considered the most effective AED in 90% of JME patients despite the risk of teratogenesis and other side effects

- Chowdhury A, Brodie M. . *Epilepsy Res*. 2016;119:62–6

Levetiracetam and lamotrigine have been used but generally less effective

Long-term treatment must be carefully weighed because of the risks of high seizure relapse in JME

Table 3 Selected anti-epileptic drugs (and alternatives to valproate in the treatment of epilepsy), adapted from Schmidt and Schachter [10]

Class of drug	Name of drug	Proposed mechanism	Side effects	Additional information
1st generation	Phenytoin	Sodium channel blocker	Enzyme inducer (hence interaction with other medications), skin hypersensitivity	First line for focal and generalised seizures with focal onset
	Ethosuxamide	T-type calcium channel blocker	Gastrointestinal side effects, insomnia, psychosis	First line for absence seizures
2nd generation	Carbamazepine	Sodium channel blocker	Enzyme inducer, skin hypersensitivity	First line for focal and generalised seizures with focal onset
	Valproate	GABA potentiation, blocks voltage gated sodium channels, epigenetically inhibits histone deacetylase	GI upset, weight gain, tremor, hair loss with curly regrowth, teratogenicity (see Table 4) In women: polycystic ovarian syndrome, hyperandrogenism Rare: fulminant liver failure	First line for focal and generalised seizures, no skin hypersensitivity, no newer drugs have been shown to have higher efficacy
3rd generation	Vigabatrin	GABA potentiation	Visual defects, weight gain, seizure aggravation, encephalopathy	Use in infantile spasms, adjunct in complex partial seizures
	Lamotrigine	GABA potentiation, suppresses glutamate release, inhibits serotonin reuptake	Tremor, dizziness, tiredness, loss of co-ordination, menstrual disturbance, dry mouth, sleep problems	First line for focal and generalised seizures, lower efficacy than valproate for absence seizures
	Oxcarbazepine	Sodium channel blocker	Enzyme inducer, hyponatraemia, skin hypersensitivity	First line for focal and generalised seizures with focal onset
	Gabapentin	Calcium channel blocker	Weight gain, psychosis, seizure aggravation, tiredness, dizziness	Adjunctive use only, used in focal and generalised seizures with focal onset
	Levetiracetam	SV2A modulation	Tiredness, dizziness, behavioural problems	First line in focal and generalised seizures with focal onset and myoclonic seizures.
	Topiramate	GABA potentiation, glutamate inhibition, sodium/calcium channel blocker	Tiredness, dizziness, skin hypersensitivity, weight loss, teratogenicity	First line for focal and generalised seizures

Australian Therapeutic guidelines- psychiatric indications

Do not use sodium valproate in pregnancy for a psychiatric disorder unless other treatment options (eg electroconvulsive therapy [ECT]) cannot be used and there is a high risk of harm if sodium valproate is stopped (eg relapse to a disabled or suicidal state)

Received: 15 May 2018 | Revised: 30 March 2019 | Accepted: 4 April 2019

DOI: 10.1002/epi4.12321

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia Open® Open Access

Clinical features and treatment outcomes of Juvenile myoclonic epilepsy patients

Yingying Zhang[1] | Jiani Chen[1] | Jiechuan Ren[2] | Wenyu Liu[1] | Tianhua Yang[1] | Dong Zhou[1]

Study findings

105 patients with JME, of whom 85 (81%) received monotherapy including valproate (VPA, 47%) and levetiracetam (LEV, 43%) treatment. Document 2

Rates of seizure freedom 1, 3, and 5 years after initiation of AED treatment were 64.8% (68/105), 29.5% (31/105), and 14.6% (12/82) in JME patients, respectively.

Patients with myoclonic seizure (MS) and absence seizure (AS) were less frequently seizure-free than those with MS and generalized tonic-clonic seizure (GTCS) ($P = 0.012$)

Patients on VPA monotherapy had better control of GTCS than patients on LEV monotherapy ($P = 0.036$)

Trend of lower rates of seizure freedom in patients treated with LEV than in those treated with VPA after 1 year

Increasing data suggest that seizure control is linked to seizure type in JME

Could possibly allow more individualized approach when counselling JME patients with regard to optimal treatment

TABLE 3 Analysis of patients who received levetiracetam (LEV) and valproate (VPA) monotherapy based on seizure type

Seizure type	Antiepileptic drugs (AEDs	Remission group	Uncontrolled group	*P* value
ALL[a]	VPA	21	19	0.417
	LEV	16	21	
GTCS[b]	VPA	27	9	0.036
	LEV	15	15	
MS[c]	VPA	22	18	0.524
	LEV	23	14	

Note. Remission group = no seizure for at least 2 years.
[a]No seizure for all seizure types in juvenile myoclonic epilepsy (JME) patients.
[b]No seizure for only JME patients with generalized tonic-clonic seizure.
[c]No seizure for JME patients with MS.

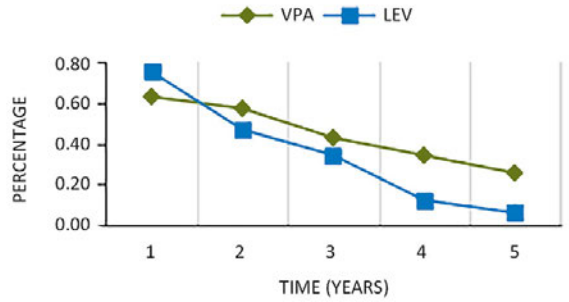


FIGURE 1 Remission rate of patients treated with valproate (VPA) and levetiracetam (LEV) vs follow-up period. Time: years without seizure; percentage: remission rate

Efficacy of valproate for mood disorders

Table 1 Efficacy of drugs used in bipolar disorder

	Treatment of acute mania	Treatment of acute depression	Mania relapse - prevention	Depression relapse - prevention
Lithium	++	++	++	++
Valproate	++	+	++	+
Carbamazepine	+	0	+	0
Lamotrigine	–	++	+	++
Olanzapine	++	+(+1)	++	+
Quetiapine	++	++	++	++

•Jon-Paul Khoo Aust Prescr 2012;35:164-8

Document 2

Long-Term Treatment of Bipolar Disorder with Valproate: Updated Systematic Review and Meta-analyses

Caitlin S Yee [1], Gustavo H Vázquez, Emily R Hawken, Aleksandar Biorac, Leonardo Tondo, Ross J Baldessarini

Included 13 reports involving 9240 subjects treated for average of 29.1 months (range, 12-124) in 21 trials

9 blinded RCTs of VPA versus placebo (n = 3), lithium (5), or olanzapine (1)

2 unblinded RCTs versus lithium (1) or quetiapine (1)

10 open-label trials versus lithium (5), quetiapine (2), carbamazepine (1), lamotrigine (1), or olanzapine (1)

Random-effects meta-analysis found VPA superior to placebo in 3 trials (odds ratio [OR] = 0.42 [95% confidence level (CI), 0.30-0.60]; p < .0001)

In 11 trials, protective effects with VPA and lithium were similar (OR = 1.20 [CI, 0.81-1.79]; p = .36) as well as in 5 comparisons versus antipsychotics quetiapine and olanzapine (OR = 0.96 [CI, 0.66-1.40]; p = .84), and 2 versus other mood-stabilizing anticonvulsants (carbamazepine and lamotrigine) (OR = 1.30 [CI, 0.75-2.26]; p = .34).

Valproate was nonsignificantly more effective versus new mania than depression ($\chi 2 = 3.03$; p = .08).

Document 2

Teratogenicity of other mood stabilisers

Reassuring data with lamotrigine

Dose-related teratogenicity with lithium

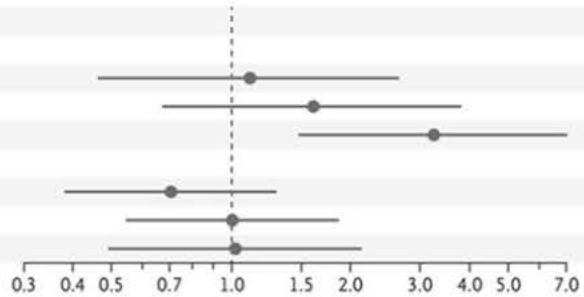
- No significantly increased risk <900/mg/day
- >900mg/day RR 3.2 2(1.47-7)

Table 2. Absolute and Relative Risk of Cardiac, Noncardiac, and Overall Malformations among Infants Exposed to Lithium during the First Trimester as Compared with Lamotrigine-Exposed or Unexposed Infants.*

Variable	No Exposure to Lithium or Lamotrigine	Exposure to Lamotrigine	Exposure to Lithium
No. of pregnancies	1,322,955	1945	663
Cardiac malformations			
Events	15,251	27	16
Prevalence per 100 births	1.15	1.39	2.41
Unadjusted risk ratio (95% CI)	Reference	1.20 (0.83–1.75)	2.09 (1.29–3.40)
Propensity-score–adjusted risk ratio (95% CI)	Reference	0.89 (0.61–1.30)	1.65 (1.02–2.68)
Unadjusted risk ratio (95% CI)	—	Reference	1.74 (0.94–3.21)
Propensity-score–adjusted risk ratio (95% CI)	—	Reference	2.25 (1.17–4.34)
Noncardiac malformations			
Events	27,816	49	22
Prevalence per 100 births	2.10	2.52	3.32
Unadjusted risk ratio (95% CI)	Reference	1.20 (0.91–1.58)	1.58 (1.05–2.38)
Propensity-score–adjusted risk ratio (95% CI)	Reference	0.90 (0.68–1.18)	1.22 (0.81–1.84)
Unadjusted risk ratio (95% CI)	—	Reference	1.32 (0.80–2.16)
Propensity-score–adjusted risk ratio (95% CI)	—	Reference	1.63 (0.96–2.78)
Overall malformations			
Events	43,067	76	38
Prevalence per 100 births	3.26	3.91	5.73
Unadjusted risk ratio (95% CI)	Reference	1.20 (0.96–1.50)	1.76 (1.29–2.40)
Propensity-score–adjusted risk ratio (95% CI)	Reference	0.90 (0.72–1.12)	1.37 (1.01–1.87)
Unadjusted risk ratio (95% CI)	—	Reference	1.47 (1.00–2.14)
Propensity-score–adjusted risk ratio (95% CI)	—	Reference	1.85 (1.23–2.78)

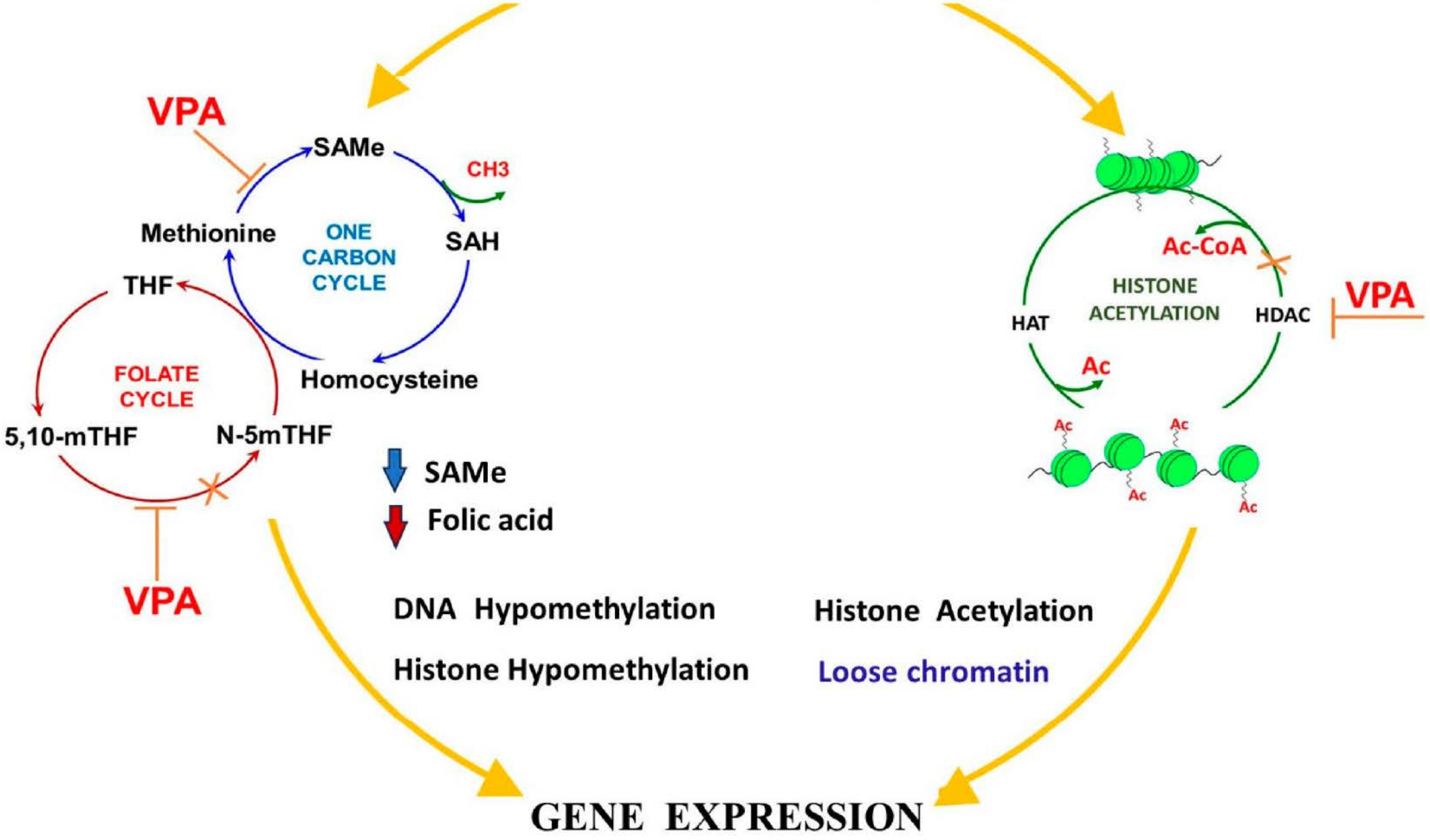
* CI denotes confidence interval. Maternal age @ delivery, race or ethnic group, year of delivery, smoking status, maternal psychiatric disorders and medical conditions, concomitant medication use, general markers of the burden of disease,

Exposure Group	No. of Pregnancies	No. of Events	Prevalence per 100 Births	Propensity-Score-Adjusted Risk Ratio (95% CI)
No exposure	1,322,955	15,251	1.15	Reference
Exposure to lithium				
≤600 mg/day	305	<11	1.64	1.11 (0.46–2.64)
601–900 mg/day	235	<11	2.13	1.60 (0.67–3.80)
>900 mg/day	123	<11	4.88	3.22 (1.47–7.02)
Exposure to lamotrigine				
≤100 mg/day	904	<11	1.11	0.70 (0.38–1.30)
101–200 mg/day	620	<11	1.61	1.00 (0.54–1.86)
>200 mg/day	421	<11	1.66	1.02 (0.49–2.13)



Patorno E et al New England Journal of Medicine. 2017 Jun 8;376(23):2245-54.

Prenatal VPA Teratogenicity



Teratogenicity of valproate

In clinical use as an anti-epileptic drug for over 40 years

Probably only major teratogen to be identified based on Birth Defects Registry data

- Increase in spina bifida (but not anencephaly) noted in the Rhone –Alps Birth Defects Registry in the late 1970's

Subsequently shown to be associated with increase in wide range of other structural anomalies

- Cardiac malformations
- Facial dysmorphism
- Oro-facial clefts
- Congenital cardiac defects
- Radial ray anomalies

Some evidence of dose-response with higher risk with doses >1000mg

Evidence of increased risk with polypharmacy- especially lamotrigine

No consistent findings regarding other adverse outcomes such as prematurity, miscarriage

Odds ratios and absolute risks of malformations in offspring of mothers

Condition	Odds ratio (median and range) in offspring of mothers who took valproate in pregnancy	Absolute risk
Spina bifida	12.7 (7.7–20.7)	0.6%
Atrial septal defect	2.5 (1.4–4.4)	0.5%
Cleft palate	5.2 (2.8–9.9)	0.3%
Hypospadias	4.8 (2.9–8.1)	0.7%
Polydactyly	2.2 (1.0–4.5)	0.2%
Craniosynostosis	6.8 (1.8–18.8)	0.1%

Adapted from Jentink J et al N Engl J Med. 2010;362(23):2185–93

Neurobehavioural teratogenicity

Increasing recognition of neurodevelopmental sequelae in exposed children (but several years after first reports of structural anomalies)

Risk of developmental delay after exposure to VPA in utero reported to be approximately 30%

Risks of neurodevelopmental disorders in offspring significantly increased when valproate administered in polytherapy with other AEDs during pregnancy, and also compared to those in children from the general population or born to untreated women with epilepsy

Risk of adverse cognitive and other neurodevelopmental outcomes far greater with physical signs of VPA embryopathy but developmental effects seen in absence of congenital malformations

Effects are dose-related so children exposed to higher doses of VPA are at greater risk

However a threshold dose below which no risk exists cannot be established based on available data

- **Tomson et al 2015**

Neurodevelopmental sequelae

For IQ, prospective studies suggest that around 20–30% of individuals with fetal valproate spectrum disorder will demonstrate below average IQ

Cochrane systematic review of neurodevelopment. concluded that there was an average reduction of 9 points in the developmental quotient between children exposed to VPA and unexposed or control children, with the risk to school aged IQ being a 7–11 point reduction in comparison to both controls and other AED exposed children.

- Bromley et al Cochrane Database Syst Rev. 2014; 10:CD010236

Studies in preschool children exposed in utero to valproate show that up to 30% to 40% of children experience delays in their early development such as speech and gross motor and other neurological disabilities including lower intellectual abilities, poor language skills (speaking and understanding) and memory problems

Clinically significant reduction in full scale IQ compared to control populations, with greater impairment of verbal IQ. Specific impairment of language skills has been documented together with deficits in auditory working memory

Available data show that children exposed to valproate in-utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population

- Christensen et al JAMA 2013;309:1696-703

Population-based cohort study from Denmark showed 48% increased risk of having ADHD after prenatal exposure to VPA compared to the unexposed population in the study

Documented cognitive and academic difficulties, as well as problems with, memory, organisational and social skills

- Bromley R, Clayton-Smith J, Wood A. Neurotoxicol Teratol. 2018;71:16–21.
- Thomas et al, 2008; Meador et al, 2009; Cummings et al, 2011

Risks of valproate in male patients- animal data

Potential testicular toxicity and effects on fertility noted in animal studies

Relevance of testicular toxicity data in juvenile animals exposed to valproate for the paediatric male population is uncertain and further studies were recommended

Currently information in section 5.3 of the UK SmPC about the risks of behavioural abnormalities in first generation offspring of mice and rats after in utero exposure

- *"Behavioural abnormalities have been reported in first generation offspring of mice and rats after in utero exposure. Some behavioural changes have also been observed in the second generation and those were less pronounced in the third generation of mice following acute in utero exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown."*

Epigenetic changes induced in male germ cells have been suggested as a potential mechanism of transmitting abnormalities to the offspring by modifying gene expression

Inhibition of histone deacetylase (HDAC) may be one mechanism of changing gene expression by remodelling of chromatin and regulation of DNA methylation (Simmons, 2008)

DNA methylation can be inherited in the germ line and epigenetic transgenerational inheritance of altered phenotypes has been observed in many species, including humans

Several studies suggesting valproate can induce altered DNA methylation by acting as an HDAC inhibitor

- Houtepen et al 2016;Phiel et al 2001;Kubota et al, 2012

Animal trans-generational effects

Jia et al (2015) demonstrated that change in gene expression in male mice after exposure to an HDAC inhibitor was also observed in offspring of these mice

In experiments in Xenopus embryos, Phiel et al(2001) found that valproate and a well characterised HDAC inhibitor (trichostatin A) were teratogenic, whereas non-teratogenic analogues of valproate did not inhibit HDAC

Choi et al (2016) observed transgenerational transmission of autism like symptoms and increased expression of excitatory postsynaptic proteins in the 1st, 2nd and 3rd generation offspring (F1, F2 and F3) of mice administered single dose of valproate during pregnancy (F0).

Study investigated transmission of effects via male germline (male offspring) and showed the paternal transmission of effects to 3rd generation

Evidence of teratogenicity was also observed in F1 (first generation) offspring (crooked tail, considered a mild form of neural tube defect) but not in F2 and F3 offspring.

Study limitations included

- small group size (6 dams per group)
- only one dose was used
- functional consequences of the effect on the proteins were not clear

Adult male fertility

Information about the possible adverse effects on male fertility are currently included in section 4.6 and 4.8 of the SmPC (sections concerning fertility, pregnancy and lactation and undesirable effects, respectively) following spontaneous reports in male patients

Reports of impaired male fertility have been received through the UK suspected adverse reaction reporting system (Yellow Card scheme) and similar schemes run by international regulators.

Mechanism of infertility in male patients is not known at present

Section 4.6 of the Epilim SmPC states that valproate administration may impair fertility in men and that fertility dysfunctions has been reported in some cases to be reversible at least 3 months after treatment discontinuation

Also notes a limited number of case reports and literature (Tallon and others, 2021) suggest that a “strong” dose reduction may improve fertility function but in some cases the reversibility of male infertility was not reported.

Potential teratogenic risk through paternal valproate exposure

Public hearing in 2017 held by EMA to address concerns by patients and stakeholders regarding potential teratogenic risks via paternal valproate exposure

Several studies assessed

Document 2

Epilepsia, 54(8):1462–1472, 2013
doi: 10.1111/epi.12226

FULL-LENGTH ORIGINAL RESEARCH

Exposure to antiepileptic drugs in utero and child development: A prospective population-based study

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Veiby et al Child development study

Mid-1999 -December 2008, children of mothers recruited at 13–17 weeks of pregnancy were studied in ongoing prospective Norwegian Mother and Child Cohort Study

Information on birth outcomes obtained from Medical Birth Registry (108,264 children), and mothers reported on their child's motor development, language, social skills, and autistic traits using items from standardized screening tools at 18 months (61,351 children) and 36 months (44,147 children) of age

Relative risk of adverse outcomes in children according to maternal or paternal epilepsy with and without prenatal exposure to antiepileptic drugs was estimated as odds ratios (ORs), using logistic regression with adjustment for maternal age, parity, education, smoking, depression/anxiety, folate supplementation, and child congenital malformation or low birth weight

Key findings

Total of 333 children were exposed to AED in utero

At 18 months, the exposed children had increased risk of abnormal scores for gross motor skills (7.1% vs. 2.9%; OR 2.0, 95% confidence interval [CI] 1.1–3.7) and autistic traits (3.5% vs. 0.9%; OR 2.7, CI 1.1–6.7) compared to children of parents without epilepsy

At age 3, exposed children had increased risk of abnormal score for gross motor skills (7.5% vs. 3.3%; OR 2.2, CI 1.1–4.2), sentence skills (11.2% vs. 4.8%; OR 2.1, CI 1.2–3.6), and autistic traits (6.0% vs. 1.5%; OR 3.4, CI 1.6–7.0)

The drug-exposed children also had increased risk of congenital malformations (6.1% vs. 2.9%; OR 2.1, CI 1.4–3.4), but exclusion of congenital malformations did not affect the risk of adverse development

Children born to women with epilepsy who did not use antiepileptic drugs had no increased risks

Children of fathers with epilepsy generally scored within the normal range

Exposure to antiepileptic drugs during pregnancy is associated with adverse development at 18 and 36 months of age, measured as low scores within key developmental domains rated by mothers

Exposures to valproate, lamotrigine, carbamazepine, or multiple antiepileptic drugs were associated with adverse outcome within different developmental domains

Document 2

Table 2. Risk for adverse development score at 18 months in children of parents with epilepsy[a] compared to a reference group of children of parents without epilepsy

		Maternal epilepsy: antiepileptic drug exposure in utero[b]							Paternal epilepsy[b]	
Adverse score Age 18 months	Reference (%) n = 60,583	All exposures n = 184	Monotherapy n = 158	Lamotrigine n = 65	Valproate n = 25	Carbamazepine n = 41	Polytherapy n = 26	Unexposed n = 221	No treatment[c] n = 216	Treatment[c] n = 147
Gross motor skills	2.9%	7.1% (13)*	5.7% (9)	7.8% (5)	16.0% (4)*	0.0% (0)	15.4% (4)*	3.2% (7)	3.7% (8)	4.1% (6)
OR (95% CI)[d]		2.0 (1.1–3.7)	1.6 (0.8–3.4)	1.7 (0.6–5.1)	7.0 (2.4–21.0)	NA	4.1 (1.3–13.3)	1.2 (0.6–2.6)	1.3 (0.7–2.7)	1.6 (0.7–3.6)
Fine motor skills	3.1%	6.1% (11)*	4.5% (7)	3.1% (2)	4.0% (1)	10.0% (4)*	15.4% (4)*	5.1% (11)	5.6% (12)*	3.5% (5)
OR (95% CI)		1.8 (1.0–3.4)	1.4 (0.7–3.0)	0.9 (0.2–3.7)	1.3 (0.2–9.7)	3.3 (1.1–9.2)	4.3 (1.4–13.0)	1.7 (0.9–3.1)	1.9 (1.0–3.4)	1.0 (0.4–2.6)
Personal-social skills	4.2%	9.4% (17)*	6.5% (10)	3.1% (2)	0.0% (0)	12.2% (5)*	26.9% (7)*	3.7% (8)	5.6% (12)	10.3% (15)*
OR (95% CI)		2.2 (1.3–3.6)	1.5 (0.8–2.9)	0.6 (0.2–2.7)	NA	3.2 (1.3–8.3)	7.1 (2.9–17.8)	0.9 (0.4–1.8)	1.4 (0.8–2.5)	2.3 (1.3–4.1)
Autism checklist[e]	7.8%	14.0% (24)*	10.9% (16)	15.6% (10)	8.3% (2)	8.8% (3)	33.3% (8)*	10.0% (20)	11.1% (24)	11.0% (16)
OR (95% CI)		1.7 (1.1–2.6)	1.3 (0.7–2.2)	1.8 (0.9–3.8)	1.0 (0.2–4.5)	1.1 (0.3–3.6)	4.5 (1.8–11.1)	1.3 (0.8–2.0)	1.4 (0.9–2.2)	1.6 (1.0–2.7)
Autistic traits[e]	0.9%	3.5% (6)*	2.0% (3)	3.1% (2)	0.0% (0)	2.9% (1)	12.5% (3)*	0.5% (1)	1.4% (3)	2.8% (4)*
OR (95% CI)		2.7 (1.1–6.7)	1.4 (0.3–5.6)	1.5 (0.2–11.0)	NA	3.3 (0.5–24.8)	8.3 (2.3–30.0)	0.5 (0.1–3.7)	1.6 (0.5–5.0)	3.7 (1.4–10.1)

NA, not applicable.
*p-value < 0.05.
[a]Each cell contains the percentage (no.) of adverse outcomes within groups and corresponding odds ratio (OR) with 95% CI.
[b]Numbers may not equal 100% within groups due to variation of missing values.
[c]Antiepileptic drug use by father within 6 months to conception.
[d]ORs are adjusted for maternal age, parity, education, smoking, anxiety/depression, periconceptional folate use, and child low birth weight and malformation.
[e]Assessable for 92% of the 18 months cohort. Autism checklist: Modified Checklist for Autism in Toddlers (MCHAT). Autistic traits: Early Screening of Autistic Traits (ESAT).

Table 3. Risk for adverse development score at 36 months in children of parents with epilepsy[a] compared to a reference group of children of parents without epilepsy

		Maternal epilepsy: antiepileptic drug exposure in utero[b]							Paternal epilepsy[b]	
Adverse score Age 36 months	Reference (%) n = 43,571	All exposures n = 139	Monotherapy n = 114	Lamotrigine n = 44	Valproate n = 19	Carbamazepine n = 31	Polytherapy n = 25	Unexposed n = 154	No treatment[c] n = 173	Treatment[c] n = 110
Gross motor skills	3.3%	7.5% (10)*	8.1% (9)*	9.8% (4)	10.5% (2)	6.5% (2)	4.3% (1)	3.3% (5)	6.0% (10)	3.6% (4)
OR (95% CI)[d]		2.2 (1.1–4.2)	2.4 (1.2–4.9)	2.4 (0.8–7.0)	3.4 (0.8–14.9)	2.3 (0.5–9.9)	1.1 (0.1–8.5)	0.9 (0.3–2.4)	1.9 (1.0–3.5)	1.2 (0.4–3.2)
Fine motor skills	3.3%	3.8% (5)	4.7% (5)	7.7% (3)	5.6% (1)	3.3% (1)	0.0% (0)	5.6% (8)	4.2% (7)	2.9% (3)
OR (95% CI)		1.1 (0.5–2.8)	1.4 (0.6–3.5)	2.1 (0.7–7.0)	1.7 (0.2–13.1)	1.0 (0.1–7.5)	NA	1.7 (0.8–3.6)	1.3 (0.6–2.8)	0.9 (0.3–2.9)
Communication skills	2.9%	5.9% (8)	4.5% (5)	7.1% (3)	10.5% (2)	0.0% (0)	12.5% (3)	1.3% (2)	5.2% (9)	2.7% (3)
OR (95% CI)		1.6 (0.8–3.4)	1.3 (0.5–3.3)	2.0 (0.6–6.7)	3.5 (0.8–15.4)	NA	2.7 (0.8–9.5)	0.4 (0.1–1.8)	1.9 (1.0–3.7)	1.0 (0.3–3.1)
Sentence skills	4.8%	11.2% (15)*	9.9% (11)*	14.3% (6)*	15.8% (3)*	6.5% (2)	17.4% (4)	3.9% (6)	3.5% (6)	6.4% (7)
OR (95% CI)		2.1 (1.2–3.6)	2.0 (1.0–3.7)	2.8 (1.2–6.9)	3.4 (1.0–12.0)	1.2 (0.3–5.1)	2.6 (0.8–7.9)	0.8 (0.4–1.9)	0.7 (0.3–1.7)	1.4 (0.7–3.1)
Autistic traits (SCQ)	1.5%	6.0% (8)*	5.6% (6)*	9.3% (4)*	5.6% (1)	3.4% (1)	8.0% (2)	0.7% (1)	2.3% (4)	0.9% (1)
OR (95% CI)		3.4 (1.6–7.0)	3.3 (1.4–7.6)	5.0 (1.7–14.4)	3.7 (0.5–28.4)	2.5 (0.3–19.1)	3.6 (0.8–15.8)	0.4 (0.1–2.9)	1.5 (0.5–4.1)	0.6 (0.1–4.2)
ADHD symptoms	4.0%	5.9% (8)	6.3% (7)	7.0% (3)	5.6% (1)	6.5% (2)	4.2% (1)	2.6% (4)	4.7% (8)	2.8% (3)
OR (95% CI)		1.3 (0.6–2.7)	1.4 (0.7–3.1)	1.5 (0.4–4.8)	1.3 (0.2–9.9)	2.0 (0.5–8.6)	0.8 (0.1–5.9)	0.5 (0.2–1.5)	1.0 (0.5–2.1)	0.7 (0.2–2.1)
Aggressive symptoms	4.1%	8.1% (11)	8.0% (9)	7.0% (3)	5.6% (1)	2.9% (4)*	8.3% (2)	3.2% (5)	2.3% (4)	2.7% (3)
OR (95% CI)		1.8 (1.0–3.4)	1.8 (0.9–3.8)	1.6 (0.5–5.2)	1.2 (0.2–9.4)	3.5 (1.2–10.2)	1.6 (0.4–6.9)	0.8 (0.3–1.9)	0.4 (0.1–1.3)	0.6 (0.2–2.0)

NA, not applicable.
*p-value < 0.05.
[a]Each cell contains the percentage (no.) of adverse outcomes within groups and corresponding odds ratio (OR) with 95% CI.
[b]Numbers may not equal 100% within groups due to variation of missing values.
[c]Antiepileptic drug use by father within 6 months to conception.
[d]ORs are adjusted for maternal age, parity, education, smoking, anxiety/depression, periconceptional folate use, and child low birth weight and malformation.

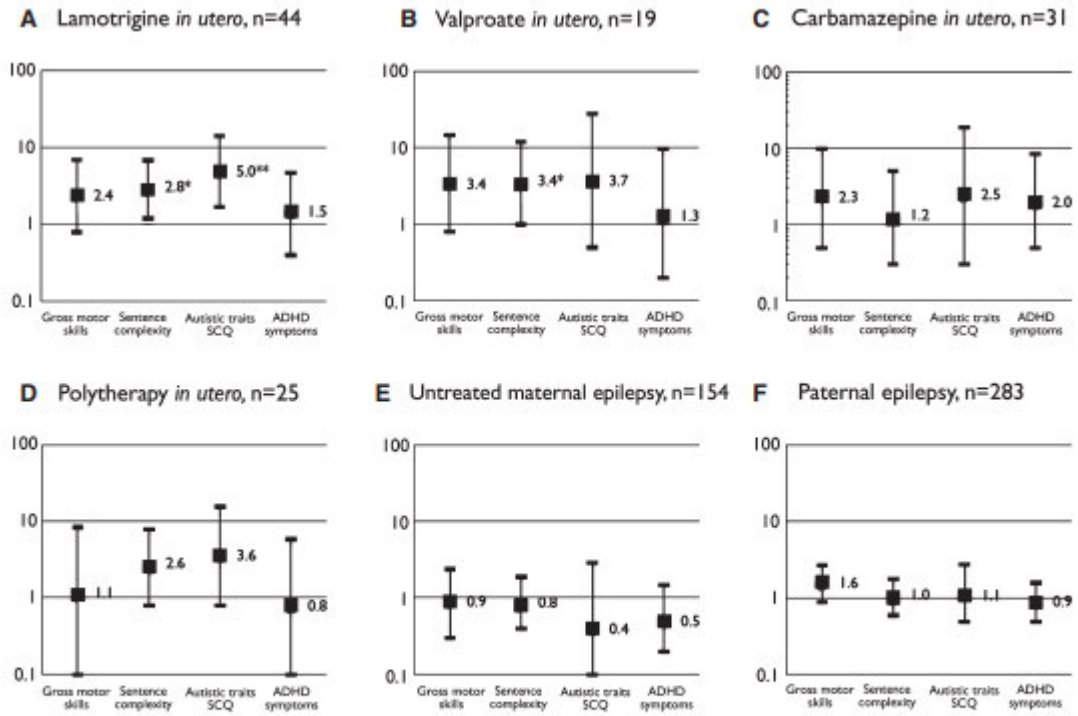
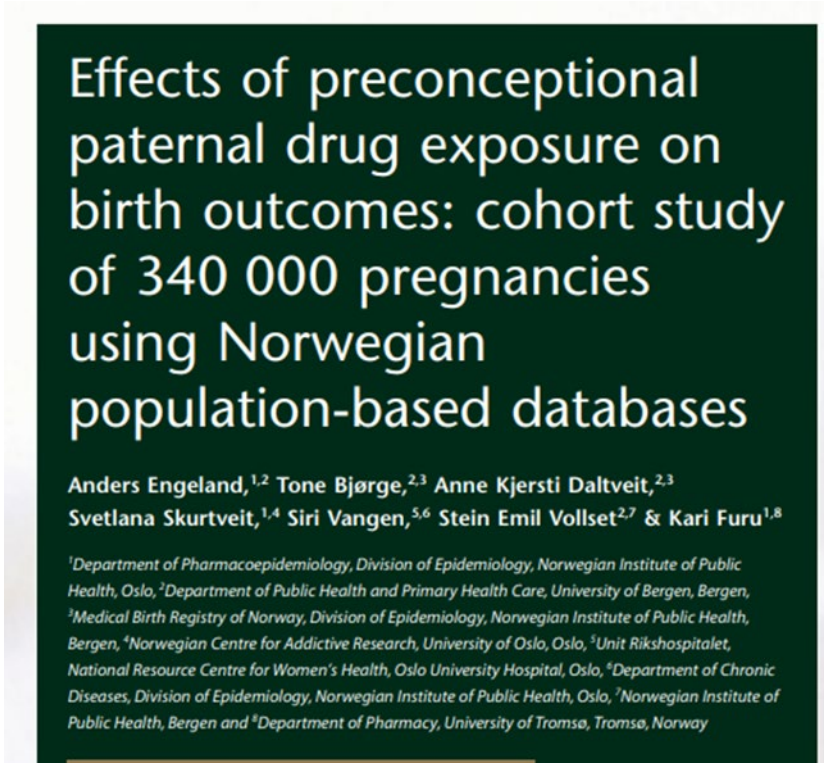


Figure 1.
Adjusted odds ratio with 95% confidence interval (log scale) for adverse development in children of parents with epilepsy compared to the reference group. SCQ, Social Communication Questionnaire (Previously Autism Screening Questionnaire). *p-value < 0.05; **p-value < 0.01.



Effects of preconceptional paternal drug exposure on birth outcomes: cohort study of 340 000 pregnancies using Norwegian population-based databases

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Cohort study linking two population-based registries, the Medical Birth Registry of Norway and the Norwegian Prescription Database

The study cohort consisted of 340 000 pregnancies in 2004–10

The association between specific drugs dispensed to the fathers during the last 3 months prior to conception and pregnancy outcomes was explored by estimating odds ratios (ORs) using multivariate logistic regression

About one quarter (26%) of the fathers were dispensed at least one drug during the last 3 months prior to conception and 1.3% were dispensed at least one drug requiring special attention

Overall, the odds of different adverse pregnancy outcomes were not increased when the father had been dispensed drugs, i.e. the OR and 95% confidence intervals (CIs) for any birth defect when the fathers had been dispensed any drug were 0.99 (0.94, 1.0)

When the fathers had been dispensed diazepam increased risk of perinatal mortality and growth retardation identified with OR and 95% CIs of 2.2 (1.2, 3.9) and 1.4 (1.2, 1.6), respectively

Drug (main groups) (ATC code)	n	%
Alimentary tract and metabolism (A)	10,185	3.0
Blood and blood forming organs (B)	1,760	0.52
Cardiovascular system (C)	6,637	2.0
Dermatologicals (D)	10,737	3.2
Genito urinary system and sex hormones (G)	2,454	0.73
Systemic hormonal preparations, excl. sex hormones and insulin (H)	3,882	1.15
Antiinfectives for systemic use (J)	21,924	6.5
Antineoplastic and immunomodulating agents (L)	823	0.24
Musculo-skeletal system (M)	19,258	5.7
Nervous system (N)	21,572	6.4
Antiparasitic products, insecticides and repellents (P)	1,312	0.39
Respiratory system (R)	23,894	7.1
Sensory organs and various (S + V)	8,683	2.6
Any drug	87,847	26

ATC, Anatomical Therapeutic Chemical.

Table 3

Number of fathers who were dispensed drugs requiring special attention (according to Schirm *et al.* [6]) during the last 3 months prior to conception ($n = 336\,893$)

Drug (ATC code)	n	%
Cimetidine (A02BA01)	82	0.02
Prednisolone (H02AB06)	1,477	0.44
Indomethacin (M01AB01)	183	0.05
Valproic acid (N03AG01)	347	0.10
Diazepam (N05BA01)	1,354	0.40
Sulfasalazine (A07EC01)	117	0.03
Morphine (N02AA01)	38	0.01
Azathioprine (L04AX01)	268	0.08
Furosemide (C03CA01)	122	0.04
Isotretinoin (systemic) (D10BA01)	80	0.02
Androgens (G03B)	121	0.04
Phenytoin (N03AB02)	31	0.01
Phenobarbital (N03AA02)	21	0.01
Ergotamine (N02CA02)	0	0.00
Spironolactone (C03DA01)	44	0.01
Lithium (N05AN01)	159	0.05
Methotrexate (L01BA01)	5	0.00
Daunorubicin (L01DB02)	0	0.00
Acitretin (systemic) (D05BB02)	44	0.01
6-Mercaptopurine (L01BB02)	3	0.00
One or more of these drugs	4,266	1.30

ATC, Anatomical Therapeutic Chemical.

Document 2

Valproate EU consortium

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

Date: 02 October 2023, Updated Abstract Following Reanalysis of Norway Data Corrigendum to Final Study Report Version 1.1 and Addendum Version 2.0

Stand Alone Abstract V2.0

Prepared For:
Valproate marketing authorisation holders being part of study consortium

Marketing authorisation holders (MAH)
APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; CONSILIENT HEALTH LIMITED; CRESCENT PHARMA LIMITED; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZ/HEXAL AG; LUPIN HEALTHCARE LIMITED; MYLAN BVBA/SPRL: BE; VIATRIS SANTE (LYON): FR; VIATRIS GX BV/SRL: BE; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; SANOFI AVENTIS GROUP; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE and; WOCKHARDT UK LIMITED

https://catalogues.ema.europa.eu/system/files/2024-02/Valproate_PASS_Abstract_V2.0_0.pdf

Valproate EU consortium

PASS (Post-authorisation safety study)

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 period began on

1 January 1997 (1 April 2004 for the secondary outcome) in Denmark

1 January 2007 in Sweden

1 January 2010 in Norway

The study time period ended on 31 December 2018 for Denmark and 31 December 2019 for both Sweden and Norway

Subjects

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 AED in the data available

Fathers' age at childbirth was similar in Denmark, Sweden, and Norway (median of 33 years in all countries); similar in both exposure groups

Findings

Across all 3 countries, fathers of offspring paternally exposed to valproate were less frequently affected by comorbidities prior to childbirth compared to those exposed to lamotrigine/ levetiracetam: neurotic disorders, affective disorder excluding bipolar disorder and mania and bipolar affective disorder

Fathers of offspring paternally exposed to valproate were more likely to receive their AED to treat epilepsy than those of offspring paternally exposed to lamotrigine/levetiracetam in the 2 countries (respectively, 75.4% and 58.3% in Denmark, 57.7% and 41.6% in Norway)

Paternal use of medication in the 3-month lookback from LMP2 was similar across the 3 countries. A lower proportion of fathers was observed with a polypharmacy index between 1 and 4 in the valproate group compared to the lamotrigine/levetiracetam group , likewise for the use of medications associated with neuropsychiatric adverse events (respectively, 49.3% and 56.0% in Denmark, 48.5% and 64.1% in Sweden, 56.4% and 64.6% in Norway).

In all countries, the most common indication for AED use was epilepsy, both among fathers exposed to valproate and lamotrigine/levetiracetam (respectively, 70.0% and 59.0% in Denmark, 70.7% and 46.1% in Sweden, 57.9% and 41.5% in Norway)

Neurodevelopmental outcomes -1

The risk of NDD including ASD associated with the paternal exposure to valproate compared to the paternal exposure to lamotrigine/levetiracetam was assessed using crude Cox regression models:

- 43 out of 793 (5.4%) and 41 out of 1,157 (3.5%) offspring in the valproate and in the lamotrigine/levetiracetam groups respectively in Denmark
- in 49 out of 930 (5.3%) and 41 out of 1,425 (2.9%) offspring, respectively in Sweden,
- 0 out of 383 (0.0%) and 23 out of 1,018 (2.3%) offspring, respectively in Norway

The resulting HRs indicated no significant higher risk of NDD including ASD with the paternal exposure to valproate compared to lamotrigine/levetiracetam in Denmark and Sweden: 0.94 (95% CI: 0.60, 1.46) in Denmark, and 1.16 (95% CI: 0.76, 1.76) in Sweden.

In Norway, no events were observed in the valproate paternal exposure group after the exclusion of influential subjects (N=15), which led to non-calculable HR.

In order to meta -analysis results from all the 3 countries, the pooled crude HR was estimated without excluding influential subjects (as no influential subjects were identified in the crude models for Denmark and Sweden)

The pooled crude HR across the 3 countries was consistent with the country-specific estimates in terms of strength and non-significance of the risk: 1.13 (95% CI: 0.85, 1.49); no heterogeneity was observed between country-specific estimates (I2=0.0, 95% CI: 0.0, 89.6)

Neurodevelopmental outcomes-2

The risk of NDD including ASD associated with paternal exposure to valproate compared to that to lamotrigine/levetiracetam was further assessed using propensity score (PS)-weighted Cox regression models after the further exclusion of offspring with outlier weights

The overall cumulative incidence proportions of NDD including ASD over the study follow-up period (0-12 years in Denmark and Sweden, and 0-10 years in Norway) were higher in offspring paternally exposed to valproate than in those to lamotrigine/levetiracetam respectively in the 3 countries:

- 35 out of 678 (5.6%) and 36 out of 1,118 (3.2%) in Denmark
- 47 out of 841 (5.6%) and 34 out of 1,334 (2.5%) in Sweden
- 13 out of 325 (4.0%) and 21 out of 910 (2.3%) in Norway

The pooled ratio of the cumulative incidence proportions (valproate over lamotrigine/levetiracetam paternal exposure groups) across the 3 countries for the 0-10 years follow-up period was 1.58 (95% CI: 1.21, 2.05); no heterogeneity was observed between country-specific estimates (I2=0.0, 95% CI: 0.0, 0.9)

A 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 was observed when pooling the country-specific adjusted risk estimates into a meta-analysis (PS-weighted adjusted HR: 1.5, 95% CI: 1.1, 2.1; I^2=0.0%)

However, 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

Methodological limitations

Study used secondary data that was not collected primarily for research purposes and therefore information on certain parameters, such as some known risk factors and/or causal factors (eg, genetic abnormalities, congenital infectious diseases, paternal condition severity that required AED use, lifestyle factors etc) were not identified nor controlled for

Assumed these factors were balanced between the 2 paternal exposure groups, but this assumption could not be verified, and unmeasured confounding may bias the risk estimates.

Especially the type of epilepsy, which may not be balanced between the 2 paternal exposure groups; indeed, valproate is the treatment of choice (or first-line drug) for male patients with idiopathic generalized epilepsy, 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

Due to methodological limitations, especially the difference in follow-up time between the 2 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

Paternal exposures and developmental toxicology

Good evidence that paternal exposures can affect fertility

- Alkylating agents
- Radiation therapy
- Anabolic steroids
- Sulphasalazine (reversible)
- Hyperthermia (tight underwear, hydrocoele)

Evidence that mutagens can potentially result in increased DNA damage=> single gene defects etc

However reassuring data on pregnancy outcomes and children of parents exposed to chemotherapy and DXRT – no different to offspring of unexposed siblingsa

Some evidence of epigenetic programming but no definitive studies or proven cases

Document 2

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DOI: 10.1002/bdr2.2215

REVIEW ARTICLE

Birth Defects Research | Society for Birth Defects Research & Prevention | WILEY

Teratogenesis and the epigenetic programming of congenital defects: Why paternal exposures matter

Michael C. Golding

- Environmentally-induced epigenetic changes exerted during formation of gametes may have similar teratogenic potential to exposures during early embryonic development
- Concept of “epiteratogens”
- Non -coding DNA changes
  - Methylation
  - Changes in gene expression

Paternal valproate exposure and ? biological plausibility

No access to developing embryo

No evidence that valproate is a mutagen

Epigenetic changes
- Should be relevant prior to as well as during a pregnancy

Importance of considering underlying paternal disease and reason for taking medication
- Epilepsy +/- associated developmental problems
- ASD/behavioural disorders
- Bipolar or other mood disorder
- Paternal age

Specific advice

1. Noting that the MHRA has not proposed a change to the indication within the UK-SPC (PI equivalent), does the Committee consider there is sufficient evidence to warrant amending the indication and/or prescribing requirements and recommendations of valproate in the Australian PI?

Advice from expert

Document 2

Proposed PI change - Section 4.6 Fertility, Pregnancy and Lactation Pregnancy Exposure Risk related to valproate

Proposed PI change by section
Treatment of mania • Valproate is contraindicated ~~as treatment for bipolar disorder~~ during pregnancy. • Valproate is contraindicated for use in women of childbearing potential, unless the physician has provided education on the potential effects of valproate during pregnancy (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use).
Section 4.6 Fertility, Pregnancy and Lactation
Pregnancy Exposure Risk related to valproate In females, ~~B~~both valproate monotherapy and valproate polytherapy including other antiepileptics, are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate. In animals teratogenic effects have been demonstrated in mice, rats and rabbits. Risk to children of fathers treated with valproate A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate ~~at time of~~ in the 3 months prior to conception compared to those treated with lamotrigine or levetiracetam. The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% ~~5.6% to 6.3%~~ in the valproate group versus between 2.3% to 3.2% ~~2.5% to 3.6%~~ in the composite lamotrigine/levetiracetam monotherapy group ~~exposure~~. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07) ~~1.47 (95% CI: 1.10, 1.96).~~ Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. ~~Further investigations are needed.~~ Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually (see section 4.4).

Proposed PI change- section 5.3

Proposed PI changes to Section 5.3

5.3 PRECLINICAL SAFETY DATA

Testicular function

In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 400 mg/kg/day and 150 mg/kg/day, respectively with associated NOAELs for testis findings of 270 mg/kg/day in adult rats and 90 mg/kg/day in adult dogs. ~~of valproate. The dose without an effect on the testes was similar to the maximum recommended human dose of 50 mg/kg/day on a mg/m² basis.~~

In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance. ~~This dose was about 1.3 times the maximum recommended human dose of 50 mg/kg/day on a mg/m² basis.~~

Proposed safety changes	Evaluator's comments
The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known. The male patient should be advised: • not to donate sperm during treatment and for 3 months after stopping the treatment, • of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception, • that he and his female partner should contact their doctor for counseling in case of pregnancy if he used valproate within 3 months prior to conception. The male patient should also be informed about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorder. The specialist should at least annually review whether valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with valproate use. ~~and consider alternative therapeutic options with the patient. In men initiating or remaining on valproate treatment, the need for effective contraception should be discussed with the patient, at least annually. The prescriber should ensure the male patient has acknowledged the risk and precautions associated with valproate use.~~ Educational materials To reinforce the warnings and provide guidance regarding use of valproate in men of reproductive potential, educational materials are available electronically through a QR code on the carton (www.sanofi.com.au/valproate). A patient guide should be provided/available to all men of reproductive potential using valproate.	

Evaluator assessment

"The risk of major congenital malformations in children after in-utero exposure to AED polytherapy including valproate is higher than that of AED polytherapy not including valproate.

The retrospective observational study known as the post authorisation safety study (PASS) was carried out using multiple registry databases in Denmark, Norway and Sweden and evaluated the association between paternal exposure to valproate and risk of neurodevelopmental disorders (NDDs), including autism spectrum disorders (ASD), as well as congenital abnormalities in offspring.

In 2022, results from the PASS were released and reported a higher risk for NDDs including ASD in offspring related to paternal exposure to valproate when compared to paternal exposure to the composite lamotrigine/levetiracetam monotherapy."

"This risk is highly dose-dependent with valproate monotherapy, and available data suggests it is dose-dependent with valproate polytherapy .However, a threshold dose below which no risk exists cannot be established."

- Tomson et al, 2015

However the Tomson study refers to maternal AED exposures so not quite sure about the relevance to the paternal exposure issue and the PASS study

Pregnancy Exposure Risk related to valproate In females, ~~B~~both valproate monotherapy and valproate polytherapy including other antiepileptics, are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate. In animals teratogenic effects have been demonstrated in mice, rats and rabbits. Risk to children of fathers treated with valproate A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate ~~at time of~~ in the 3 months prior to conception compared to those treated with lamotrigine or levetiracetam. The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% ~~5.6% to 6.3%~~ in the valproate group versus between 2.3% to 3.2% ~~2.5% to 3.6%~~ in the composite lamotrigine/levetiracetam monotherapy group ~~exposure~~. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07) ~~1.47 (95% CI: 1.10, 1.96).~~ Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. ~~Further investigations are needed.~~ Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually (see section 4.4 **Special Warnings and Precautions For Use**).	Acceptable. Adds or strengths safety warning. Within scope of SRR with data. **Suggest adding section title: (See section 4.4 Special Warnings and Precautions For Use)**

Views of global experts - OTIS/ENTIS

"In 2024, the European Medicines Agency advised caution in prescribing valproic acid to men based on an unpublished study on the internet reporting an association between preconception exposure and neurodevelopmental problems in offspring (182). After adjustment by propensity score, the findings lost statistical significance. Men on valproic acid were more likely to have a seizure disorder than men on the comparator drugs, and there was no adjustment for family history of disease, including a family history of autism"

- *Reprotox*

"An extended abstract is available online. It may be an opportunity for OTIS and ENTIS to comment publicly."

"The discussion begs the question of whether these are data when they are unpublished and apparently not statistically confirmed. I am hopeful that the US FDA has not done anything...yet."

- Tony Scialli editor of Reprotox

Scientific Committee of the European Network of Teratology Information Service (ENTIS) is concerned with the lack of data transparency supporting the decision to issue precautionary measures based on the available data. They have submitted a paper outlining their concerns (under review)..

Response to question 1

I do not consider there is sufficient evidence to warrant amending the indication and/or prescribing requirements and recommendations of valproate in the Australian PI?

At this stage the main data upon which the recommendation has been based has been withdrawn for further analysis

The evaluator also appeared to confuse some of the data around paternal versus maternal exposures

Specific advice

2. Previous advice from PBAC was based on PBS's stance on avoiding gender-based access to valproate. Noting that that the latest MHRA prescribing restrictions are applicable to both men and women, does the Committee support the referral of this issue to PBAC for consideration of relevant prescribing amendments?

Advice from expert

Response to question 2

Terminology needs to be very clear- it is sex or biological sex and not gender

There are clearly differences between risks of exposure during pregnancyie continued exposure of an embryo/fetus to a medication as opposed to potential exposure of gonads and gametes (ie both ovaries and testes and oocyte and sperm) prior to pregnancy

At this stage I do not believe there is sufficient data to support the referral of this issue to PBAC for consideration of relevant prescribing amendments

Specific advice

3. Are there other risk minimisation activities that the TGA could consider for this issue?

Advice from expert

Response to question 3

Appropriate prescribing

- Lowest effective dose
- Avoiding polypharmacy
- Minimising prescribing for condition other than epilepsy
- Regular review- some way of implementing limited prescriptions
- Requirement for annual follow up and review.

Education of patients and clinicians

- Evidence-based prescribing
- Pregnancy planning
- Contraception

Pharmacovigilance

- Important to follow up cases and conduct appropriate prospective studies

Conflicting evidence about folic acid but still should recommend

Macfarlane and Greenhalgh *BMC Pregnancy and Childbirth* (2018) 18:200
https://doi.org/10.1186/s12884-018-1842-x

BMC Pregnancy and Childbirth

DEBATE Open Access

Sodium valproate in pregnancy: what are the risks and should we use a shared decision-making approach?

Alastair Macfarlane[1*] and Trisha Greenhalgh[2]

Document 2

Shared decision-making regarding use of valproate for bipolar disorders during pregnancy

Frequently asked questions	Continuing the current dose of valproate	Lowering the dose of valproate	Discontinuing valproate	Changing to another medication
What does it involve?	No change to medication or dose	Over a period of weeks to months, decreasing the amount of valproate	Over a period of weeks to months, gradually stopping valproate	Switching to a different medication (e.g. lamotrigine or an antipsychotic)
What are the risks to me?	Usual side effects of valproate	Usual side effects of valproate, potential for relapse	Higher risk of relapse (depends on a variety of factors – discuss with your clinician), increased risk of puerperal psychosis	Risk of relapse if the other medication is not as effective as valproate; risk of new side effects
What are the risks to my baby?	Congenital malformations (see Table 4) long-term developmental disorders (estimated one in 3)	Reduced risk of congenital malformations and developmental disorders (risk depends on the dose, discuss with your clinician)	Indirect risks, e.g. disinhibition from poorly controlled bipolar disorder (discuss with your clinician)	Some medications are much safer for your unborn baby (specifically lamotrigine, some antipsychotics)
What are the benefits?	You are less likely to relapse or suffer from puerperal psychosis	Your unborn baby will have a lower risk of malformations than if you continue the full dose	Your unborn baby will have the same risk of malformations as the general population	If you can tolerate the new drug, you are less likely to relapse or suffer from puerperal psychosis; the other medication could have adverse effects
Who would benefit most from this?	People with unstable bipolar disorder and frequent relapses who are not controlled on other medication or lower doses of valproate	People with bipolar disorder who are not controlled on other medication	People who have been stable off valproate and do not wish to take other medications during pregnancy	People who are stable on alternatives to valproate

Folic acid to prevent teratogenicity?

VPA and many AED (phenytoin, barbiturates, carbamazepine and lamotrigine) may interfere with folic acid absorption or metabolism

Possibly an additional cause for their induction of congenital anomalies

Therefore recommendation is that women taking AEDs take folic acid prior to conception and in the first 2–3 months of pregnancy with folic acid, to reduce risks of NTD and possibly cardiac and oro-facial malformations

While use of folic acid supplementation has been shown to generally decrease the incidence of NTD in humans, there is conflicting data as to the benefit of folic acid in reducing the rate of AED-induced congenital malformations and NTD, especially following VPA intake

Despite the uncertainty of effectiveness, it is still recommended for women on AED therapy to take 4–5 mg/day of folic acid prior to any planned pregnancy.

Conflicting data

One study found that periconceptional folic acid significantly reduced the rate of spontaneous abortions and premature delivery in women treated with VPA and carbamazepine

Rate of congenital anomalies was not studied

- **Pittschieler S et al.. *J. Neurol.* 2008;255:1926–1931**

Other studies were inconclusive as to beneficial effects of folic acid even in reducing the rate of spontaneous abortions

- **Błaszczyk B et al. *Int. J. Mol. Sci.* 2022;23:1369. ; Baxter P. *Dev. Med. Child Neurol.* 2014;56:604.**

Australian Pregnancy Registry data on 2104 women treated during pregnancy with VPA, did not find any beneficial effects of 5 mg/day of folic acid prior to and during pregnancy on prevention of VPA-related birth malformations

- **Vajda F.J et. *Aust. N. Z. J. Obstet. Gynaecol.* 2007;47:468–474**

Original Investigation

September 26, 2022

Cancer Risk in Children of Mothers With Epilepsy and High-Dose Folic Acid Use During Pregnancy

Håkon Magne Vegrim, MD[1]; Julie Werenberg Dreier, PhD[1,2]; Silje Alvestad, MD, PhD[1,3]; et al

» Author Affiliations | Article Information

JAMA Neurol. 2022;79(11):1130-1138. doi:10.1001/jamaneurol.2022.2977

And to complicate things even more…

Scandinavian cohort study

Among 27 784 children (51.4% male) born to mothers with epilepsy, 5934 (21.4%) were exposed to high-dose folic acid (mean dose, 4.3 mg), with 18 exposed cancer cases compared with 29 unexposed, producing an adjusted hazard ratio of 2.7 (95% CI, 1.2-6.3), absolute risk if exposed of 1.4% (95% CI, 0.5%-3.6%), and absolute risk if unexposed of 0.6% (95% CI, 0.3%-1.1%)

In children of mothers without epilepsy, 46 646 (1.4%) were exposed to high-dose folic acid (mean dose, 2.9 mg), with 69 exposed and 4927 unexposed cancer cases and an adjusted hazard ratio of 1.1 (95% CI, 0.9-1.4; absolute risk, 0.4% [95% CI, 0.3%-0.5%]).

There was no association between children born to mothers with epilepsy who were prenatally exposed to antiseizure medications, but not high-dose folic acid, and an increased risk of cancer (absolute risk, 0.6%; 95% CI, 0.2%-1.3%).

Pregnancy prevention/contraceptive advice

Experience with isotretinoin has shown the difficulties in implementing effective pregnancy prevention plans

However important to emphasise importance of contraception

- Mandate referral for appropriate contraceptive discussion (if neurologist/psychiatrist unable to do so)

MotherSafe data suggests that there have been fewer valproate calls regarding pregnancy and more regarding planning since 2018 – maybe the message has been getting through…

Specific advice

4. Regarding the emerging information on the risk of exposure to valproate through paternal exposure, and noting the sponsor-initiated PI update to include the risk of neurodevelopmental disorders in children born to males being treated with valproate/reproductive toxicity in males, does the Committee consider that further risk minimisation measures are currently required in Australia?

Advice from expert

Response to question 4

At this stage I do not believe there is sufficient data on the risk of exposure to valproate through paternal exposure to support further risk minimisation measures in Australia

My opinion is that the sponsor-initiated PI update to include the risk of neurodevelopmental disorders in children born to males being treated with valproate/reproductive toxicity is

1. Not based on sound data

    Results of one sponsor-generated study with acknowledged limitations including lack of data around diagnoses, genetic conditions etc

    Data withdrawn and being re-analysed

2. Not scientifically valid or biologically plausible

3. Implies causation when there are no grounds to do so (and study authors acknowledge this)

Other advice/final thoughts..

Such a measure could produce significant anxiety in patients, their partners and healthcare providers

Could result in under-treatment of men with seizure disorders and or psychiatric conditions

cessation of needed medications with consequences including untreated seizures

self-harm /suicide

Sets a dangerous precedent

Should never change policy/ guidelines/prescribing based on a single (as yet unpublished) study

Item 3.01 sodium valproate Post-market item

ACM 44

4 AND 5 APRIL 2024

SPEAKER: s22 [redacted]

Decision-Making Algorithm

Does the data show a (new) safety signal of concern? [And is there a biologically plausible mechanism?]
I do not feel this has reached the threshold for taking drastic action

Do local utilisation patterns (prescribing and shared decision-making) suggest that intervention (including education) is required?
Insufficient data provided

How should that intervention be targeted and delivered to achieve desired outcome while minimising unintended consequences?
Noting that the burden may be carried mainly by GPs and patients

Valproate Clinical Indications

Registered

- Epilepsy
- Mania

Off-label

- Migraine prevention
- Neuropathic pain
- “Mood stabilisation”

Urgent

- Status epilepticus
- Status migrainosus

Adverse Effects: Dose Matters!

Weight gain

Tremor

Alopecia

Female fertility

Polycystic ovarian syndrome

Osteopenia/osteoporosis

In utero exposure

- Congenital malformations
- Low IQ
- Neurodevelopmental disorders

Male fertility

Paternal exposure

Swedish study

Registry-based cohort study

1,144,795 births (741,726 fathers without epilepsy) v 4,544 births (2,955 fathers with epilepsy)

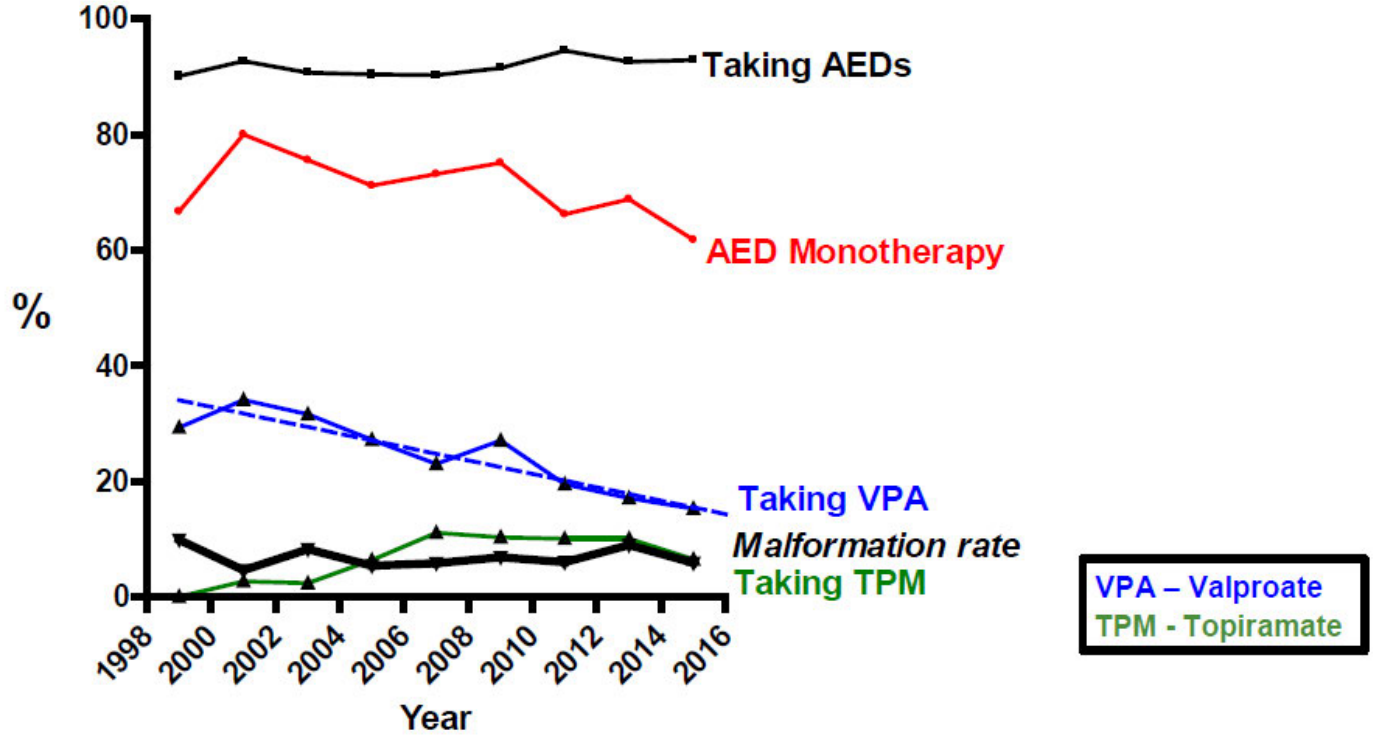
No difference in risk of MCM, ASD, ADHD or ID with or without conceptional ASM exposure

Valproate monotherapy subgroup: slightly higher rates of autism, ID not judged statistically significant

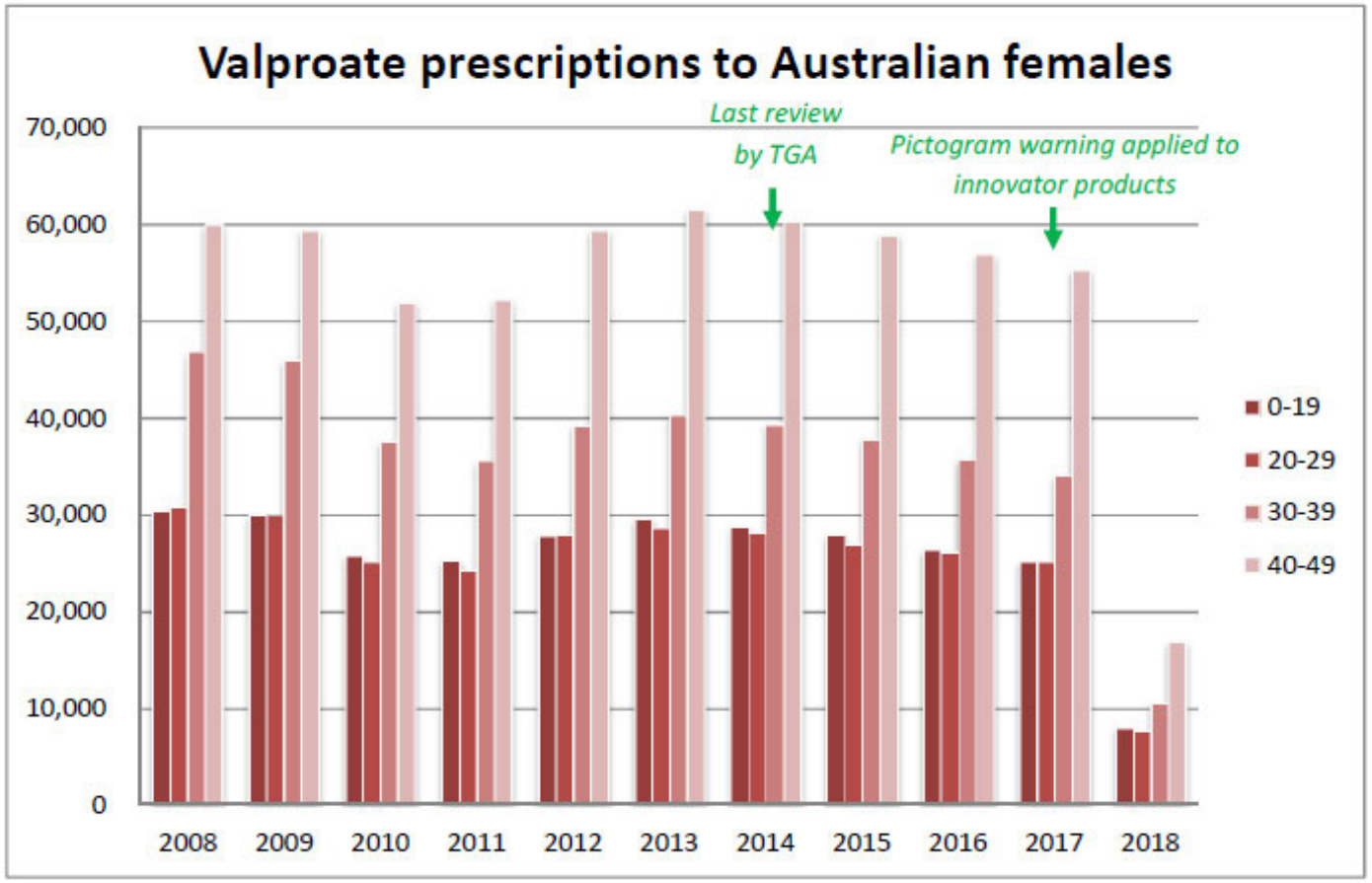
Tomson T, Muraca G, Razaz N. Paternal exposure to antiepileptic drugs and offspring outcomes: a nationwide population-based cohort study in Sweden. J Neurol Neurosurg Psychiatry. 2020 Sep;91(9):907-913. doi: 10.1136/jnnp-2020-323028. Epub 2020 Jul 10. PMID: 32651245.

Secular Trends in Prescribing (APR)

Figure 2. Proportion of pregnancies exposed to AEDs from 1998-2016 compared with malformation rate.[11]



PBS Prescriptions



Prescribers?

Table 4. Australian PBS/RPBS prescriptions by speciality group, 2008-April 2018.[13]

Calendar Year	Major Specialty					Total
	Neurology	Psychiatry	GP*	Paediatrics	Other	
2008	24,374	61,023	569,508	18,940	25,870	699,715
2009	23,665	59,131	579,399	19,971	23,774	705,940
2010	18,258	53,137	547,645	18,516	19,917	657,473
2011	18,144	51,947	560,305	17,703	19,047	667,146
2012	23,509	58,637	615,648	18,493	21,657	737,944
2013	25,299	60,974	636,362	19,556	20,511	762,702
2014	25,318	60,454	640,712	19,082	19,449	765,015
2015	25,045	59,060	640,922	17,784	18,690	761,501
2016	25,085	56,113	634,505	16,649	18,668	751,020
2017	25,092	53,633	632,448	15,723	22,859	749,755
2018**	7,745	16,054	195,176	4,927	6,992	230,894
TOTAL	**241,534**	**590,163**	**6,252,630**	**187,344**	**217,434**	**7,489,105**

*GPs include GP Trainee, GP Unclassified, NONVRGP and VRGP
** 2018 data is up to April only

Submission information

The MHRA has introduced new safety measures to reduce the known harms of valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the emerging data on the risk of harms in male patients.

It is recommended that this issue be reviewed by the Advisory Committee on medicines (ACM) to determine if it is appropriate for Australia to introduce stricter prescribing requirements for this medication. The TGA will need to refer to the PBAC if considering making changes to existing PBS listings.

Pregnancy Prevention Programme

- Valproate medicines are now therefore contraindicated, i.e. must not be used, in girls and women able to have children unless the terms of a special **pregnancy prevention programme** are followed. These include:
  - an *assessment* of each patient's potential for becoming pregnant,
  - *pregnancy tests* before starting and during treatment as needed,
  - *counselling*about the risks of valproate treatment and the need for *effective contraception* throughout treatment,
  - a *review of ongoing treatment* by a specialist at least annually,
  - introduction of a new *risk acknowledgement form* that patients and prescribers will go through at each such annual review to confirm that appropriate advice has been given and understood.

New MHRA Measures

- From January 2024, 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 unless there are compelling reasons that the reproductive risks do not apply.
- All female patients of childbearing potential and girls who are currently taking valproate will be reviewed at their next annual specialist review, using a revised valproate Annual Risk Acknowledgement Form, which will include the need for a second opinion's signature if the patient is to continue with valproate.
- A similar system will be introduced later in 2024 for male patients currently taking valproate. This follows advice from an independent expert group of the Commission on Human Medicines, with representation from across the healthcare system, that the measures should be introduced in a phased manner to ensure ongoing patient care is not disrupted.

Specific advice

1. Noting that the MHRA has not proposed a change to the indication within the UK-SPC (PI equivalent), does the Committee consider there is sufficient evidence to warrant amending the indication and/or prescribing requirements and recommendations of valproate in the Australian PI?

If the sponsor were agreeable, add:

Prescribers are encouraged to weigh the potential fertility and teratogenic risks associated with valproate users of all genders in determining whether valproate is the best treatment choice.

Specific advice

2. Previous advice from PBAC was based on PBS's stance on avoiding gender-based access to valproate. Noting that that the latest MHRA prescribing restrictions are applicable to both men and women, does the Committee support the referral of this issue to PBAC for consideration of relevant prescribing amendments?

Instead, the PBS enhanced access to lamotrigine and levetiracetam for women of childbearing potential – is improving access on the basis of gender more principled than gender-based restriction?

The PBAC could be asked to consider expanding access to lamotrigine and levetiracetam for patients of all genders – thus providing a market advantage compared to other ASMs

This presents an opportunity to refresh gendered language and to reconsider a PBS restriction on valproate (authority non-streamlined) for persons of childbearing potential

Specific advice

3. Are there other risk minimisation activities that the TGA could consider for this issue?

Requiring a second specialist opinion is a substantial burden

Annual consent process is an opportunity for improved patient education, if implemented sensibly (low burden, opt-out, clear medicolegal benefit)

Specific advice

4. Regarding the emerging information on the risk of exposure to valproate through paternal exposure, and noting the sponsor-initiated PI update to include the risk of neurodevelopmental disorders in children born to males being treated with valproate/reproductive toxicity in males, does the Committee consider that further risk minimisation measures are currently required in Australia?

The evidence is maturing and I suggest that taking regulatory action beyond updating PI and educational measures would be premature

Any other advice

Consider improving PBS access to lamotrigine for patients with bipolar disorder

Decision-Making Algorithm

Does the data show a (new) safety signal of concern? [And is there a biologically plausible mechanism?]
I do not feel this has reached the threshold for taking drastic action

Do local utilisation patterns (prescribing and shared decision-making) suggest that intervention (including education) is required?
Insufficient data provided

How should that intervention be targeted and delivered to achieve desired outcome while minimising unintended consequences?
Noting that the burden may be carried mainly by GPs and patients

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

REQUEST FOR ACM ADVICE

ACM Meeting **2024/44 ACM**

Date of Meeting **4/5 April 2024**

Agenda Item and Title

Medicine **Strength/Dose form**	Sodium valproate and use in pregnancy and women of child-bearing potential/ risk of neurodevelopmental disorders in children born to males being treated with valproate
Sponsor	*Apotex Pty Ltd* *AFT Pharmaceuticals Pty Ltd* *Alphapharm Pty Ltd* *Sanofi-Aventis Australia Pty Ltd* *Juno Pharmaceuticals Pty Ltd* *Wockhardt Bio Pty Ltd*
Indication	Epilepsy Mania
Summary of Issues	The MHRA has introduced new safety measures to reduce the known harms of valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the emerging data on the risk of harms in male patients. These changes include that from January 2024, 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 unless there are compelling reasons that the reproductive risks do not apply. All UK female patients of childbearing potential and girls who are currently taking valproate will be reviewed at their next annual specialist review, using a revised valproate Annual Risk Acknowledgement Form, which will include the need for a second opinion's signature if the patient is to continue with valproate. A similar system will be introduced later in 2024 for male patients currently taking valproate. This signal was previously discussed at the ACM in 2018. At the time it was recommended that prescribers be educated on the risk of sodium valproate use in pregnancy and to undertake risk

	communications in relation with prescribing. The introduction of a pregnancy prevention program in Australia was not deemed necessary at that stage. After the ACM on 31 May 2018 the TGA acted on the advice of ACM to request sponsors of generic products include pregnancy warning picture and wording on the outer packaging of products. The TGA wrote to the therapeutic guidelines to recommend updating information about valproate in pregnancy for non-epilepsy indications. The TGA sent letters to the RACP, RACP (paediatrics), RACGP, and RANZCP to liaise about improving education for valproate prescribing. Consideration of prescribing restrictions were considered in 2018 but were unable to be implemented due to advice received from Pharmaceutical Benefits Advisory Committee (PBAC) that the PBS avoided using gender as criteria for PBS item prescribing and the likelihood that practitioners would instead use an unrestricted item to reduce administrative burden. The related signal of risk of neurodevelopmental disorders in children born to males being treated with valproate/reproductive toxicity in males has recently been addressed by Sanofi in the form of a safety related request (SRR) submission to update sections 4.4 and 4.6 of the Australian PI. The sponsor proposed adding important safety information regarding the risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD) after paternal exposure to valproate and to include additional nonclinical information relating to testicular function. The TGA's Clinical Evaluation Report (CER) of this SRR submission references a retrospective observational study on electronic medical records in 3 European Nordic countries that indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate at time of in the 3 months prior to conception compared to those treated with lamotrigine or levetiracetam. The SRR submission was evaluated by the TGA (Prescription Medicines Authorization Branch), with a recommendation to accept the proposed inclusion of this risk in section 4.4 and 4.6 of the PI. The sponsor proposed changes to section 5.3 were rejected due to the evaluator finding them outside the scope of the SRR with data (attachment 3). There is extensive information already included in the Australian valproate PI (Epilim) regarding the risks associated with the use of valproate in pregnancy and women of child-bearing potential, including information on dosing and administration in *section 4.2*, a contraindication in pregnancy/women of childbearing potential for both epilepsy (unless no suitable alternative) and mania in *section 4.3,* a 3-page precaution including advice on counselling, need for effective contraception, risk of teratogenicity and a link to the Sanofi valproate patient and HCP resources in *section 4.4.* It is listed as a category D medication in pregnancy in *section 4.6.* There have been Australian cases of exposure to valproate in pregnancy reported to the TGA since the 2018 review. The majority of cases were reported in 2020 and 2021, with the

	2020 cases being the result of a literature article which included retrospective cases of exposure. It was difficult to quantify the exact number of Australian pregnancies that were exposed to valproate given the potential for overlap between reporting of literature article cases and case reports (attachment 1). There have been no reported Australian cases involving paternal exposure to valproate. The Australian therapeutic guidelines list the risk of foetal exposure to sodium valproate including major congenital malformations, and neurodevelopmental disorders. It recommends prescribers do not use sodium valproate in pregnancy for a psychiatric disorder unless other treatment options cannot be used and there is a high risk of harm if sodium valproate is stopped (eg relapse to a disabled or suicidal state). Female patients with epilepsy who are planning a pregnancy are recommended to consult an expert to discuss the harms and benefits of valproate and its alternatives. The MHRA recommendations do not include further labelling changes. Given the extensive information about this risk in the current Australian PI it is unlikely this warning can be strengthened further within the PI unless restrictions were implemented regarding prescribing to certain age groups. It is recommended that this issue be reviewed by the Advisory Committee on medicines (ACM) to determine if it is appropriate for Australia to introduce stricter prescribing requirements for this medication. The TGA will need to refer to the PBAC if considering making changes to existing PBS listings.
Advice sought	The committee is requested to provide advice on the following specific issues: 1. Noting that the MHRA has not proposed a change to the indication within the UK-SPC (PI equivalent), does the Committee consider there is sufficient evidence to warrant amending the indication and/or prescribing requirements and recommendations of valproate in the Australian PI? 2. Previous advice from PBAC was based on PBS's stance on avoiding gender-based access to valproate. Noting that that the latest MHRA prescribing restrictions are applicable to both men and women, does the Committee support the referral of this issue to PBAC for consideration of relevant prescribing amendments? 3. Are there other risk minimisation activities that the TGA could consider for this issue? 4. Regarding the emerging information on the risk of exposure to valproate through paternal exposure, and noting the sponsor-initiated PI update to include the risk of neurodevelopmental disorders in children

	born to males being treated with valproate/reproductive toxicity in males, does the Committee consider that further risk minimisation measures are currently required in Australia? The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on this matter.
Attachments	*1.* MSSI signal analysis (TRIM D23-4538555) *2.* MHRA - Valproate review of safety data and expert advice on management of risks - Public Assessment Report (TRIM D23-4526748) *3.* Clinical Evaluation Report SRR with data -sodium valproate- February 2024 (TRIM: D24-598569)

8/03/2024

X s22 [redacted]

s22 [redacted]

Signed by: s22 [redacted]

[electronically signed] 08/03/ 2024

Delegate of the Secretary under regulation 35A(1) of the *Therapeutic Goods Regulations 1990* Date

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MSSI Signal Analysis

Signal	Sodium valproate and use in pregnancy and women of child-bearing potential/ risk of neurodevelopmental disorders in children born to males being treated with valproate							
Source	**RAP**		**ROS**		**Other**	Other regulator (MHRA) notification		
Date Referred	28/11/23						**TRIM**	D23-4358078
RAP	**RAP**	**X**	**Date completed**	12/12/23			**TRIM**	D23-4471584

Reason for review	The MHRA has introduced new safety measures to reduce the known harms of valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the emerging data on the risk of harms in male patients. The MHRA provided the TGA with the Public Assessment Report (PAR) titled '*Valproate: review of safety data and expert advice on management of risks*'. The purpose of this evaluation is to review this signal, including the MHRA PAR, Australian cases reports and Australian guidelines and determine if any regulatory action is required by the TGA, including consideration of maternal and paternal exposure with valproate.
Actions Recommended by Other Regulator (MHRA)	• From January 2024, 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 unless there are compelling reasons that the reproductive risks do not apply. • All female patients of childbearing potential and girls who are currently taking valproate will be reviewed at their next annual specialist review, using a revised valproate Annual Risk Acknowledgement Form, which will include the need for a second opinion's signature if the patient is to continue with valproate. • A similar system will be introduced later in 2024 for male patients currently taking valproate. This follows advice from an independent expert group of the Commission on Human Medicines, with representation from across the healthcare system, that the measures should be introduced in a phased manner to ensure ongoing patient care is not disrupted.
Australian Regulatory Action History:	This issue was previously discussed at the ACM in 2018[i]. It was recommended that prescribers be educated on the risk of sodium valproate use in pregnancy and to undertake risk communications in relation with prescribing. The introduction of a pregnancy prevention program in Australia was not deemed necessary at that stage. The related signal of risk of neurodevelopmental disorders in children born to males being treated with valproate/reproductive toxicity in males has recently been addressed by Sanofi in the form of an SRR submission to update *sections 4.4* and *4.6* of the Australian PI. This SRR submission is currently being evaluated by PMAB.

***Evaluation Fins and Discussion*Australian PI**

Part One - Discussion and Analysis

Australian PI

There is extensive information already included in the Australian valproate PI (Epilim) regarding the risks associated with the use of valproate in pregnancy and women of child-bearing potential. This includes information on dosing and administration in *section 4.2*, a contraindication in pregnancy/women of childbearing potential for both epilepsy (unless no suitable alternative) and mania in *section 4.3,* a 3-page precaution including advice on counselling, need for effective contraception, risk of teratogenicity and a link to the Sanofi valproate patient and HCP resources in *section 4.4.* It is listed as a category D medication in pregnancy in *section 4.6.*

Current Australian regulatory action:

This issue was previously discussed at the ACM in 2018 [i]. It was recommended that prescribers be educated on the risk of sodium valproate use in pregnancy and to undertake risk communications in relation with prescribing. The introduction of a pregnancy prevention program in Australia was not deemed necessary at that stage.

In 2018 a suggestion to avoid exposure to sodium valproate during pregnancy and to minimise use in female patients of childbearing age by altering the PBS listing was considered by the TGA. The TGA was informed that the PBS avoids using a patient's sex as a criteria for access, so implementing a more restrictive listing for women than for men was unlikely to be considered appropriate and would be contrary to the usual practices [ii]. There was also a concern that if a separate PBS item listing was created for women of childbearing potential, then prescribers would instead use the unrestricted item to reduce administrative burden.

The related signal of risk of neurodevelopmental disorders in children born to males being treated with valproate/reproductive toxicity in males has recently been addressed by Sanofi in the form of an SRR submission to update *sections 4.4* and *4.6* of the Australian PI. This SRR submission is currently being evaluated by PMAB.

Other regulatory analysis:

The MHRA conducted a review of the available data and asked for advice from the independent Commission on Human Medicines (CHM), which also considered the views of patients and healthcare professionals. Consideration was given to the risks of epilepsy and the risks of changing treatment in patients with epilepsy.

The CHM advised that the current measures to reduce the risk of harm to patients and their children should be strengthened. The CHM advised that no one under the age of 55 should be initiated on valproate unless 2 specialists independently consider and document that there is no other effective or tolerated treatment. The CHM also advised that for existing patients, 2 specialists should independently consider and document that there is no other effective or tolerated treatment or that the risks do not apply to that individual patient.

The full recommendations from the CHM are included in the report, as well as the information they considered. The MHRA communicated this information to the UK public and to healthcare professionals in December 2022.

The CHM then formed an implementation group which included experts and representatives. They recommended that the measures should be introduced in a phased way to ensure ongoing patient care is not disrupted. The implementation group proposed that measures should apply firstly to all new patients under 55 years old and women already under specialist review, due to the level of reproductive risk being greatest for women of childbearing potential. Further communication on the implementation of the new safety measures was communicated to the public and healthcare providers in November 2023.

The report details the risks of valproate use in pregnancy including the magnitude and type of birth abnormalities. It discussed the potential reproductive risks of valproate use in male patients, including the risks of impaired fertility or male infertility and testicular toxicity in animal studies. The review also noted the potential of transgenerational risks and exposure and the possibility of teratogenic risk through paternal exposure to valproate, noting the MHRA is currently reviewing a retrospective post authorisation safety study of the paternal risk of valproate.

The report discussed the use of valproate in England, in September 2021 there were 20,192 prescriptions for valproate in women, of which 206 were issued to female patients newly starting valproate compared to 195 in September 2020. The report detailed concerns about the prescribing of valproate outside of its authorised uses. The number of pregnant women in the UK prescribed valproate in a 6-month period fell from 68 women in April to September 2018, to 17 women in October 2021 to March 2022. The report noted these babies have an 11% risk of birth defects and a 30 to 40% risk of neurodevelopmental disabilities, which can be permanent.

The report noted that current risk minimisation measures in the UK include the Pregnancy Prevention Programme (PPP), the England antiepileptics in pregnancy registry, and ensuring women receive information on the risks, including a patient information leaflet (PIL), manufacturers' specific and unique warnings and pictograms. All UK women of childbearing potential taking valproate received communication on the risks of valproate and the requirement to be on effective contraception. However, the MHRA assessment showed that some pregnancies continued to be exposed to valproate despite the significant risks and pregnancy prevention measures.

Overall, the MHRA report is a high quality report and shows evidence of due consideration of the complexities of this issue. The report details the benefits and risks of changing the advice around valproate prescribing and considers the implications of these changes on consumers and healthcare professionals. It is well produced and the TGA should consider whether similar changes need to be applied in Australia.

Australian case review:
A case search was performed on 15 December 2023 for 'sodium valproate' and 'valproic acid' and the PTs 'exposure during pregnancy', 'foetal exposure during pregnancy', 'maternal exposure during pregnancy' revealed 109 cases with the following breakdown of recent years: 2019: 2 cases, 2020: 20 cases, 2021: 33 cases, 2022: 1 case, 2023: 1 case (table 1).

Table 1: Summary of Australian case reports

Summary	Cases	Notes
2019	2	
2020	20	19 cases were from a literature article, these included possible duplicates of cases within the literature article. Not all cases were for the year they were coded as, and some retrospective cases involved children born in the early 2000s
2021	33	5 cases from a literature article, the remaining cases may include duplicates of cases reported in the literature article.

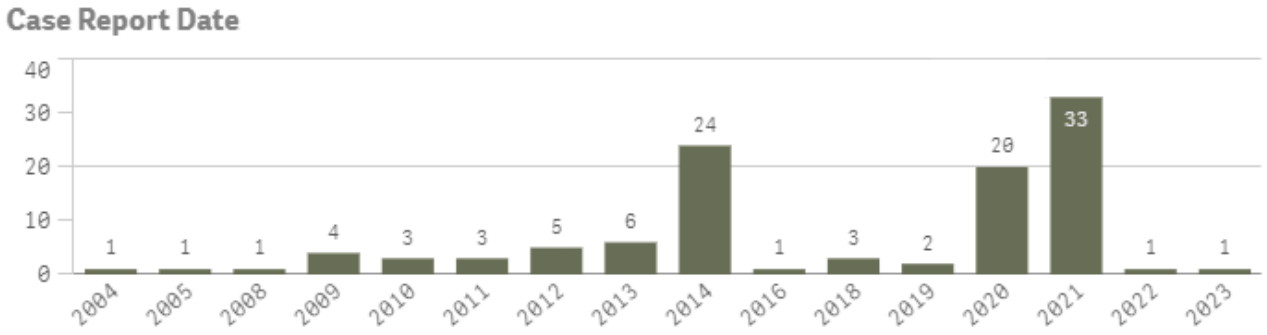
2022	1	
2023	1	

Cases included retrospective literature articles and included duplicate cases, it was difficult to determine whether cases were duplicate cases or separate cases due to a lack of clinical information. Not all cases were for the year they were coded as, and some retrospective cases involved children born in the early 2000s . The majority of cases were for valproic acid.

The most recent 2023 case was of a neonate patient exposure to levetiracetam and valproic acid in utero. The patient developed a congenital cardiac defect (type unknown). Mention of a gene mutation was also included in the report, but no further information was given.

Overall the volume of case reports received fluctuates from year to year (figure 1). A brief review shows in 2014 there was a literature article published which included retrospective cases. At least 18 reports in 2014 were in relation to this literature article.

Figure 1: Case reports for 'sodium valproate' and 'valproic acid' and the PTs 'exposure during pregnancy', 'foetal exposure during pregnancy', 'maternal exposure during pregnancy' by year.



Australian guidelines:
The therapeutic guidelines list the risk of foetal exposure to sodium valproate including major congenital malformations, and neurodevelopmental disorders. It recommends prescribers do not use sodium valproate in pregnancy for a psychiatric disorder unless other treatment options cannot be used and there is a high risk of harm if sodium valproate is stopped (eg relapse to a disabled or suicidal state). The therapeutic guidelines recommends females with epilepsy who are planning a pregnancy to consult an expert to discuss the harms and benefits of valproate and its alternatives with the patient.

Discussion
The Australian PI contains extensive information about the risk of valproate and pregnancy, including a contraindication for use in pregnancy or women of childbearing potential for both epilepsy (unless no suitable alternative) and mania. The MHRA is proposing significant changes to the prescribing requirement for valproate for all patients aged under 55 years. The MHRA recommendations do not include further labelling changes. Given the extensive information about this risk in the current Australian PI it is unlikely this warning can be strengthened further within the PI unless restrictions were implemented regarding prescribing to certain age groups.

There have been Australian cases of exposure to valproate in pregnancy reported to the TGA since the 2018 review. The majority of cases were reported in 2020 and 2021, with the 2020 cases being the result of a literature article which included retrospective cases of exposure. It was difficult to quantify the exact number of Australian pregnancies that were exposed to valproate given the potential for overlap between reporting of literature article cases and case reports.

Any consideration to restricting valproate prescribing in certain age groups, or to require the input of 2 specialists in order to prescribe would need to be considered by an expert committee and would need to balance risks of changing medications in patients versus the potential risks of exposure in pregnancy. Consideration would need to be given to whether any changes would be implemented for all patients given emerging information about risk of exposure to valproate through paternal exposure. Consideration would also need to be made to the practicalities of changing the PBS listing.

It is recommended that this issue be reviewed by the Advisory Committee on medicines (ACM) to determine if it is appropriate for Australia to introduce stricter prescribing requirements for this medication. The TGA will need to also seek advice of the Pharmaceutical Benefits Advisory Committee (PBAC) if considering making changes to existing PBS listings.

[1] https://www.tga.gov.au/resources/publication/meeting-statements/acm-meeting-statement-meeting-9-31-may-1-june-2018#sb

[ii] PBAC response, 15 November 2018, D18-11293046

Clearance

Place an X in the right hand column next to the appropriate option

I endorse the above signal analysis and proposed recommendations for action	**X**
I endorse the above signal analysis and proposed recommendations for action with minor amendments (see comments)	
I agree with the proposed recommendation to return to routine monitoring	
Comments: As indicated in this analysis, the quality and nature of reported AE data since 2018 limits the current assessment of this risk in the Australian context. Given the recent COR actions for further risk mitigation, ACM advice would be beneficial in characterizing these risks and the appropriate risk management measures, if necessary.	

Plan Cleared by	s22 [redacted]	**Date cleared**	**07 Jan 2024**

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Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Clinical Evaluation Report - Safety Related Request with Data

Prescription Medicines Authorisation Branch

Active substance: Sodium valproate

Product name: EPILIM, VALRPO, SODIUM VALPROATE SANDOZ, VALPROATE WINTHROP

Sponsor: Sanofi-Aventis Australia Pty Ltd

Submission number: PM-2023-01589-1-1

eSubmission number: e002448 - (0038) e002448 - (0031)

Evaluator: s22 [redacted]

Date of report: 12/02/2024

Clinical File:

TRIM reference:

This report contains confidential information to be removed from the copy provided to the sponsor.

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy, when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

Contents

List of abbreviations

Abbreviation	Meaning
AED	Anti-epileptic Drugs
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ASD	Autism Spectrum Disorders
CCDS	Company Core Data Sheet
GABA	Gama aminobutyric acid
NDD	Neurodevelopmental disorders
NOAEL	The no-observed-adverse-effect-level
PI	Product Information
SmPC	Summary of Product Characteristics
SRR	Safety Related Request

List of tables

1. Submission details

Table 1 Submission details for PM-2023-01589-1-1

Submission ID	PM-2023-01589-1-1
Submission Type	SRR with data
Sponsor	Sanofi Aventis Australia Pty Ltd
Trade name	Epilim / Epilim IV / Valproate Winthrop / Sodium Valproate Sandoz / Valpro EC
Active Ingredient	Sodium valproate
Clinical File Number	2014/005496
PI/CMI File Number	2014/006295
Data	e002448 - (0038) e002448 - (0031)
Application form	e002448 (0031-) - Application form
PROPOSED PI -Annotated	e002448 (0038-) - Epilim IV - Product information – annotated e002448 (0038-) - Epilim - Product information – annotated e002448 (0038-) - Valproate Winthrop - Product information – annotated e002448 (0038-) - Valpro EC - Product information – annotated e002448 (0038-) - Sodium Valproate Sandoz - Product information – annotated
Scope of review	To assess if the proposed changes in the PI are acceptable within the scope of a Safety Related Request and that the evidence submitted supports the changes

1.1. Submission type

This is an application proposing to amend the Australian Product Information (PI) for Epilim / Epilim IV / Valproate Winthrop / Sodium Valproate Sandoz / Valpro EC (sodium valproate) under provisions of s.9D(2) consisting of a Safety Related Request with data (submission PM-2023-01589-1-1).

This SRR with data submission for the above products containing sodium valproate was originally submitted by the sponsor on 6 April 2023 to add important safety information changes regarding risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD) after paternal exposure to valproate and to include additional nonclinical information relating to testicular function. The application was subsequently placed on hold until 30 November 2023 to allow for a correction of a meta-analysis that formed part of the supporting 2.5 Clinical Overview.

Based on the updated information revisions to the Product Information (PI) has been made in accordance with Company Core Data Sheet (CCDS) version 38, a list of the sections with proposed changes is below:

- **Section 4.4 Special Warnings and Precautions for Use**
- **Section 4.6 Fertility, Pregnancy and Lactation**
- **Section 4.8 Adverse Effects (UNDESIRABLE EFFECTS)**

1.2. Drug class and therapeutic indication

The mode of action of Sodium Valproate has not been fully established. Its anticonvulsant effect is attributed to the blockade of voltage dependent Na+ channels and increased brain levels of γ-aminobutyric acid (GABA). The GABA-ergic effect is also believed to possibly contribute towards the antimanic properties of sodium valproate.

In animals, Sodium Valproate Sandoz raises cerebral and cerebellar levels of the inhibitory synaptic transmitter, GABA, possibly by inhibiting GABA degradative enzymes, such as GABA transaminase and/or succinic semialdehyde dehydrogenase and/or by inhibiting the reuptake of GABA by neuronal cells.

Sodium Valproate Sandoz exhibits marked anticonvulsant activity in animals, demonstrated by the various tests used to detect antiepileptic activity.

Sodium Valproate Sandoz appears to have no significant hypnotic effect (an incidence of about 0.2% was noted for drowsiness in a survey of unwanted effects), nor does it have any significant action on the autonomic nervous system, respiration, blood pressure, renal function or body temperature. It does have a spasmolytic action on the isolated ileum preparation but no effect on the nictitating membrane.

1.2.1. Therapeutic indications

Epilepsy
Primary generalised epilepsy (petit mal absences, various forms of myoclonic epilepsy and tonic-clonic grand mal seizures). Partial (focal) epilepsy either alone or as adjuvant therapy.

Mania
For the treatment of mania where other therapy has proved inadequate or is inappropriate.

1.3. Dosage forms, strengths

Table 2: Approved products included in this submission

Product name	Active ingredient	Presentation	AUST R
EPILIM	sodium valproate	100 mg crushable tablet blister pack	15373
EPILIM EC200	sodium valproate	200 mg tablet blister pack	15369
EPILIM EC500	sodium valproate	500 mg tablet blister pack	15370
EPILIM LIQUID	sodium valproate	40 mg/mL sugar free oral liquid bottle	74711
EPILIM IV	sodium valproate	400 mg powder for injection vial with diluent ampoule	104416

EPILIM SYRUP	sodium valproate	40 mg/mL oral liquid bottle	15372
SODIUM VALPROATE SANDOZ	sodium valproate	200 mg enteric coated tablet blister pack	134367
SODIUM VALPROATE SANDOZ	sodium valproate	500 mg enteric coated tablet blister pack	134368
VALPRO EC200	sodium valproate	200 mg enteric coated tablet blister pack	286315
VALPRO EC500	sodium valproate	500 mg enteric coated tablet blister pack	286316
VALPROATE WINTHROP EC200	sodium valproate	200 mg tablet blister pack	125620
VALPROATE WINTHROP EC500	sodium valproate	500 mg tablet blister pack	125621

2. Background

2.1. Clinical rationale

The sponsor is proposing to add important safety information regarding risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD) after paternal exposure to valproate and to include additional nonclinical information relating to testicular function.

2.2. Guidance

The following TGA-adopted guidance/other documents are considered relevant to this submission:

- Australian Regulatory Guidelines for Prescription Medicines (ARGPM) | Therapeutic Goods Administration (TGA)
- Form for providing product information | Therapeutic Goods Administration (TGA)
- Variation https://www.tga.gov.au/publication/variations-prescription-medicines-excluding-variations-requiring-evaluation-clinical-or-bioequivalence-data-appendix-1-variation-types-chemical-entities

3. Contents of the clinical dossier

The clinical dossier comprises the following:

Module 1

- Cover letter: e002448 (0038-) - Cover letter
- e002448 (0038-) - Response to request for information
- Application form: e002448 (0031-) - Application form
- e002448 (0038-) - Epilim IV - Product information – annotated

- e002448 (0038-) - Epilim - Product information – annotated
- e002448 (0038-) - Valproate Winthrop - Product information – annotated
- e002448 (0038-) - Valpro EC - Product information – annotated
- e002448 (0038-) - Sodium Valproate Sandoz - Product information – annotated
- e002448 (0038-) - Epilim IV - Product information – clean
- e002448 (0038-) - Epilim - Product information – clean
- e002448 (0038-) - Valproate Winthrop - Product information – clean
- e002448 (0038-) - Valpro EC - Product information – clean
- e002448 (0038-) - Sodium Valproate Sandoz - Product information – clean
- e002448 (0038-) - HCP guide
- e002448 (0038-) - patient guide-female
- e002448 (0038-) - Risk management plan-dhcp-letter
- e002448 (0038-) - patient-guide-male

Module 2: Clinical Overview

- e002448 (0038-) - Clinical Overview
- e002448 (0038-) - Clinical Overview-risk-of-neuro

Module 5: Clinical Study Reports - Literature references

e002448 (0038-) - ayan2015p248-50

e002448 (0038-) - colella2012p358-66

e002448 (0038-) - phiel2001p36734-41

e002448 (0038-) - tomson2020p907-913

e002448 (0038-) - veiby2013p1462-72

4. Proposed changes to Sections 4 and 5

The Sponsor proposes changes to sections that include the proposed changes. The proposed changes are outlined below. New text proposed by the Sponsor from CCDSv38 is shown in underlined blue. ~~Deleted blue line~~ represents deleted text from CCDSv36. Text proposed by the Sponsor for deletion from currently approved PI/CMI is shown as ~~strikethrough red~~ strike-through. New text proposed by the evaluator is shown in red. Evaluator comments requiring actions are **bolded.**

Table 3: Changes proposed by the Sponsor

Proposed PI change by section
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Use in males of reproductive potential A retrospective observational study indicates an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to ~~at~~ ~~time of~~ conception, compared to those treated with lamotrigine or levetiracetam (see section 4.6).

Proposed PI change by section
~~As a precautionary measure~~ Despite study limitations, by way of precaution, the prescriber should inform the male patients of this potential risk. The prescriber should discuss with the patient, the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment. The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known. The male patient should be advised: • not to donate sperm during treatment and for 3 months after stopping the treatment, • of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception, • that he and his female partner should contact their doctor for counseling in case of pregnancy if he used valproate within 3 months prior to conception. The male patient should also be informed about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorder. The specialist should at least annually review whether valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with valproate use. ~~and consider alternative therapeutic options with the patient. In men initiating or remaining on valproate treatment, the need for effective contraception should be discussed with the patient, at least annually. The prescriber should ensure the male patient has acknowledged the risk and precautions associated with valproate use.~~ Educational materials To reinforce the warnings and provide guidance regarding use of valproate in men of reproductive potential, educational materials are available electronically through a QR code on the carton (www.sanofi.com.au/valproate). A patient guide should be provided/available to all men of reproductive potential using valproate.

Proposed PI change by section
• **Section 4.6 Fertility, Pregnancy and Lactation**
Use in Pregnancy Category D Treatment of epilepsy • Valproate is contraindicated as ~~treatment for epilepsy~~ during pregnancy unless there is no suitable alternative. • Valproate is contraindicated for use in women of childbearing potential, unless the physician has provided education on the potential effects of valproate during pregnancy (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use).

Proposed PI change by section
Treatment of mania • Valproate is contraindicated ~~as treatment for bipolar disorder~~ during pregnancy. • Valproate is contraindicated for use in women of childbearing potential, unless the physician has provided education on the potential effects of valproate during pregnancy (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use).
Section 4.6 Fertility, Pregnancy and Lactation
Pregnancy Exposure Risk related to valproate In females, ~~B~~both valproate monotherapy and valproate polytherapy including other antiepileptics, are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate. In animals teratogenic effects have been demonstrated in mice, rats and rabbits. Risk to children of fathers treated with valproate A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate ~~at time of~~ in the 3 months prior to conception compared to those treated with lamotrigine or levetiracetam. The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% ~~5.6% to 6.3%~~ in the valproate group versus between 2.3% to 3.2% ~~2.5% to 3.6%~~ in the composite lamotrigine/levetiracetam monotherapy group ~~exposure~~. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07) ~~1.47 (95% CI: 1.10, 1.96).~~ Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. ~~Further investigations are needed.~~ Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually (see section 4.4).
Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) ***List of adverse effects by system organ class*** Neoplasms benign, malignant and unspecified (including cysts and polyps) Myelodysplastic syndrome is rare. Unknown: acquired Pelger–Huet anomaly

Proposed PI changes to Section 5.3
5.3 PRECLINICAL SAFETY DATA Testicular function In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 400 mg/kg/day and 150 mg/kg/day, respectively with associated NOAELs for testis findings of 270 mg/kg/day in adult rats and 90 mg/kg/day in adult dogs. ~~of valproate. The dose without an effect on the testes was similar to the maximum recommended human dose of 50 mg/kg/day on a mg/m² basis.~~ In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance. ~~This dose was about 1.3 times the maximum recommended human dose of 50 mg/kg/day on a mg/m² basis.~~

4.1. Supporting evidence

- Safety Evaluation Report and supporting literature: Risk of neurodevelopmental disorders including autism spectrum disorders after paternal exposure to valproate (version 3.0). e002448 (0038-) - Clinical Overview-risk-of-neuro
- Safety Evaluation Report and supporting literature: valproate and acquired or pseudo-pelger-huët anomaly. e002448 (0038-) - Clinical Overview
- Epilim CCDS v38 https://www.medsafe.govt.nz/profs/datasheet/e/Epilimtabsyrliqiv.pdf

4.2. Evaluator's assessment and recommendations

4.2.1. Review of supporting evidence

Table 4: Evaluator's assessment of proposed changes

Proposed safety changes	Evaluator's comments
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE	
Use in males of reproductive potential A retrospective observational study indicates an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to ~~at time of~~ conception, compared to those treated with lamotrigine or levetiracetam (see section 4.6 Fertility, Pregnancy and Lactation). ~~As a precautionary measure~~ Despite study limitations, by way of precaution, the prescriber should inform the male patients of this potential risk. The prescriber should discuss with the patient, the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment.	Acceptable. Adds or strengths safety warning. Within scope of SRR with data. **Please add section title (Fertility, Pregnancy and Lactation)**

Proposed safety changes	Evaluator's comments
The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known. The male patient should be advised: • not to donate sperm during treatment and for 3 months after stopping the treatment, • of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception, • that he and his female partner should contact their doctor for counseling in case of pregnancy if he used valproate within 3 months prior to conception. The male patient should also be informed about the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorder. The specialist should at least annually review whether valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with valproate use. ~~and consider alternative therapeutic options with the patient. In men initiating or remaining on valproate treatment, the need for effective contraception should be discussed with the patient, at least annually. The prescriber should ensure the male patient has acknowledged the risk and precautions associated with valproate use.~~ Educational materials To reinforce the warnings and provide guidance regarding use of valproate in men of reproductive potential, educational materials are available electronically through a QR code on the carton (www.sanofi.com.au/valproate). A patient guide should be provided/available to all men of reproductive potential using valproate.	

Evaluator assessment:

Since the general marketing of valproate in 1974, the product information for doctors has included a warning about the possible risk of birth defects after in-utero exposure (in pregnancy).

The NDDs are a group of conditions with onset in the developmental period. The disorders typically manifest early in development, often before the child enters grade school, and are characterized 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.

Proposed safety changes	Evaluator's comments
As noted in the current Summary of Product Characteristics (SmPC) for valproate[1], a meta-analysis (including registries and cohort studies) showed that approximately 11% of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations (Weston and others, 2016)[2]. This is greater than the risk of major malformations in the general population (approximately 2–3%). Studies in children exposed in-utero to valproate show that up to 30–40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems (Bromley and others, 2010[3]; Cummings and others, 2011[4]; Meador and others, 2009[5]).	
Evaluator recommendation: Accept proposed changes to PI	
Section 4.6 Fertility, Pregnancy and Lactation	
Use in Pregnancy Category D Treatment of epilepsy • Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative. • Valproate is contraindicated for use in women of childbearing potential, unless the physician has provided education on the potential effects of valproate during pregnancy (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use). Treatment of mania • Valproate is contraindicated as treatment for bipolar disorder during pregnancy. • Valproate is contraindicated for use in women of childbearing potential, unless the physician has provided education on the potential effects of valproate during pregnancy (see Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for Use).	Acceptable. Adds or strengths safety warning and reduces patient population. Within scope of SRR with data.
Evaluator assessment: Valproate is a known teratogenic medicine, resulting in both physical birth defects and neurological disorders, some of which may lead to permanent disability. The SmPCs for valproate products state that a meta-analysis (including registries and cohort studies) (Weston and others, 20162) showed that approximately 11% of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (approximately 2–3%). Studies in children exposed in-utero to valproate show that up to 30–40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. **Evaluator recommendation: Accept proposed changes to PI**	

Proposed safety changes	Evaluator's comments
Pregnancy Exposure Risk related to valproate In females, ~~B~~both valproate monotherapy and valproate polytherapy including other antiepileptics, are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate. In animals teratogenic effects have been demonstrated in mice, rats and rabbits. Risk to children of fathers treated with valproate A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate ~~at time of~~ in the 3 months prior to conception compared to those treated with lamotrigine or levetiracetam. The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% ~~5.6% to 6.3%~~ in the valproate group versus between 2.3% to 3.2% ~~2.5% to 3.6%~~ in the composite lamotrigine/levetiracetam monotherapy group ~~exposure~~. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07) ~~1.47 (95% CI: 1.10, 1.96).~~ Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. ~~Further investigations are needed.~~ Alternative therapeutic options and the need for effective contraception while using valproate and for 3 months after stopping the treatment should be discussed with male patients of reproductive potential, at least annually (see section 4.4 **Special Warnings and Precautions For Use**).	Acceptable. Adds or strengths safety warning. Within scope of SRR with data. **Suggest adding section title: (See section 4.4 Special Warnings and Precautions For Use)**
Evaluator assessment: The risk of major congenital malformations in children after in-utero exposure to AED polytherapy including valproate is higher than that of AED polytherapy not including valproate. The retrospective observational study known as the post authorisation safety study (PASS) was carried out using multiple registry databases in Denmark, Norway and Sweden and evaluated the association between paternal exposure to valproate and risk of neurodevelopmental disorders (NDDs), including autism spectrum disorders (ASD), as well as congenital abnormalities in offspring. In 2022, results from the PASS were released and reported a higher risk for NDDs including ASD in offspring related to paternal exposure to	

Proposed safety changes	Evaluator's comments
valproate when compared to paternal exposure to the composite lamotrigine/levetiracetam monotherapy. This risk is highly dose-dependent with valproate monotherapy, and available data suggests it is dose-dependent with valproate polytherapy (Tomson and others, 2015[7]). However, a threshold dose below which no risk exists cannot be established. The current review did not consider any new data on the magnitude and nature of congenital abnormalities or neurological disorders in children of women who took valproate in pregnancy. However, it did include a summary of evidence for the risks in pregnancy, as well as data for risks with other AEDs. Valproate crosses the placenta freely (Semczuk-Sikora and others, 2010[6]). The risk of structural malformations is greatest in the first trimester; however, the risk of neurodevelopmental harm is thought to be present throughout all three trimesters. There is therefore no established safe period of exposure.	
Evaluator recommendation: ▪ **Accept proposed changes to PI** ▪ **All proposed minor editorial changes to this section of the PI are acceptable.**	

Proposed safety changes to Section 4.8	Evaluator's comments
List of adverse effects by system organ class Neoplasms benign, malignant and unspecified (including cysts and polyps) Myelodysplastic syndrome is rare. Unknown: acquired Pelger–Huet anomaly	Acceptable. Within scope of SRR with data submission as adds a warning/precaution.
Evaluator recommendation: Accept proposed changes to PI	

Proposed safety changes to Section 5.3	Evaluator's comments
5.3 PRECLINICAL SAFETY DATA Testicular function In sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 400 mg/kg/day and 150 mg/kg/day, respectively with associated NOAELs for testis findings of 270 mg/kg/day in adult rats and 90 mg/kg/day in adult dogs. ~~of valproate. The dose without an effect on the testes was similar to the maximum recommended human dose of 50 mg/kg/day on a mg/m² basis.~~ In a fertility study in rats, valproate at doses up to 350 mg/kg/day did not alter male reproductive performance. ~~This dose was about 1.3 times the maximum recommended human dose of 50 mg/kg/day on a mg/m² basis.~~	Unacceptable, outside the scope of SRR with data
Evaluator recommendation: Reject proposed changes to section 5.3 of the PI.	

Recommendation regarding authorisation

Section 9D (2) of the Therapeutic Goods Act 1989 states that 'If:

(a) the person in relation to whom the therapeutic good are registered or listed has requested the Secretary to vary the information included in the entry in the register that relates to the goods; and

(b) the only effect of the variation would be:

(i) to reduce the class of persons for whom the goods are suitable; or

(ii) to add a warning, or precaution, that does not include any comparison of the goods with any other therapeutic goods by reference to quality, safety and efficacy'; the secretary must vary the entry in accordance with the request.'

Some of the changes to the PI proposed by the Sponsor are acceptable under section 9D(2) of the Act. Some of the changes are not considered acceptable as they cannot be classified as either a reduction in the class of persons for whom the goods are suitable or a warning or precaution.

The Evaluator recommends that:

Proposed changes to section 4.4, section 4.6 and section 4.8 are accepted.

All the proposed minor editorial changes not referenced in the report are acceptable.

Proposed amendments to section 5.3 are rejected.

5. References

1-SMPC sodium valproate https://www.medicines.org.uk/emc/product/1500/smpc#gref

2-Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016 Nov 7;11(11):CD010224 https://pubmed.ncbi.nlm.nih.gov/27819746/

3-Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L, Briggs M, Clayton-Smith J, Shi X, Baker GA; Liverpool and Manchester Neurodevelopment Group [LMNDG]. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia. 2010 Oct;51(10):2058-65.https://pubmed.ncbi.nlm.nih.gov/20633039/

4-Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child. 2011 Jul;96(7):643-7. doi: 10.1136/adc.2009.176990. https://pubmed.ncbi.nlm.nih.gov/21415043/

5-Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244-52 https://pubmed.ncbi.nlm.nih.gov/23352199/

6-Semczuk-Sikora A, Czuczwar S, Semczuk A, Kwasniewska A, Semczuk M. Valproic acid transfer across human placental cotyledon during dual perfusion in vitro. Ann Agric Environ Med. 2010;17(1):153-7. https://pubmed.ncbi.nlm.nih.gov/20684493/

7-Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, Sabers A, Thomas SV, Vajda F; EURAP Study Group. Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. Neurology. 2015 Sep 8;85(10):866-72 https://pubmed.ncbi.nlm.nih.gov/26085607/

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