[redacted]

27/05/2016 12:34 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: Follow up request for feedback on toolkit to be emailed through and contact details while Dee is away

Hi Dee

Thanks for the opportunity to comment on the toolkit.

Below are some comments from Medsafe's perspective:

- The toolkit has been put together and is the property of the sponsor, Sanofi. This is the case in the UK also.
- Sanofi are looking at releasing this toolkit in Q3 2016. They are yet to update us exactly when this might be and there may be a few amendments to what is currently available.
- The wording in the healthcare professional brochure is the same as overseas, though it is presented slightly differently.
- The wording in the consumer brochure is less detailed; there is concern regarding health literacy in the NZ context and the intention was that the resource would be available in conjunction with a discussion with a healthcare professional.

Medsafe does want to support the use of educational material, but there is some concern that having two toolkits available may be confusing.
Perhaps there should be consideration that only additional information should be included in any additional toolkit from FACS NZ/ACC. For example, there could be information for healthcare professionals about how to start a conversation like this with their patients, how to explain risk-benefit balance (as there will be a population of women where valproate is the only suitable treatment option) and a detailed literature review that clearly shows what is known about fetal valproate syndrome (FVS). For patients/consumers there could be further information about the risks of taking valproate during pregnancy that are not currently included in the consumer brochure as well as information about what it is like to have a child affected by FVS (this might be particularly helpful when explaining risks and benefits; outcome of this risk decision is important).

If a checklist is to be included as well then it is important to consider how often the checklist is to be completed (eg, only at diagnosis, only when considering pregnancy, yearly, with each prescription) and context regarding what the background rates of birth defects and developmental disorders are as well as the risks associated with uncontrolled seizures during pregnancy (again, helps with discussing risks and benefits).

I hope these comments help, if there are any questions please get in touch.

Have a good break.

Kind regards
Rowan

**Rowan Pollock** | Senior Advisor Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health [redacted]

MEDSAFE

Dee Young Hi all This is just a quick email to th... 27/05/2016 09:26:25 a.m.

[redacted]

25/08/2016 03:42 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: FACS Prevention Toolkit - your feedback requested by Friday September 2nd please.

Hi Dee

The new designs of information leaflets are looking good! Please see below for comments:

Cover Letter

- Consider first sentence change to '... help healthcare professionals manage their female patients who take anticonvulsant medicines and raise awareness of the risks of these medicines during ...' This toolkit is only for managing female patients that take anticonvulsants/antiepileptics, not all female patients.

Healthcare professional information

- First sentence needs altering for similar reasons to above, it implies that it is helpful for all females who are pregnant or planning on pregnancy, rather than just those on anticonvulsants. Consider 'This booklet: is for healthcare professionals who prescribe or dispense anticonvulsants to female patients who are or wish to become pregnant'
- Second point could be changed to ' This booklet: helps to understand the level of risk in these women' or 'helps to raise awareness of the risks in these women'
- Third point could be ' This booklet: is provided as part of a Foetal Anticonvulsant Syndrome prevention initiative.' I don't think that explaining what the syndrome is in this section is helpful and should be removed.
- Key messages about risk. This needs to be quantified; low risk and high risk does not really mean anything. There needs to be a definition.
- I don't think it would be very beneficial recommending providing a copy of the patient information booklet to a patient that gets pregnant while taking anticonvulsants as this is a preventative measure. Also some scary information in there, see point below in consumer information.
- There is mention in one section that there is no known dose of sodium valproate that is free of risk and then in another state that the lowest possible dosage (dose) should be used.
- Some of the advice is about anticonvulsants in general and some are about sodium valproate specifically - could this specific information all be moved to the one section?
- Reporting an adverse reaction - please add a link to CARM for online reporting

Consumer information

- Consider first sentence change to " This booklet: is for females who take anticonvulsant medicines and are considering pregnancy.' The aim is to provide this information prior to the woman becoming pregnant?
- Introduction - there are women that are not of child bearing age or capacity as they are older or do not have a uterus. I don't think we should assume all women that are not of child bearing age are young and need parent or guardian input. Have to remember that valproate has been around for a long time and there may be a number of women who are stable on valproate.
- Consider changing sentence about contraception to '...it is extremely important that you are using an effective contraceptive method'. For example there are long-acting methods of contraception that do not involve taking a tablet.
- Change '...you and an unborn baby' to 'you and your unborn baby'.
- Please change the dot point about already having a child with a malformation increases the risk or change it as I don't think it is correct. The risk does not increase, the risk is the same with each pregnancy if the medicine remains the same. May need checking however...
- This is my opinion, but if I were to receive a leaflet with one and a half pages of problems that could happen to my baby if I were taking an anticonvulsant then I would not continue with my medicine!
- Again, please provide a website link for CARM.

I hope this is helpful.

Kind regards
Rowan

**Rowan Pollock** | Senior Advisor Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health [redacted]

Dee Young Dear all The Toolkit communication... 23/08/2016 04:31:54 p.m.

From: [redacted]
To:

Date: 23/08/2016 04:31 p.m.
Subject: FACS Prevention Toolkit - your feedback requested by Friday September 2nd please.



Dear all

The Toolkit communications testing has been completed and we've had a first go at design and layout. Here is a brief overview from [redacted] with a few additional comments from me added in brackets and italics:

**Testing participants included**:

- 5 health professional interviews: GP, psychiatrist, LMC, family planning nurse and a pharmacist.
- Neurologists via email and phone calls
- 2 consumer advocates -epilepsy and mental health
- 2 interviews with parents with daughters who take anticonvulsant medication
- Focus group of 4 women with young children (*used as a proxy as there were ethical issues around testing with actual young women on anticonvulsants, especially within our short time frames* ).

**Consensus**

All the participants recognised that there was a need for health professionals, women and parents to receive information on the risks of AEDs in pregnancy, but felt the toolkit needed to shift away from pregnant woman to all woman of childbearing age (*Currently the new name of the toolkit has been amended to Anticonvulsant Medication Considerations for Females).*

**Overall response to toolkit**

- Neurologists support the idea of toolkit, but had concerns about the content (see below)
- Largely positive response from all the other health professionals, consumer advocates, women and parents.

**Neurologists concerns**

- Too heavy-handed and unbalanced with regard to the risks, and contrary to advice they are giving in their clinics
- Concerned that a woman reading this might stop her medication without consulting their GP or specialist, which could result in death of the woman and the unborn baby
- No mention of level of risk to the mother of stopping medications (*we did talk about not stopping meds but we didn't spell out the risks if they do stop - I have since learnt these are a 10 fold increase in sudden death, largely attributed to women stopping their medication inappropriately* ).
- FACS is no longer recognised as an entity (*Nick thinks this point is debatable as it's still used in some settings in NZ and overseas, plus unless we are given an alternative this will confuse people. Rod thinks we should say this is an old term).*
- Statistics are overstated (*Rod disagrees. We have tweaked our wording on some of these* )
- Focus on Sodium Valproate with little mention of other drugs known to cause foetal abnormalities e.g. toprimate, pregabalin or phenobarbitone (*phenobarbitone is a controlled drug anyway so we have chosen not to include this* ).

**Feedback on specific items**

Patient booklet may need readapting for people with English as another language, learning difficulties, low literacy skills and teenagers (*we plan to send it to an agency that specialises in this once we have received the next, and hopefully final round of feedback* ).

- Patient booklet would be better as an A5 size so it can fit in a handbag (*the new versions attached are designed as A5 booklets* ).

- Would like to have an additional smaller, more concise version of information available (*so we are resurrecting the old brochure to fit this request* ).

- Would like it available in hard copy and online.

- Two posters were presented (*one photo was of a clothed woman and the other was the version the project team had viewed* ) there were mixed reactions as the one with the baby on the stomach had greater cut through and call to action (but some health care professionals may not use it if they thought it could be seen as offensive), whereas the second poster was less startling but likely to go unnoticed. (*We are currently road testing two more poster alternatives* to [redacted] original, these are pages 1 and 4 of the poster document attached – we are aware the photo one has the wrong pill packet on it for the NZ audience so that would need changing if that was the preference).

**Next steps**

We have had a go at updating the information in the new versions attached. It would be great

to get you all to review this one last time if you can. **Please focus on whether there are any glaring errors or anything that is not clear,** rather than rewriting each line to your preference as we've realised that collating 15 people's preferences in these documents is nigh on impossible. If you have any feedback on the design and layout please pass that on too. **Please send me your feedback by the end of Friday September 2nd** (and don't forget to invoice us for your time spent if relevant).

To save time Nick suggests we take current drafts further up the clinical leadership tree at ACC, MoH and HQSC now for input too.

Following this next round of feedback it will go to Foolproof to be tweaked with regard to consumer literacy and proof read. At that point we hope you will only need to see it once more before it goes through sign off.

Please do not hesitate to contact me directly to talk this over further.

Best regards

Dee Young, Senior Injury Prevention Specialist, ACC
[redacted]

[redacted] 12/04/2017 11:43 a.m.

To: [redacted]
cc:
bcc:

Subject: RE: Patient info document AED and pregnancy

Hi there

Thanks again for your work on this Susan and Lynette.

I agree that the documents will be best to send out showing no mark ups so it's easier for people to digest.

I understand that having made the changes you are best placed to explain them but I do need to be across this too so I will get people to respond to me also.

Best regards

Dee Young, Senior Injury Prevention Specialist, Treatment Injury, ACC
[redacted]
ACC cares about the environment – please don't print this email unless it is really necessary. Thank you



**From:** [redacted]
**Sent:** Wednesday, 12 April 2017 11:34 a.m.
**To:** [redacted]
**Cc:** [redacted]
**Subject:** Re: Patient info document AED and pregnancy

Hi Dee,
Susan and I have finished going through the health professionals document. It is attached. I have changed it to show no mark ups as it is very messy with the changes we have made (a bit of reorganising) and is easier to look at out of track changes mode. This can of course be changed in the review section back to show the track changes. It is shorter now and we both don't think that the section at the end about reporting an adverse drug reaction is necessary but have left it in for now - with out that it can get down to 4 pages.
I would recommend that when you send both of these documents out for final review by the wider group that you send them as PDF's without track changes on, and ask the group to provide comments/suggestions (rather than changes) to Susan and myself and we can then respond to these. Given we have been the last to review the documents it would be logical for us to respond to why we have made changes and to comment on suggestions.

Best wishes,
Lynette

**From:** [redacted]
**Sent:** Wednesday, 5 April 2017 3:23 p.m.
**To:** [redacted]
**Cc:** [redacted]
**Subject:** RE: Patient info document AED and pregnancy

Hi both

It was good to digest the suggestions you have made here. I am delighted to see that you've managed to keep it relevant to antiepileptic medicines rather than make it sodium valproate specific.

I think you have made some really useful improvements. A number of the issues you picked up we hope to fix further when it goes through health literacy and design at the next stage (post agreeing the wording).

I look forward to seeing what improvements you make to the health professionals booklet.

Once we have your versions of both documents we still need to send them out to the wider project team for final comment before they go through health literacy and design. Given they have been involved with this material development from the start it is only fair that they can make final comments.

Thanks again for all your work on this. Don't forget to invoice us for your hours Lynette.

Best regards

Dee Young, Senior Injury Prevention Specialist, Treatment Injury, ACC
[redacted]
ACC cares about the environment – please don't print this email unless it is really necessary. Thank you

**From:** [redacted]
**Sent:** Tuesday, 4 April 2017 11:35 a.m.
**To:** [redacted]
**Cc:** [redacted]
**Subject:** Patient info document AED and pregnancy

Dear Dee,

Susan and I met today after Susan had the chance to look over the documents I sent her.

We initially discussed the concerns you, Nick and Peter expressed regarding the current documents having moved too far from the original Medsafe evidence and advice. You felt that you would struggle to get the documents placed on The NZ Formulary and in BPAC publications given the current differences. We have compared the two documents and do not see any conflicting information. Susan felt that the Medsafe document may be out of date given when it was written but we felt that even if it did represent up to date information it does not have any conflicting info and has too much detail for what we need - particularly in the patient info document. If there is any concern from BPAC or NZF Susan is happy to say that Medsafe are ok with these documents.

Secondly we discussed your concern that more detailed information should be added to the medical content particularly the patient info document. She disagrees and feels that in fact there is possibly too much there already.

Susan's main comments regarding the patient info document were:

- that the main message of the document should be "If you are on AEDS you need to plan your pregnancy" and that message was not always clear
- that the document was too long
- that there was too much detail in the text with regard to the medical factual content and that it needed simplification. The detail we had should go into a graphic and no more content or detail should be added.

Susan had run the risk section through a readability checker and it came out at 18 – 19 years of age which implies it is too complicated

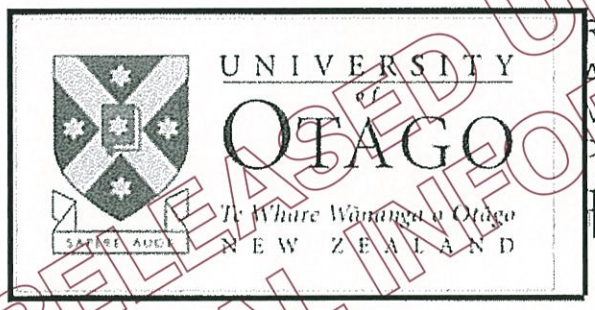
for the audience.

I agree with all of Susan's comments.

We went through the patient info document with her comments in mind and made suggested changes. I have attached the version we worked on with comments.

We will be meeting next Tuesday to go over the health professional booklet.

regards,
Lynette




Regards,
Associate Professor Lynette Sadleir
MBChB, Dip Paeds, FRACP, MD; Paediatric Neurologist
Department of Paediatrics and Child Health
University of Otago, Wellington
[redacted]





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"This message and any attachments may contain confidential and privileged information. If you believe you have received this email in error, please advise us immediately by return email or telephone and then delete this email together with all attachments. If you are not the intended recipient, you are not authorised to use or copy this message or any attachments or disclose the contents to any other person."

[redacted] 12/04/2017 12:09 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: Patient info document AED and pregnancy

Good idea.
Lynette

**From:** [redacted]
**Sent:** Wednesday, 12 April 2017 11:43 a.m.
**To:**
**Cc:** [redacted]
**Subject:** RE: Patient info document AED and pregnancy

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[redacted] Dee Young, Senior Injury Prevention Specialist, Treatment Injury, ACC
[redacted]
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**Sent:** Wednesday, 12 April 2017 11:34 a.m.
**To:**
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**Cc:** [redacted]
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Best regards

Dee Young, Senior Injury Prevention Specialist, Treatment Injury, ACC
[redacted]

**From:** [redacted]
**Sent:** Tuesday, 4 April 2017 11:35 a.m.
**To:** [redacted]
**Cc:**
**Subject:** Patient info document AED and pregnancy

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regards,
Lynette



UNIVERSITY of OTAGO
Te Whare Wānanga o Otāgo
NEW ZEALAND

Regards,
Associate Professor Lynette Sadleir
MBChB, Dip Paeds, FRACP, MD; Paediatric Neurologist
Department of Paediatrics and Child Health
University of Otago, Wellington
[redacted]


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[redacted]

To: [redacted]
cc:
bcc:

18/11/2005 04:23 p.m. Subject: MARC 15 Dec 2005

Hi Kerryn

Here is the Summary Sheet of the Watching briefs along with all the ones Ruth and Michael were set down to do.

There is however one glitch – Ruth has prepared the Watching Brief for Topiramate and Psychiatric reactions which is listed under your name Kerryn and she has not done the Tramadol and hepatic reactions. Probably best if we leave it till next time now.

Janelle

Janelle Ashton

Manager Information Systems

NZ Pharmacovigilance Centre

P O Box913

DUNEDIN

[redacted]

- Watching brief - Bupropion and CVS ADR's.doc
- Watching brief - DTaP_IPV_Hib_HepB & SIDS.doc
- Watching brief - MMR arthritis.doc

- Watching brief - rosiglitazone_1_CHF.doc
- Watching brief - rosiglitazone_2_HDL.doc
- Watching brief - rosiglitazone_3_ pancreatitis.doc
- Watching brief - topiramate psychiatric.doc
- Watching brief - Valproate feotal abnormalities.doc
- Watching briefs since 2001- responsible people Oct 05.doc

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## WATCHING BRIEF – Valproate and Foetal abnormalities

**Watching Brief Recommended**
December 2004

**CARM case reports**

| CARM reports prior to WB | CARM reports post WB |
|---|---|
| Foetal disorders 7 | Foetal disorders 0 |

**MARC Review and Regulatory Outcomes**
Dec 2004
MARC reviewed a report of a male child born with a probable foetal valproate syndrome and developmental delay. The mother had been started on valproate [redacted] The committee noted that previous reports had occurred in children of mothers who were taking valproate for epilepsy. It was argued that in these cases foetal abnormalities might have been caused by epileptic seizures rather than the medicine itself. The committee considered the foetal abnormalities in the report to be possibly related and recommended that a watching brief be maintained on maternal valproate use and foetal abnormalities.

**International Regulatory Action**
None located.

**Literature Review – Papers Since 2004**
Artama, M., A. Auvinen, et al. (2005). "Antiepileptic drug use of women with epilepsy and congenital malformations in offspring." Neurology **64**(11): 1874-1878.

> Objective: To compare the risk for congenital malformations in offspring between women with epilepsy being treated with antiepileptic drugs (AEDs) during pregnancy and those who discontinued their antiepileptic medication before pregnancy in a population-based cohort of female patients with epilepsy. Cohort: All patients with epilepsy (n = 20,101) eligible for AED reimbursement for the first time during 1985 to 1994 were identified from the Social Insurance Institution of Finland. Results: Congenital malformations were more common among offspring of women on antiepileptic medication (65/1,411; 4.6 %) than among offspring of untreated patients (26/ 939; 2.8 %) (p = 0.02). The risk of malformations was substantially higher in the offspring of patients using valproate as monotherapy (OR = 4.18; 95 % CI: 2.31, 7.57) or valproate as polytherapy (OR = 3.54; 95 % CI: 1.42, 8.11) than of untreated patients. Polytherapy without valproate was not associated with increased risk of malformations. Conclusion: Excess risk was

confined to patients using valproate during pregnancy. The risk for malformations was not elevated in offspring of mothers using carbamazepine, oxcarbazepine, or phenytoin (as monotherapy or polytherapy without valproate).

**Comment**
Most recent paper cited above adds evidence to valproate alone as an aetiological factor conferring risk in foetal abnormalities.

**Recommendation**
That the watching brief be discontinued.

[redacted]

15/11/2006 12:05 p.m.

To: [redacted]
cc:
bcc:

Subject: valproate

Dear Kerryn

text attached and am just sending fax with explanatory note

Thanks
Ruth

The following section of this message contains a file attachment
prepared for transmission using the Internet MIME message format.
If you are using Pegasus Mail, or any other MIME-compliant system,
you should be able to save it or view it from within your mailer.
If you cannot, please ask your system administrator for assistance.

```
---- File information -----------
  File:  valproatefetal.doc
  Date:  15 Nov 2006, 10:56
  Size:  63488 bytes.
  Type:  Unknown
```

- valproatefetal.doc

## Foetal Valproate Syndrome

A description of this syndrome is given below, taken from the US National Institute of Health website, <www.nlm.nih.gov/cgi>

### Multiple Congenital Anomaly/Mental Retardation (MCA/MR) Syndromes

| | |
|---|---|
| **Syndrome** | **fetal valproate syndrome (FVS)** |
| **Synonym** | valproic acid embryopathy |
| **Summary** | Fetal abnormalities due to the maternal use of valproic acid in anticonvulsant therapy of epilepsy during pregnancy. Common craniofacial anomalies include epicanthal folds, broad nose with a flat bridge, anterverted nostrils, shallow philtrum, a thin upper and thick lower lip. Associated disorders may include developmental delay, neurologic abnormalities congenital heart defects, finger abnormalities, and other defects. |
| **Major Features** | **Head and neck:** Trigonocephaly, defects of the calvaria, metopic ridging, micrognathia, midfacial hypoplasia, and narrow forehead. |
| | **Ears:** Low-set posteriorly rotated ears with occasional prominent malformed lobes. |
| | **Eyes:** Infraorbital crease or groove connecting with epicanthal folds. |
| | **Nose:** Short nose with a flat bridge and anteverted nostrils and shallow long philtrum. |
| | **Mouth and oral structures:** Small mouth with downturned corners and a thin vermilion border of the upper and full lower lip, giving the mouth a "carp-like" appearance. Occasional cleft palate and cleft lip may be associated. |
| | **Abdomen:** Inguinal hernia. |
| | **Hand and foot:** Polydactyly, finger-like thumbs, and rudimentary digits. |
| | **Spine:** Spina bifida. |
| | **Cardiovascular system:** Ventricular septal defect, patent ductus arteriosus, and aortic coarctation. |
| | **Respiratory system:** Occasional tracheomalacia with stridor and lower respiratory tract anomalies. |
| | **Urogenital system:** Hypospadias, microscrotum, cryptorchidism, and incomplete fusion of the mullerian duct. |
| | **Growth and development:** Growth, motor, and mental retardation in some cases. |

**Etiology and pathogenesis:** Teratogenic action of valproic acid or sodium valproate used in the treatment of seizures in pregnancy.

**Introduction**

CARM report was received at about the time an editorial was published in the BMJ regarding the teratogenicity of antiepileptic medicines. The editorial by Breen and Davenport is in the dossier **** and summarises data from pregnancy registries set up in various countries since the late 1990s.

**Points from BMJ editorial.**

*Congenital Malformations*

UK Epilepsy and Pregnancy Registry

- 3500 females
- 4.2 % congenital malformations for AEDs cf 3.5% with epilepsy but no AEDs.
- 6.0% congenital malformations with polytherapy v 3.7% monotherapy
- 6.2% congenital malfomations with valproate monotherapy, (highest)
- 2.2% congenital malformations with carbamazepine (lowest)
- Lamotrigine > 200 mg daily similar to valproate ≤ 1000 mg daily

Australian registry

Similar findings for valproate.

North American registry

10.7% congenital malformations with valproate monotherapy.

Editorial authors emphasise that this is observational data only and include many variables that could influence the results.

*Developmental Delay*

Adab N et al found that valproate monotherapy in pregnancy was associated with decreased verbal IQ cf phenytoin or carbamazepine monotherapy and this was dose related.

Further study by same first author indicated 30% of children exposed to valproate in utero needed special educational support cf 3-6% of those exposed to monotherapy with other AEDs.

Dean et al , (also in this dossier as paediatrician for patient in CARM report referred me to it), however, showed developmental delay for carbamazepine, valproate and phenytoin compared with a small number of control children of mothers with epilepsy who did not take AEDs.

**NEAD study**

This study was published just prior to the editorial and its results are therefore not included above. An abstract is in the dossier. *****.

A prospective observational study across 25 epilepsy centres.

Serous adverse outcomes for monotherapy ranged from 1% for lamotrigine to 20.3% for valproate.

**Suggested advice.**

Breen and Davenport indicate that current advice is that the most effective drug should be chosen before conception and prescribed at its lowest effective dose, ideally as monotherapy. Following their review they suggest that "women should consider stopping, minimizing or switching drugs before pregnancy". "Women with focal seizures alone, women who have been seizure free for at least two years, or women who have infrequent generalised seizures may prefer to stop their AEDs, but this must be assessed on an individual basis"

The authors of the NEAD study suggest that "For women who fail other AEDs and require valproate the dose should be limited if possible".

Dr Ruth Savage, CARM, NZPhvC
November, 2006.



*Kerryn , the abstract belowthis report is for detaching to put with the other papers in the dossier. I am faxing the other papers but you will probably be able to get a better copy of the BMJ editorial on-line.*

---

Neurology. 2006 Aug 8;67(3):407-12. Full Text Neurology Links

Comment in:
Neurology. 2006 Aug 8;67(3):E6-7.

**In utero antiepileptic drug exposure: fetal death and malformations**

- 
- 
- 
- Meador KJ,

- Baker GA,
- Finnell RH,
- Kalayjian LA,
- Liporace JD,
- Loring DW,
- Mawer G,
- Pennell PB,
- Smith JC,
- Wolff MC;
- NEAD Study Group.

Department of Neurology, University of Florida, Gainesville 32610, USA. kimford.meador@neurology.ufl.edu



BACKGROUND: Pregnancy outcomes following in utero exposure to antiepileptic drugs (AEDs) are uncertain, limiting an evidenced-based approach. OBJECTIVE: To determine if fetal outcomes vary as a function of different in utero AED exposures. METHODS: This ongoing prospective observational study across 25 epilepsy centers in the USA and UK enrolled pregnant women with epilepsy from October 1999 to February 2004 to determine if differential long-term cognitive and behavioral neurodevelopmental effects exist across the four most commonly used AEDs. This initial report focuses on the incidence of serious adverse outcomes including major congenital malformations (which could be attributable to AEDs) or fetal death. A total of 333 mother/child pairs were analyzed for monotherapy exposures: carbamazepine (n = 110), lamotrigine (n = 98), phenytoin (n = 56), and valproate (n = 69). RESULTS: Response frequencies of pregnancies resulting in serious adverse outcomes for each AED were as follows: carbamazepine 8.2%, lamotrigine 1.0%, phenytoin 10.7%, and valproate 20.3%. Distribution of serious adverse outcomes differed significantly across AEDs and was not explained by factors other than in utero AED exposure. Valproate exhibited a dose-dependent effect. CONCLUSIONS: More adverse outcomes were observed in pregnancies with in utero valproate exposure vs the other antiepileptic drugs (AEDs). These results combined with several recent studies provide strong evidence that valproate poses the highest risk to the fetus. For women who fail other AEDs and require valproate, the dose should be limited if possible.



PMID: 16894099 [PubMed - indexed for MEDLINE]

[redacted]

19/10/2014 09:12 p.m.

To: [redacted]
cc:
bcc:

Subject: PU Information - Sodium valproate and Foetal Valproate Syndrome

Hi Susan
As I was not party to the discussions on the requirements for this information, I have included a cover sheet detailing what has been extracted and the results.

You will see there are 13 cases where Foetal valproate syndrome has been identified. According to the information passed on by Michael you only want the case report listing which I have attached, however I note in the "Details of Data Request" you indicated more detail required. If you want more information, let me know.
Janelle

Janelle Ashton | Manager Information Systems | New Zealand Pharmacovigilance Centre [www.nzphvc.otago.ac.nz]
NZPhvC, PO Box 913, Dunedin 9054, New Zealand | [redacted]

[redacted] PU_2014_4_Sodium Valproate_FVS.pdf

New Zealand Pharmacovigilance Centre
Department of Preventive and Social Medicine
University of Otago
PO Box 913, Dunedin, New Zealand
Telephone: 64-3-479 7185
Fax: 64-3-479 7150
Email: nzphvc@otago.ac.nz
Website: www.otago.ac.nz/carm

**Report Title:** **Sodium Valproate and Foetal valproate syndrome**

**Prepared for:** **Medsafe**

**Prepared by:** **New Zealand Pharmacovigilance Centre**
**October 2014**

**Period Covered:** The search includes all cases in the CARM database
As at 30 September 2014 where

- Sodium valproate administration has resulted in Foetal valproate syndrome

**Summary:** There are 344 cases where Sodium valproate is assessed as a causal agent

There are **13** cases of Foetal Valproate Syndrome
Cases identifying an age of 900 or greater is the number of months of age.
An age of 900 indicates "identified at birth"

Listing of the 13 individual cases follows

REACTIONS REPORTED to CARM - Sodium Valproate
Severity : 1 = Severe 2 = Not Severe

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 035805 | SEP97 | 2 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM<br>PHENOBARBITONE | [redacted] | | | | | | | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) : [redacted]96
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors:

Patient Age: [redacted]0 Date of Birth: [redacted]1997
Sex: Male
Location:
Reporter:
Outcome:
Predisposing Conditions:

Company Reference No:

---

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 062131 | SEP04 | 3 2 DEVELOPMENTAL DELAY<br>3 2 AUTISTIC DISORDER<br>3 1 FOETAL VALPROATE SYNDROME<br>3 1 OTITIS MEDIA | * VALPROATE SODIUM | [redacted] | | | | 000000 - | | [redacted] | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) : 000000
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors:

Patient Age: Date of Birth: [redacted]2000
Sex: Male
Location:
Reporter:
Outcome:
Predisposing Conditions:

Company Reference No:

---

REACTIONS REPORTED to CARM - Sodium Valproate
Severity : 1 = Severe 2 = Not Severe

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 073289 | SEP06 | 2 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | [redacted] | [redacted] | [redacted] | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) : [redacted]06
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors: [redacted]

Patient Age: [redacted] Date of Birth: [redacted]2005
Sex: Male
Location:
Reporter:
Outcome:
Predisposing Conditions: [redacted]

Company Reference No:

---

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 082615 | JAN09 | 1 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | - | | [redacted] | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) :
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors: [redacted]

Patient Age: [redacted] Date of Birth:
Sex: Unknown
Location:
Reporter:
Outcome:
Predisposing Conditions: [redacted]

Company Reference No: [redacted]

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REACTIONS REPORTED to CARM - Sodium Valproate
Severity : 1 = Severe 2 = Not Severe

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 084192 | MAY09 | 2 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | | | | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) : [redacted]94
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors:
[redacted]

Patient Age: [redacted] Date of Birth: [redacted]1994
Sex: Male
Location:
Reporter:
Outcome:
Predisposing Conditions:
[redacted]

Company Reference No:

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| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 086159 | AUG09 | 1 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | | | | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) : [redacted]01
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors:
[redacted]

Patient Age: [redacted]0 Date of Birth: [redacted]2001
Sex: Female
Location:
Reporter:
Outcome:
Predisposing Conditions:
[redacted]

Company Reference No:

REACTIONS REPORTED to CARM - Sodium Valproate
Severity : 1 = Severe 2 = Not Severe

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 086160 | AUG09 | 1 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | | | [redacted] | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) : [redacted]01
Dechallenge : [redacted]
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors: [redacted]

Patient Age: [redacted]0 Date of Birth: [redacted]2001
Sex: Female
Location: [redacted]
Reporter:
Outcome:
Predisposing Conditions:

Company Reference No:

---

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 087081 | NOV09 | 3 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | | | [redacted] | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) : [redacted]007
Dechallenge : [redacted]
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors: [redacted]

Patient Age: [redacted] Date of Birth: [redacted]2001
Sex: Female
Location: [redacted]
Reporter:
Outcome:
Predisposing Conditions:

Company Reference No:

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REACTIONS REPORTED to CARM - Sodium Valproate
Severity : 1 = Severe 2 = Not Severe

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 088850 | MAR10 | 1 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | | | | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) : [redacted]07
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors:

Patient Age: [redacted]0 Date of Birth: [redacted]2007
Sex: Female
Location:
Reporter:
Outcome:
Predisposing Conditions:

Company Reference No:

---

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 093093 | NOV10 | 2 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | | | | |
| | | 4 1 HYPERTONIA | | | | | | | | | |
| | | 4 1 GAIT ABNORMAL | | | | | | | | | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) :
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors:

Patient Age: [redacted]0 Date of Birth: [redacted]2002
Sex: Female
Location:
Reporter:
Outcome:
Predisposing Conditions:

Company Reference No:

REACTIONS REPORTED to CARM - Sodium Valproate
Severity : 1 = Severe 2 = Not Severe

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 107356 | JUN13 | 2 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | | | | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) : [redacted]
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors: [redacted]

Patient Age: [redacted] Date of Birth: [redacted]2010
Sex: Female
Location: [redacted]
Reporter:
Outcome:
Predisposing Conditions:

Company Reference No:

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| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 108377 | SEP13 | 2 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | | | | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) :
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors: [redacted]

Patient Age: Date of Birth: [redacted]2007
Sex: Male
Location: [redacted]
Reporter:
Outcome:
Predisposing Conditions:

Company Reference No:

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REACTIONS REPORTED to CARM - Sodium Valproate
Severity : 1 = Severe 2 = Not Severe

| REPORT | DATE | REL/SEVERITY/REACTIONS | DRUGS | ROUTE | DOSE | UNIT | FREQ | ADMINISTRATION | DURATION | MANUF | REASON FOR USE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 111180 | APR14 | 2 1 FOETAL VALPROATE SYNDROME | * VALPROATE SODIUM | [redacted] | | | | | | | |
| | | 2 1 MEDICATION ERROR | QUETIAPINE | | | | | | | | |

OTHER RELEVANT INFORMATION:
Onset (DDMMYY) : [redacted]2
Dechallenge :
Rechallenge :
Drug Reduced :
Seriousness :
Other Factors:

Patient Age: [redacted]0 Date of Birth: [redacted]2012
Sex: Male
Location:
Reporter:
Outcome:
Predisposing Conditions:

Company Reference No:

[redacted]
M.B., Ch.B. (N.Z.), F.N.Z.C.G.P.

HOURS:
Appointment.

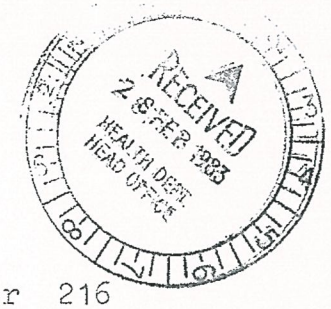
142/70/2501

[redacted]
TELEPHONE [redacted]

142/70/2501

24.2.83

The Director,
Division of Clinical Services,
Dept. of Health,
P.O.Box 5013,
Wellington.




Dear Sir,

Re Clinical Services Letter 216

I A D R R S - Sodium valproate.

Could you please supply references for the report of spina bifida occurring in 1 per cent of foetuses on the above. I have a patient who takes this drug and is planning a pregnancy and further information on this adverse reaction seems indicated.

Yours Faithfully,

[redacted]



83.

ts and two
ital anomalies
is information

Dr [redacted] please reply.
Filed

File

142/70/2501

3 March 1983

[redacted]

Dear [redacted]

SODIUM VALPROATE

Thank you for your letter of 24 February 1983.

... Enclosed for your information are two reports and two opinions regarding possible risks of congenital anomalies with sodium valproate therapy. We trust this information will be useful to you.

Yours sincerely

K H Goh
for Director
Division of Clinical Services

Encl

File

[redacted]

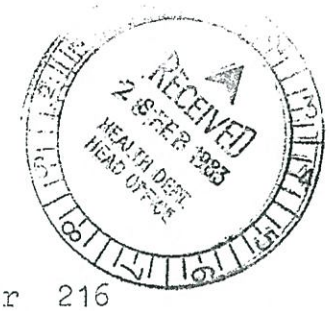
[redacted]

142/70/2501

HOURS:
Appointment.

24.2.83

The Director,
Division of Clinical Services,
Dept. of Health,
P.O.Box 5013,
Wellington.




Dear Sir,

Re Clinical Services Letter 216

I A D R R S - Sodium valproate.

Could you please supply references for the report of spina bifida occurring in 1 per cent of foetuses on the above. I have a patient who takes this drug and is planning a pregnancy and further information on this adverse reaction seems indicated.

Yours Faithfully,

[redacted]



83.

ts and two
ital anomalies
is information

Dr Boyd/S

Dr Gold please reply.

Filed

File

142/70/2501

3 March 1983

[redacted]

Dear [redacted]

SODIUM VALPROATE

Thank you for your letter of 24 February 1983.

... Enclosed for your information are two reports and two opinions regarding possible risks of congenital anomalies with sodium valproate therapy. We trust this information will be useful to you.

Bjerkedal Lancet 2 : 1046, 13 Nov 82
Jeavons, " 2 : 1282, 4 Dec 82
Editor, " 2 : , 11 Dec 82

Yours sincerely

K H Goh
for Director
Division of Clinical Services

Encl

File

4 July 2013

Health and Disability Commissioner
*Te Toihau Hauora, Hauātanga*

Chris James
Manager
Clinical Risk Management
Medsafe
Ministry of Health
PO Box 5013
WELLINGTON 6145



Dear Mr James

**Complaint:** [redacted]
**Our ref:** **C13HDC00670**

The Commissioner has received a complaint from [redacted] which raises concerns about the treatment she received from provider regarding the prescription of Epilim and Diamox and the information provided to her relating to the possible effects of this medication on unborn children if taken during pregnancy.

One of the Commissioner's functions, as set out under section 14(1)(m) of the Health and Disability Commissioner Act 1994, is "*to gather such information as in the Commissioner's opinion will assist the Commissioner in carrying out the Commissioner's functions under this Act.*"

To assist the Commissioner to decide what action, if any, to take on this matter, we would appreciate receiving comment from you on the issues raised in [redacted] complaint. Please also provide any relevant drug information and research relating to this matter.

Please provide this information by **25 July 2013**.

Thank you for your assistance.

Yours sincerely

[redacted]
**Complaints Assessment Manager**

Enc: Copy of complaint

PO Box 1791 Auckland 1140; Level 10, Tower Centre, 45 Queen Street, Auckland 1010, New Zealand
Ph: 09 373 1060 Fax: 09 373 1061 Toll Free Ph: 0800 11 22 33 www.hdc.org.nz

TT35-07-5-4-5

MEDSAFE
NEW ZEALAND MEDICINES
AND MEDICAL DEVICES
SAFETY AUTHORITY
A BUSINESS UNIT OF
THE MINISTRY OF HEALTH
www.medsafe.govt.nz

15 July 2013

[redacted]
Complaints Assessment Manager
Health and Disability Commissioner
PO Box 1791
Auckland 1140



Dear [redacted]

**Complaint: [redacted]**
**HDC ref: C13HDC00670**

Thank you for your letter of 4 July 2013 asking for Medsafe's comments on the complaint you have received from [redacted].

Medsafe is sorry to hear of [redacted] experiences after receiving sodium valproate (Epilim) during pregnancy and subsequently giving birth to twins that have been diagnosed with Fetal Valproate Syndrome.

Medsafe has also been contacted directly with [redacted] following earlier correspondence and has provided [redacted] with information about the use of sodium valproate. Medsafe has also provided advice about medicines legislation in New Zealand in terms of mandating Patient Information Leaflets.

The risks associated with prescribing sodium valproate during pregnancy are known and are well documented. Medicine information for sodium valproate is available to both healthcare professionals (medicine data sheets) and consumers (consumer medicine information) via the Medsafe website. A copy of the medicine information for healthcare professionals and consumers is enclosed.

The medicine data sheet contains extensive information about the risks associated with taking sodium valproate during pregnancy. This information is designed to inform healthcare professionals of the risks so they can discuss these with patients prior to making decisions about treatment. The consumer medicine information is specifically written for patients and recommends that they talk to their doctor if they are, or are trying to, become pregnant while taking sodium valproate. Both documents are freely available on Medsafe's website.

[redacted] has recommended that a patient information leaflet should be included in every box of Epilim sold. Medsafe encourages all manufacturers of medicines to provide information for consumers. However, under the current Medicines Act 1981 there is no legal requirement for patient information leaflets to be provided with dispensed medicines in New Zealand. This means a company cannot be compelled to do so. However, medicine data sheets and consumer medicine information are freely available on the Medsafe website. Consumer information can also be printed by the dispensing pharmacy when these medicines are dispensed so consumers can take information about their medicine with them.

Medsafe has recommended that [redacted] can contribute to making Patient Information Leaflets a legal requirement by participating in a future consultation in the lead up to ANZTPA (Australia New Zealand Therapeutic Products Agency). [redacted] can also make her views known to her local MP or the Minister of Health.

[redacted] has also recommended that warnings are written on boxes of tablets. This is unlikely to have a significant effect in terms of providing information to consumers as boxes are not commonly dispensed in their entirety in New Zealand. This means blister strips are 'down-packed' by pharmacies during the dispensing process in order to dispense the prescribed number of tablets.

I hope you find this information useful. Please contact me if you require further information or clarification.

Yours sincerely

Chris James
Acting Group Manager
Medsafe

[redacted]

To: [redacted]
cc:
bcc:

12/06/2009 01:26 p.m. Subject: Re: fetal valproate exposure

Hi Jan

As mentioned yesterday, here is the study of fetal valproate exposure and IQ at age 3 years

Regards

David

Associate Professor David Reith MBBS FRACP MMedSc(Pharm) PhD
Dunedin School of Medicine
University of Otago
New Zealand

[redacted] VPA.fetal exposure NEJMApr09.pdf

[redacted] 07/12/2010 01:28 p.m.

To: [redacted]

cc: [redacted]

bcc:

Subject: Valproate information as requested at the December 2010 MARC meeting

Dear MARC Members,

As discussed at the MARC meeting on Thursday, please find attached:

- Copies of reports presented to the MARC on this issue since March 2004 -- 10 attachments
- A collation of sections of MARC minutes in which this issue was discussed since March 2004 -- 1 attachment (History of MARC minutes)
- An analysis of information contained in international valproate prescribing documents regarding use in women of child-bearing potential and in pregnancy -- 1 attachment (International prescribing information)

If you consider further information is needed or that the data sheet does not sufficiently describe the risk, please let me know as soon as possible so that this topic can be incorporated into the agenda for the next MARC meeting.

Kind regards,

Kimberly Bridgewater
Advisor Science, Pharmacovigilance,
MARC Secretary
[redacted]

http://www.medsafe.govt.nz
[redacted]



MARC Report 1.pdf
MARC Report 1 - Annex 1.pdf
MARC Report 2.pdf
MARC Report 2 - Annex 1.pdf
MARC Report 2 - Annex 2.pdf
MARC Report 2 - Annex 3.pdf
MARC Report 3.pdf
MARC Report 3 - Annex 1.pdf
MARC Report 3 - Annex 2.pdf
MARC Report 3 - Annex 3.pdf
History of MARC minutes.pdf
International prescribing information.pdf

## WATCHING BRIEF – VALPROATE AND FOETAL ABNORMALITIES

**Watching Brief Recommended**
December 2004

**First Approved in NZ**
1975

**CARM Case Reports**

| CARM reports prior to WB | CARM reports post WB |
|---|---|
| Foetal disorders 7 | Foetal disorders 0 |

**MARC Review and Regulatory Outcomes**
Dec 2004
MARC reviewed a report of a male child born with a probable foetal valproate syndrome and developmental delay. The mother had been started on valproate [redacted] The Committee noted that previous reports had occurred in children of mothers who were taking valproate for epilepsy. It was argued that in these cases foetal abnormalities might have been caused by epileptic seizures rather than the medicine itself. The Committee considered the foetal abnormalities in the report to be 'possibly' related and recommended that a watching brief be maintained on maternal valproate use and foetal abnormalities.

**International Regulatory Action**
None located.

**Data sheet**
**Epilim (sodium valproate)**
Containdications
Pregnancy

Precautions –Use in Pregnancy
The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations and multiple anomalies involving various body systems has been reported in children born to mothers with epilepsy treated with valproate. Mothers taking more than one anticonvulsant drug might have a higher risk of having a baby with a malformation than mothers taking one drug. Sodium valproate (valproic acid), if taken in the first trimester of pregnancy, is suspected of causing an increased risk of neural tube defects (especially spina bifida) in the exposed foetus. This has been estimated to be in the region of 1-2%.

There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This syndrome is related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Phenobarbital and other enzyme inducers may also induce haemorrhagic syndrome. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

Women taking sodium valproate (valproic acid) who become or wish to become pregnant should be encouraged to consider routine ultrasound and amniocenteses for prenatal diagnosis of such abnormalities. As folic acid may have a role in the prevention of neural tube defects in infants of women taking antiepileptic therapy, such women are recommended to take folic acid supplementation (5mg daily) four weeks prior to and 12 weeks after conception. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.

Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment.

Some data have suggested an association between in-utero valproate exposure and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ.

Notwithstanding the potential risks, no sudden discontinuation of antiepileptic therapy should be undertaken, as this may lead to breakthrough seizures that could have serious consequences for both the mother and the foetus.

Overall, the risk of having a child with abnormalities as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

It is recommended that:

- women on antiepileptic drugs (AEDs) receive prepregnancy counselling with regard to the risk of foetal abnormalities;
- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- folic acid supplementation (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.
- Dosage reviewed before conception and the lowest effective dose used in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage.

Before Epilim is prescribed for use in women with epilepsy of any form, who could become pregnant, they should receive specialist advice. Due to the potential risks to

the foetus, the benefits of its use should be weighed against the risks. When treatment with Epilim is deemed necessary, precautions to minimise the potential teratogenic risk should be followed (see above recommendations).

**Literature Review – Papers Since 2004**

Artama, M., A. Auvinen, et al. (2005). "Antiepileptic drug use of women with epilepsy and congenital malformations in offspring." Neurology **64**(11): 1874-1878.

> Objective: To compare the risk for congenital malformations in offspring between women with epilepsy being treated with antiepileptic drugs (AEDs) during pregnancy and those who discontinued their antiepileptic medication before pregnancy in a population-based cohort of female patients with epilepsy. Cohort: All patients with epilepsy (n = 20,101) eligible for AED reimbursement for the first time during 1985 to 1994 were identified from the Social Insurance Institution of Finland. Results: Congenital malformations were more common among offspring of women on antiepileptic medication (65/1,411; 4.6 %) than among offspring of untreated patients (26/ 939; 2.8 %) (p = 0.02). The risk of malformations was substantially higher in the offspring of patients using valproate as monotherapy (OR = 4.18; 95 % CI: 2.31, 7.57) or valproate as polytherapy (OR = 3.54; 95 % CI: 1.42, 8.11) than of untreated patients. Polytherapy without valproate was not associated with increased risk of malformations. Conclusion: Excess risk was confined to patients using valproate during pregnancy. The risk for malformations was not elevated in offspring of mothers using carbamazepine, oxcarbazepine, or phenytoin (as monotherapy or polytherapy without valproate).

**Comment**

Most recent paper cited above adds evidence to valproate alone as an aetiological factor conferring risk in foetal abnormalities.

**Recommendation**

That the watching brief be discontinued.

**FOETAL VALPROATE SYNDROME**
**Report for MARC, November 2006**
**R Savage, NZPhvC**

A description of foetal valproate syndrome is given below, taken from the US National Institute of Health website, www.nlm.nih.gov/cgi

**Multiple Congenital Anomaly/Mental Retardation (MCA/MR) Syndromes**

| | |
|---|---|
| **Syndrome** | **fetal valproate syndrome (FVS)** |
| **Synonym** | valproic acid embryopathy |
| **Summary** | Fetal abnormalities due to the maternal use of valproic acid in anticonvulsant therapy of epilepsy during pregnancy. Common craniofacial anomalies include epicanthal folds, broad nose with a flat bridge, anterverted nostrils, shallow philtrum, a thin upper and thick lower lip. Associated disorders may include developmental delay, neurologic abnormalities congenital heart defects, finger abnormalities, and other defects. |
| **Major Features** | **Head and neck:** Trigonocephaly, defects of the calvaria, metopic ridging, micrognathia, midfacial hypoplasia, and narrow forehead. |
| | **Ears:** Low-set posteriorly rotated ears with occasional prominent malformed lobes. |
| | **Eyes:** Infraorbital crease or groove connecting with epicanthal folds. |
| | **Nose:** Short nose with a flat bridge and anteverted nostrils and shallow long philtrum. |
| | **Mouth and oral structures:** Small mouth with downturned corners and a thin vermilion border of the upper and full lower lip, giving the mouth a "carp-like" appearance. Occasional cleft palate and cleft lip may be associated. |
| | **Abdomen:** Inguinal hernia. |
| | **Hand and foot:** Polydactyly, finger-like thumbs, and rudimentary digits. |
| | **Spine:** Spina bifida. |
| | **Cardiovascular system:** Ventricular septal defect, patent ductus arteriosus, and aortic coarctation. |
| | **Respiratory system:** Occasional tracheomalacia with stridor and lower respiratory tract anomalies. |
| | **Urogenital system:** Hypospadias, microscrotum, cryptorchidism, and incomplete fusion of the mullerian duct. |
| | **Growth and development:** Growth, motor, and mental retardation in some cases. |
| | **Etiology and pathogenesis:** Teratogenic action of valproic acid or sodium valproate used in the treatment of seizures in pregnancy. |

## Introduction

CARM report 73289 (see Section PQ, page 22) was received at about the time an editorial was published in the *BMJ* regarding the teratogenicity of antiepileptic medicines (see Appendix 1). The editorial by Breen and Davenport summarises data from pregnancy registries set up in various countries since the late 1990s.

## Points from *BMJ* editorial.

*Congenital Malformations*

UK Epilepsy and Pregnancy Registry

- 3500 females
- 4.2 % congenital malformations for AEDs cf 3.5% with epilepsy but no AEDs.
- 6.0% congenital malformations with polytherapy v 3.7% monotherapy
- 6.2% congenital malfomations with valproate monotherapy, (highest)
- 2.2% congenital malformations with carbamazepine (lowest)
- Lamotrigine > 200 mg daily similar to valproate ≤ 1000 mg daily

Australian registry

Similar findings for valproate.

North American registry

10.7% congenital malformations with valproate monotherapy.

Editorial authors emphasise that this is observational data only and include many variables that could influence the results.

*Developmental Delay*

Adab N et al found that valproate monotherapy in pregnancy was associated with decreased verbal IQ compared with phenytoin or carbamazepine monotherapy and this was dose related.

Further study by same author indicated 30% of children exposed to valproate in utero needed special educational support compared with 3-6% of those exposed to monotherapy with other AEDs.

## Dean et al

See Appendix 2. Dean et al showed developmental delay for carbamazepine, valproate and phenytoin compared with a small number of control children of mothers with epilepsy who did not take AEDs.

**NEAD study**

See Appendix 3. This study was published just prior to the editorial and its results are therefore not included above.

A prospective observational study across 25 epilepsy centres.

Serous adverse outcomes for monotherapy ranged from 1% for lamotrigine to 20.3% for valproate.

**Suggested advice**

Breen and Davenport indicate that current advice is that the most effective drug should be chosen before conception and prescribed at its lowest effective dose, ideally as monotherapy. Following their review they suggest that "women should consider stopping, minimizing or switching drugs before pregnancy". "Women with focal seizures alone, women who have been seizure free for at least two years, or women who have infrequent generalised seizures may prefer to stop their AEDs, but this must be assessed on an individual basis"

The authors of the NEAD study suggest that "For women who fail other AEDs and require valproate the dose should be limited if possible".

Dr Ruth Savage, CARM, NZPhvC
November, 2006.

# *SODIUM VALPROATE: EXPOSURE DURING PREGNANCY*

***Response to MARC Recommendation.***
Prepared by Abby Cutfield, Medsafe, November 2009.

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**Annexes:**

1. Meador K., *et al.* (2009). Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *New England Journal of Medicine*. **360**(16): 1597 – 1605.
2. Medsafe. (2009). Anticonvulsants and congenital malformations. *Prescriber Update*. **30**(1): 4.
3. Review of wording in New Zealand Epilim data sheet regarding pregnancy.

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## 1.0 PURPOSE

The purpose of this report is to provide the Committee with information regarding a recommendation they made during the 138th meeting of the Medicines Adverse Reactions Committee in June 2009 (detailed in section 2.1). The Committee is asked to review the information provided and determine whether the data sheet for sodium valproate contains sufficient information regarding exposure during pregnancy.

## 2.0 BACKGROUND

Congenital anomaly is a known risk associated with the use of sodium valproate during pregnancy. The Centre for Adverse Reactions Monitoring (CARM) brought the issue to the attention of the Medicines Adverse Reactions Committee (MARC) in June 2009 following a local report of foetal valproate syndrome.

The report identified twin babies who were diagnosed with foetal valproate syndrome at birth. The mother was receiving sodium valproate when she became pregnant. No further details were provided.

Of the 286 reports of adverse events associated with sodium valproate received by CARM, four reports detail foetal valproate syndrome including developmental delay and autistic disorder; multiple malformations; skeletal malformation with ventricular and atrial septal defects; hypospadias and/or withdrawal syndrome.

In response to these reports, the Committee recommended that the New Zealand data sheets for sodium valproate be reviewed to ensure they contain sufficient information regarding exposure during pregnancy.

## 3.0 MINUTES OF PREVIOUS MARC MEETINGS

### 3.1 Extract from June 2009 minutes (item 4.1.6.1)

Case Report

Twin babies were diagnosed with foetal valproate syndrome at birth. The mother was receiving sodium valproate when she became pregnancy. No further details were provided.

Discussion

A member advised that an article has recently been published in the *New England Journal of Medicine* entitled 'Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs' **(Annex 3/1)**. The study concluded that in-utero exposure to valproate was associated with an increased risk of impaired cognitive function at three years of age, when compared with other commonly used antiepileptic drugs.

The Committee considered that the number of women of child-bearing age being treated with valproate was increasing. The Committee noted that the warnings section in the product data sheet focussed primarily on the use of valproate for the treatment of epilepsy. They recommended that the data sheet for sodium valproate be reviewed at the next MARC meeting to determine if the warning information should be strengthened.

The Committee noted that the diagnosis of foetal valproate syndrome would have been made on exposure and clinical presentation and considered the causal associated with sodium valproate to be 'certain' rather than 'possible' for foetal valproate syndrome.

The Committee noted that both babies has been diagnosed with foetal valproate syndrome, and recommended that NZPhVC create a second report to reflect this.

Recommendation

The Committee recommended that NZPhVC change the causality from 'possible' to 'certain' for foetal valproate syndrome.

The Committee recommended that the data sheet for sodium valproate be reviewed to determine if the warning information should be strengthened.

The Committee noted that both babies had been diagnosed with foetal valproate syndrome, and recommended that NZPhVC create a second report to reflect this.

***Medsafe comment:***

*The NEJM paper referred to in the minutes is an interim analysis and does not constitute strong evidence to warrant a change to the data sheet. Medsafe will review the data again once the final analysis is published.*

## 4.0 NEW ZEALAND STATUS AND REGULATORY ACTION

### 4.1 New Zealand status

Epilim is the only medicine containing sodium valproate with ministerial consent for distribution in New Zealand. Epilim is marketed in New Zealand in the following dose forms:

- 100mg crushable tablet
- 500mg enteric coated, modified release tablet
- 200mg/5mL sugar free oral solution
- 200mg/5mL syrup
- 100mg/mL intravenous injection

### 4.2 New Zealand regulatory action

#### 4.2.1 *Prescriber Update*

Following previous reports of foetal valproate syndrome, Medsafe published an article titled "Anticonvulsants and congenital malformations" in the February 2009 issue of *Prescriber Update* (**Annex 3/2**).

#### 4.2.2 Data sheets

There are two data sheets for Epilim – one for the intravenous form and one which covers the tablets, syrup and oral solution. Both data sheets are identical with the exception of IV-specific and short term use in the Epilim IV data sheet. Table 1 in **Annex 3/3** provides a review of the information contained in the Epilim data sheets regarding use in pregnancy.



## 5.0 MEDSAFE COMMENT

The information contained in the Epilim data sheets regarding exposure during pregnancy is identical to that contained in the Australian Prescribing Information.

It is of note that the Epilim data sheets are set out in a very similar way to the data sheets for other antiepileptic medicines with multiple indications. The Committee is welcome to make suggestions on how to improve the readability of these documents however it may be difficult to enforce any changes that would make the data sheets significantly different to the product information elsewhere.

## 6.0 QUESTIONS TO THE MARC

Medsafe has provided the above information in response to a recommendation by the MARC in June 2009. Medsafe is interested in the Committee's comments on the strength of the warnings in the Epilim data sheets regarding exposure during pregnancy.

Specifically:

- Does the Committee consider that the *Precautions* section of the Epilim data sheet contains sufficient information regarding exposure during pregnancy for both the epilepsy and bipolar indications?
- If not, how could the information be strengthened and the readability improved?

## Anticonvulsants and congenital malformations

Prescribers are reminded of the risk of congenital malformations associated with the use of anticonvulants (anti-epileptics) during pregnancy, and the importance of counselling for all women of child-bearing age prescribed anticonvulsants.

Observational data from 3500 females included in the United Kingdom Epilepsy and Pregnancy Registry demonstrated the following:

- 4.2% congenital malformations for all antiepileptics versus 3.5% with untreated epilepsy.
- 6.0% congenital malformations with polytherapy versus 3.7% with monotherapy.
- 6.2% congenital malformations with valproate monotherapy.
- 2.2% congenital malformations with carbamazepine monotherapy.[1]

A prospective observational study across 25 epilepsy centres (NEAD study) demonstrated that serious adverse outcomes for monotherapy ranged from 1% for lamotrigine to 20.3% for valproate.[2]

Common craniofacial anomalies include epicanthal folds, broad nose with a flat bridge, anteverted nostrils, shallow philtrum and a thin upper and thick lower lip. Associated disorders may include developmental delay, neurologic abnormalities, congenital heart defects and finger abnormalities.

As uncontrolled epilepsy in pregnant woman is a serious and potentially life-threatening condition for both mother and child, treatment options must be carefully considered. Medsafe recommends that the most effective medicine should be used at its lowest effective dose.

It is important that all women of child-bearing age taking anticonvulsants receive counselling on the risk of congenital malformations associated with the use of anticonvulsants. However, the occurrence of an unexpected pregnancy should not trigger sudden discontinuation of therapy.

### References


1. Breen D. and Davenport R. (2006). Teratogenicity of antiepileptic drugs: Women should consider stopping, minimizing, or switching drugs before pregnancy. *British Medical Journal*. 333:615-6.
2. Meador J. et al. (2006). In-utero antiepileptic drug exposure: Fetal death and malformations. *Neurology*. 67:407-12.

**Table 1:** Information contained in the Epilim data sheet regarding use in pregnancy

| Section | Wording contained |
|---|---|
| Pharmacokinetics - Distribution | In animals, the drug crosses the placenta. |
| Contraindications | Pregnancy (see Precautions) |
| Precautions -<br>Check the following before use | **Women of child bearing potential:** Adequate counselling should be made available to all women of child bearing potential with epilepsy regarding the risks associated with pregnancy. |
| Precautions – Use in Pregnancy<br><br>*Bolded text:*<br>*in Epilim IV data sheet only* | **Category D**<br><br>During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and for the unborn child.<br><br>The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations and multiple anomalies involving various body systems has been reported in children born to mothers with epilepsy treated with valproate.<br><br>**Women treated with Epilim IV have a potentially increased risk of giving birth to a baby with an abnormality due to the higher Cmax of the intravenous formulation compared with the oral formulation.**<br><br>Mothers taking more than one anticonvulsant medicine might have a higher risk of having a baby with a malformation than mothers taking one medicine. Sodium valproate (valproic acid), if taken in the first trimester of pregnancy, is suspected of causing an increased risk of neural tube defects (especially spina bifida) in the exposed foetus. This has been estimated to be in the region of 1-2%.<br><br>Some data have suggested an association between in-utero valproate exposure and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ. Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Autism spectrum disorders have also been reported in children exposed to valproate in-utero.<br><br>Women taking sodium valproate (valproic acid) who become or wish to become pregnant should be encouraged to consider routine ultrasound and amniocenteses for prenatal diagnosis of such abnormalities. As folic acid may have a role in the prevention of neural tube defects in infants of women taking antiepileptic therapy, such women are recommended to take folic acid supplementation (5mg daily) four weeks prior to and 12 weeks after conception. |

| | |
|---|---|
| *Bolded text:*<br>*in Epilim <u>Oral</u> data sheet only* | **No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.**<br><br>Notwithstanding the potential risks, no sudden discontinuation of antiepileptic therapy should be undertaken, as this may lead to breakthrough seizures that could have serious consequences for both the mother and the foetus.<br><br>Overall, the risk of having a child with abnormalities as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.<br><br>It is recommended that:<br>• women on antiepileptic drugs (AEDs) receive prepregnancy counselling with regard to the risk of foetal abnormalities;<br>• AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;<br>• If appropriate, folic acid supplementation (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception;<br>• specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.<br>• **Dosage reviewed before conception and the lowest effective dose used in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage.** |
| *Bolded text:*<br>*in Epilim <u>Oral</u> data sheet only* | Before Epilim is prescribed for use in women with epilepsy of any form, who could become pregnant, they should receive specialist advice. Due to the potential risks to the foetus, the benefits of its use should be weighed against the risks. When treatment with Epilim is deemed necessary, precautions to minimise the potential teratogenic risk should be followed (see above recommendations).<br><br>There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This syndrome is related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Phenobarbital and other enzyme inducers may also induce haemorrhagic syndrome. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates. |

Previous MARC reviews of valproate and congenital abnormalities
(between March 2004 and December 2010)

**December 2004 -- CARM Reports section -- 4.1.3.1**
Sodium valproate and developmental delay, foetal valproate syndrome, otitis media (62131)

**Discussion**
It was noted that previous reports of foetal valproate syndrome have occurred in children of mothers who were taking valproate for the treatment of epilepsy. In these cases, it was argued that the foetal abnormalities might have been caused by epileptic seizures rather than the medicine itself.

The causality assessment was deemed "possible" for developmental delay, foetal valproate syndrome and otitis media.

**Recommendation**
The Committee recommended that a watching brief be maintained on maternal valproate use and foetal abnormalities.

**December 2005 -- PhV Reports section -- 3.1.16**
Valproate and foetal abnormalities

**Issue**
This watching brief was recommended in December 2004. Valproate was first approved in NZ in 1975 as a prescription medicine.

Prior to initiation of the watching brief there were seven reports of foetal disorders with valproate in the CARM database. Subsequently, there have been no further reports.

The MARC recommended the watching brief in December 2004 following a spontaneous case report to CARM of a child born with probable foetal valproate syndrome.

There had been no regulatory action on this issue, and the current valproate data sheet contained extensive warnings regarding the risks of use in pregnancy.

NZPhvC commented that a recent paper added evidence to valproate alone as an aetiological factor conferring risk in foetal abnormalities. As this reaction was well known and adequate warnings were contained in the data sheet, it was recommended that this issue be removed from the watching brief list.

**Discussion**
The Committee noted that foetal abnormalities with valproate were well documented in the data sheet and considered that prescribers should be aware of this issue. As this issue had been adequately explored they agreed that it should be removed from the watching brief list.

**Recommendation**
The Committee recommended that valproate and foetal abnormalities should be removed from the watching brief list.

Previous MARC reviews of valproate and congenital abnormalities
(between March 2004 and December 2010)

**December 2006 -- CARM Reports section -- 4.1.5.1**
Sodium valproate and foetal valproate syndrome (73289)

**Discussion**
See minute item 4.2.2 for discussion and recommendations on this issue.

The Committee considered that congenital malformations are a well known adverse event of all antiepileptic agents and that the degree of risk varies between the agents. The Committee discussed the counselling required for women on antiepileptic agents on the risks of foetal abnormalities.

The causal association with sodium valproate was considered to be 'probable' for foetal valproate syndrome.

**Recommendation**
That an article is written for publication in Prescriber Update on anticonvulsants and risk of congenital malformations, and the importance of pre-pregnancy counselling for all women of child-bearing age taking anti-convulsants.

**December 2006 -- CARM Reports section -- 4.2.2**
Foetal valproate syndrome

**References**

1. NZPhvC report for the MARC. November 2006.
2. Breen D and Davenport R. Teratogenicity of antiepileptic drugs: Women should consider stopping, minimising, or switching drugs before pregnancy. *BMJ.* 2006; 333: 615-6
3. Dean J et al. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. *J Med Genet* 2002; 39: 251-259
4. NEAD Study Group (Meador J et al). In utero antiepileptic drug exposure: Fetal death and malformations. *Neurology* 2006; 67: 407-412


**Issue**
Foetal valproate syndrome is caused by maternal use of valproic acid for the treatment of epilepsy during pregnancy. Common craniofacial anomalies include epicanthal folds, broad nose with a flat bridge, anteverted nostrils, shallow philtrum and a thin upper and thick lower lip. Associated disorders may include developmental delay, neurologic abnormalities congenital heart defects, finger abnormalities, and other defects.

The CARM report discussed under minute item 4.1.6.1 was received at about the time an editorial was published in the *British Journal of Medicine* (Breen and Davenport) regarding the teratogenicity of antiepileptic medicines. The editorial summarised observational data from pregnancy registries set up in various countries since the late 1990s. The following was found in the United Kingdom Epilepsy and Pregnancy Registry:

- 3500 females
- 4.2% congenital malformations for all anti-epileptics versus 3.5% with untreated epilepsy

- 6.0% congenital malformations with polytherapy versus 3.7% with monotherapy
- 6.2% congenital malformations with valproate monotherapy (highest)
- 2.2% congenital malformations with carbamazepine monotherapy (lowest)
- Lamotrigine > 200 mg daily similar to valproate < 1000 mg daily

The Australian registry gave similar findings for valproate. The North American registry found 10.7% congenital malformations with valproate monotherapy.

Dean et al showed developmental delay occurring with maternal use of carbamazepine, valproate and phenytoin compared with a small number of control children of mothers with epilepsy who did not take any anti-epileptic.

The NEAD study was a prospective observational study across 25 epilepsy centres. It found that serious adverse outcomes for monotherapy ranged from 1% for lamotrigine to 20.3% for valproate.

**Discussion**
The Committee noted the report and discussed the issues around prescribing in women with epilepsy. The Committee agreed with the current advice, that the most effective medicine should be chosen, and prescribed at its lowest effective dose. The Committee noted the recommendation under 4.1.5.



**March 2007 -- Prescriber Update section -- 1.5.1**
Anticonvulsants and congenital malformations

The planned article on anticonvulsants and congenital malformations was discussed. The Committee had previously recommended that an article on anticonvulsants and malformations be written following a CARM case report on sodium valproate and foetal valproate syndrome (73289). The Committee considered that prescribers need to be reminded about the risk of congenital malformations with anticonvulsants, and the importance of pre-pregnancy counselling for all women of child bearing age taking anticonvulsants.

A member raised the issue of lithium and congenital malformations. As sodium valproate was used for bipolar affective disorder a member had received queries about lithium for bipolar affective disorder and congenital malformations. The Committee discussed whether the planned article could be extended to include lithium. The members considered that the issue of bipolar agents and congenital malformations was a separate topic and would be considered at another time if warranted.

**March 2007 -- Actions Arising (Standing Agenda) section -- 2.1.10**
Sodium valproate and foetal valproate syndrome (73289)

**Issue**
The Committee recommended that an article is written for publication in *Prescriber Update* on anticonvulsants and risk of congenital malformations, and the importance of pre-pregnancy counselling for all women of child-bearing age taking anticonvulsants.

Previous MARC reviews of valproate and congenital abnormalities
(between March 2004 and December 2010)

**Outcome**
A *Prescriber Update* article will be authored, probably by Medsafe.

**Discussion**
See minute item 1.5.1. The Committee asked to be kept informed once the *Prescriber Update* article had been written.

**June 2007 -- Actions Arising (Standing Agenda) section -- 2.2.6**
Sodium valproate and foetal valproate syndrome (73289)

**Issue**
In December 2006, the Committee recommended that an article is written for publication in *Prescriber Update* on anticonvulsants and risk of congenital malformations, and the importance of pre-pregnancy counselling for all women of child-bearing age taking anti-convulsants.

**Outcome**
A *Prescriber Update* article will be authored, probably by Medsafe.

**Discussion**
The Committee noted the above.

**September 2007 -- Actions Arising (Standing Agenda) section -- 2.2.12**
Sodium valproate and foetal valproate syndrome (73289)

**Issue**
In December 2006, the Committee recommended that an article be written for publication in Prescriber Update on anticonvulsants and risk of congenital malformations, and the importance of pre-pregnancy counselling for all women of child-bearing age taking anti-convulsants.

**Outcome**
A Prescriber Update article will be authored by Medsafe.

**Discussion**
The Committee noted the above.

**June 2009 -- CARM Reports section -- 4.1.6.1**
Sodium valproate and foetal valproate syndrome, drug exposure during pregnancy (82615)

**Discussion**
A member advised that an article had recently been published in the *New England Journal of Medicine* entitled 'Cognitive Function at 3 years of Age after Fetal Exposure to Antiepileptic Drugs'. The study concluded that in utero exposure to valproate was associated with an increased risk of

impaired cognitive function at three years of age, when compared with other commonly used antiepileptic drugs.

The Committee considered that the number of women of child bearing age being treated with valproate was increasing. The Committee noted that the warnings section in the product datasheet focused primarily on the use of valproate for the treatment of epilepsy. They recommended that the datasheet for sodium valproate be reviewed at the next MARC meeting to determine if the warning information should be strengthened.

The Committee noted that the diagnosis of foetal valproate syndrome would have been made on exposure and clinical presentation and considered the causal association with sodium valproate to be 'certain' rather than 'possible' for foetal valproate syndrome.

The Committee noted that both babies had been diagnosed with foetal valproate syndrome, and recommended that NZPhvC create a second report to reflect this.

**Recommendation**
The Committee recommended that NZPhvC change the causality from 'possible' to 'certain' for foetal valproate syndrome.

The Committee recommended that the datasheet for sodium valproate be reviewed to determine if the warning information should be strengthened.

The Committee noted that both babies had been diagnosed with foetal valproate syndrome, and recommended that NZPhvC create a second report to reflect this.

*Secretary's note:*
*A typographical error was noted by the Committee and the severity of the foetal valproate syndrome reaction amended to 'severe'.*



**September 2009 -- Standing Agenda section -- 2.1.20**
Sodium valproate and foetal valproate syndrome, drug exposure during pregnancy (82615)

**MARC Recommendation**
In June 2009 the Committee recommended that NZPhvC change the causality from 'possible' to 'certain' for foetal valproate syndrome.

In June 2009 the Committee recommended that the datasheet for sodium valproate be reviewed to determine if the warning information should be strengthened.

In June 2009, the Committee noted that both babies had been diagnosed with foetal valproate syndrome, and recommended that NZPhvC create a second report to reflect this.

**Outcome**
NZPhvC has amended the causality as above.

Medsafe will review the datasheet for sodium valproate to determine if the warning information should be strengthened.

**Discussion**
The Committee noted the above.

**December 2009 -- Standing Agenda section -- 2.1.25**
Sodium valproate and foetal valproate syndrome, drug exposure during pregnancy (82615)

**References**
1. Meador K., *et al.* (2009). Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *New England Journal of Medicine*. **360**(16): 1597 - 1605.
2. Medsafe. (2009). Anticonvulsants and congenital malformations. *Prescriber Update*. **30**(1): 4.
3. Review of wording in New Zealand Epilim data sheet regarding pregnancy.

**MARC Recommendation**
In June 2009 the Committee recommended that the datasheet for sodium valproate be reviewed to determine if the warning regarding use in pregnancy should be strengthened.

**Outcome**
Medsafe's report was included in the December 2009 dossier.

The report included details of the information contained in the New Zealand Epilim (sodium valproate) data sheet regarding use in pregnancy. Medsafe advised that this information is identical to that contained in the Australian Prescribing Information, and noted that the Epilim data sheets are set out in a very similar way to the data sheets for other antiepileptic medicines with multiple indications.

The Committee was asked to consider whether the *Precautions* section of the Epilim data sheet contains sufficient information regarding exposure during pregnancy for both the epilepsy and bipolar indications, and if not, how the information could be strengthened and the readability improved.

**Discussion**
The Committee noted the November 2009 Medsafe report. They agreed that while the recent article published in the *New England Journal of Medicine* (reference 1 above) was an interim analysis, it was important that this information be published in the product data sheet.

The Committee recommended that the Precautions section of the Epilim data sheet be revised to ensure that the risk-benefit statement is clear at the beginning of the section. The Committee also recommended that the sponsor be requested to include information in the data sheet from the Meador et al paper.

**Recommendation**
The Committee recommended that the Precautions section of the Epilim data sheet be revised to ensure that the risk-benefit statement is clear at the beginning of the section. The Committee also

recommended that the sponsor be requested to include information from the Meador paper in the Epilim data sheet.

**March 2010 -- Standing Agenda section -- 2.1.3**
Sodium valproate and foetal valproate syndrome, drug exposure during pregnancy (82615)

**MARC Recommendation**
In December 2009, the Committee recommended that the Precautions section of the Epilim data sheet be revised to ensure that the risk-benefit statement is clear at the beginning of the section. The Committee also recommended that the sponsor be requested to include information in the data sheet from the Meador et al paper.

**Outcome**
The New Zealand sponsor of Epilim has been contacted and requested to update the *Precautions* section of the data sheet to improve the clarity of the information regarding the use of sodium valproate in pregnancy.

**Discussion**
The Committee noted the above.

**June 2010 -- Standing Agenda section -- 2.1.3**
Sodium valproate and foetal valproate syndrome, drug exposure during pregnancy (82615)

**MARC Recommendation**
In December 2009, the Committee recommended that the Precautions section of the Epilim data sheet be revised to ensure that the risk-benefit statement is clear at the beginning of the section. The Committee also recommended that the sponsor be requested to include information in the data sheet from the Meador et al paper.

**Outcome**
The data sheets are in the process of being updated and published with improved presentation of information regarding the use of sodium valproate in pregnancy.

**Discussion**
The Committee noted the above.

**Table 1:** Indications and contraindications as listed in various data sheets for sodium valproate.

| | Indications | Contraindications regarding women or pregnancy |
|---|---|---|
| **NZ Data sheet**<br>(Epilim -- May 2010) | Epilepsy<br>Bipolar Disorder | Contraindicated in pregnancy |
| **Australian PI**<br>(Epilim -- March 2009) | Epilepsy<br>Mania | Contraindicated in pregnancy |
| **UK SPC**<br>(Epilim -- October 2010) | Epilepsy | No contraindication in pregnancy |
| **US PI**<br>(Depakote -- June 2010) | Epilepsy<br>Mania<br>Migraine | No contraindication in pregnancy |

**Table 2:** Warnings regarding use in women of child bearing potential and use in pregnancy as listed in various data sheets for sodium valproate.

| | |
|---|---|
| **NZ Data sheet**<br>(Epilim – May 2010) | Adequate counselling should be made available to all women of child bearing potential with epilepsy regarding the risks associated with pregnancy.<br><br>Before Epilim is prescribed for use in women with epilepsy of any form, who could become pregnant, they should receive specialist advice. Due to the potential risks to the foetus, the benefits of Epilim should be weighed against the risks. When treatment with Epilim is deemed necessary, precautions to minimise the potential teratogenic risk should be followed.<br><br>Overall, the risk of having a child with abnormalities as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.<br><br>Notwithstanding the potential risks, no sudden discontinuation of antiepileptic therapy should be undertaken, as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.<br><br>During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and for the unborn child.<br><br>The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations and multiple anomalies involving various body systems has been reported in children born to mothers with epilepsy treated with valproate. Mothers taking more than one anticonvulsant medicine might have a higher risk of having a baby with a malformation than mothers taking one medicine. Sodium valproate (valproic acid), if taken in the first trimester of pregnancy, is suspected of causing an increased risk of neural tube defects (especially spina bifida) in the exposed foetus. This has been estimated to be in the region of 1-2%.<br><br>Some data have suggested an association between in-utero valproate exposure and the risk of impaired cognitive function, including developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ. Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Autism spectrum disorders have also been reported in children exposed to valproate in-utero.<br><br>There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This syndrome is related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Phenobarbital and other enzyme inducers may also induce haemorrhagic syndrome. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.<br><br>*Treatment advice:*<br>It is recommended that women of child-bearing potential taking sodium valproate should:<br>• receive counselling with regard to the risk of foetal abnormalities;<br>• have their drug treatment reviewed before conception. This may involve dose adjustments or alternative therapy options. If sodium valproate is to be continued, monotherapy should be used if possible at the lowest effective dose given in divided doses, as risk of abnormality is greater in women taking combined medication and in women taking a higher total daily dose;<br>• undergo routine ultrasound and amniocenteses for specialist prenatal diagnosis of such abnormalities;<br>• take folic acid supplementation (5mg daily) for at least 4 weeks prior to and 12 weeks after conception as folic acid may have a role in the prevention of neural tube defects in infants of women taking antiepileptic therapy. |

| | |
|---|---|
| **Australian PI**<br>(Epilim -- March 2009)<br><br>***NOTE:***<br>The wording in the Australian PI is identical to that which was previously included in the New Zealand data sheet until Medsafe requested changes recommended by the MARC. | Adequate counselling should be made available to all women of child bearing potential with epilepsy regarding the risks associated with pregnancy.<br><br>During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and for the unborn child.<br><br>The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. An increased incidence of minor or major malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations and multiple anomalies involving various body systems has been reported in children born to mothers with epilepsy treated with valproate. Mothers taking more than one anticonvulsant medicine might have a higher risk of having a baby with a malformation than mothers taking one medicine. Sodium valproate (valproic acid), if taken in the first trimester of pregnancy, is suspected of causing an increased risk of neural tube defects (especially spina bifida) in the exposed foetus. This has been estimated to be in the region of 1-2%.<br><br>Some data have suggested an association between in-utero valproate exposure and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ. Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment. Autism spectrum disorders have also been reported in children exposed to valproate in-utero.<br><br>Women taking sodium valproate (valproic acid) who become or wish to become pregnant should be encouraged to consider routine ultrasound and amniocenteses for prenatal diagnosis of such abnormalities. As folic acid may have a role in the prevention of neural tube defects in infants of women taking antiepileptic therapy, such women are recommended to take folic acid supplementation (5mg daily) four weeks prior to and 12 weeks after conception.<br><br>Notwithstanding the potential risks, no sudden discontinuation of antiepileptic therapy should be undertaken, as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus.<br><br>Overall, the risk of having a child with abnormalities as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.<br><br>It is recommended that:<br>• women on antiepileptic drugs (AEDs) receive prepregnancy counselling with regard to the risk of foetal abnormalities;<br>• AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;<br>• If appropriate, folic acid supplementation (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception;<br>• specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.<br><br>Before Epilim is prescribed for use in women with epilepsy of any form, who could become pregnant, they should receive specialist advice. Due to the potential risks to the foetus, the benefits of its use should be weighed against the risks. When treatment with Epilim is deemed necessary, precautions to minimise the potential teratogenic risk should be followed (see above recommendations).<br><br>There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This syndrome is related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Haemorrhagic syndrome may also be induced by phenobarbital and other enzyme inducers. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates. |

| | |
|---|---|
| **UK SPC**<br>(Epilim -- October 2010)<br><br>***NOTE:***<br>These are relevant excerpts from the SPC. | A decision to use Epilim in women of childbearing potential should not be taken without specialist neurological advice, and only if the benefits of its use outweigh the potential risks of congenital anomalies to the unborn child. This decision is to be taken; before Epilim is prescribed for the first time as well as before a woman already treated with valproic acid is planning pregnancy. Adequate counselling should be made available to all women of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus.<br><br>When Epilim treatment is deemed necessary, precautions to minimise the potential teratogenic risk should be followed.<br><br>No sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus. Antiepileptic drugs should be withdrawn under specialist supervision.<br><br>During pregnancy, maternal tonic clinic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and the unborn child.<br><br>This is animal experimental evidence that high plasma peak levels and the size of an individual dose are associated with neural tube defects.<br><br>In humans, available data suggest an increased incidence of minor or major malformations including neural tube defects, cranio-facial defects, malformations of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other antiepileptic drugs.<br><br>Folate supplementation, prior to pregnancy, has been demonstrated to reduce the incidence of neual tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued.<br><br>During pregnancy, Epilim anti-epileptic treatment should not be discontinued without reassessment of the benefit/risk. |
| **US PI**<br>(Depakote -- June 2010)<br><br>***NOTE:***<br>These are relevant excerpts from the PI. | Depakote should be considered for women of childbearing potential only after the risks have been thoroughly discussed with the patient and weighed against the potential benefits of treatment.<br><br>Use of Depakote during pregnancy can cause congenital malformations including neural tube defects. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Depakote should be considered for women of childbearing potential only after the risks have been thoroughly discussed with the patient and weighed against the potential benefits of treatment.<br><br>**NB -** The PI also notes the increased risk of neural tube defects and other possible congenital anomalies such as craniofacial defects, cardiovascular malformations and anomalies involving various body systems, and discusses the use of folic acid, but does not suggest dosage or timing. |

[redacted] 20/12/2010 02:41 p.m.

To: [redacted],
cc:
bcc:

Subject: Re: Valproate information as requested at the December 2010 MARC meeting

Hi Marius,

No problem at all. I suspect the only correspondence on the matter in the near future will be Stewart's response to PTAC upon completion of the review. I will ensure that a copy of this letter is forwarded to you. As we have informed Sisira, this response should be expected in March/April next year.

I hope you have a lovely Christmas too!

Kind regards,
Abby

Abby Cutfield
Advisor Science, Pharmacovigilance
Clinical Risk Management
Medsafe
Population Health Directorate
Ministry of Health
[redacted]
http://www.medsafe.govt.nz
[redacted]



[redacted] 20/12/2010 02:12 p.m.

To [redacted]
cc

Subject Re: Valproate information as requested at the December 2010 MARC meeting

Dear Abby,

I have been corresponding with Sisira (see last email below). I am happy with the MARC position, but he still needs a reply from Medsafe, which is what you are planning. Could you include me in any correspondence back to PTAC on this issue, just for my information?

Thanks. Have a great Xmas.

Marius

Dr Marius Rademaker BM FRCP FRACP DM
Hon Associate Professor
Dermatology Department, Waikato Hospital
Hamilton, New Zealand

Dear Marius

Now I understand the complexities associated with the process better. From neurologists perspective (I wrote the letter on their behalf) they strongly feel it should be contraindicated in the pregnancy based on the emerging data. To give them a meaningful response it may be reasonable to review the new evidence. I haven't thought about psychiatrists perspective in relation to stable mental health patient on valproate.

Sisira

On 20/12/2010, at 1:44 PM, [redacted] wrote:

Dear MARC Members,

This e-mail follows on from the package of information Kim sent out on 7 December and the subsequent comments made by David. Thank you for your time in reading the information. So far, there has been no expression from the MARC that this issue needs to be reviewed by the Committee in March 2011.

I can confirm that Medsafe will be conducting its own review of the available data in response to the concerns from PTAC. If warranted, Medsafe will approach the committee for expert advice to aid in the review. Otherwise, Medsafe will notify the MARC of the outcome in the subsequent Signal Detection and Evaluation paper (or what ever its new name will be).

Kind regards,
Abby Cutfield
Advisor Science, Pharmacovigilance
Clinical Risk Management
Medsafe
Population Health Directorate
Ministry of Health
[redacted]

http://www.medsafe.govt.nz
[redacted]



----- Document: Re: Fw: Valproate information as requested at the December 2010 MARC meeting, forwarded by Abby Cutfield on 20/12/2010 01:33 pm -----

Sent By: [redacted] 7/12/2010 3:12:07 p.m.
[redacted]
Copy To: [redacted]
Subject: Re: Fw: Valproate information as requested at the December 2010 MARC meeting

Hi David,

Thanks for your comments.

Just to confirm, the data sheet currently published on the Medsafe website (and quoted in the attachment - "International prescribing information") is the up-to-date data sheet which was revised following the MARC recommendation you refer to.

Prior to the MARC recommendation, the wording regarding use in women of child-bearing potential and pregnancy in the NZ data sheet was identical to the current wording of the Australian PI (as quoted in the attachment - "International prescribing information")

I hope this helps,
Abby

Abby Cutfield
Advisor Science, Pharmacovigilance
Clinical Risk Management
Medsafe
Population Health Directorate
Ministry of Health
[redacted]

http://www.medsafe.govt.nz
[redacted]

[redacted]

To [redacted]
cc
Subject
Fw: Valproate information as requested at the December 2010 MARC meeting

Kimberly Bridgewater
Advisor Science, Pharmacovigilance,
MARC Secretary
Clinical Risk Management
Medsafe
Population Health Directorate
Ministry of Health
[redacted]

http://www.medsafe.govt.nz
[redacted]

----- Forwarded by Kimberly Bridgewater/MOH on 07/12/2010 15:03 -----
David Reith [redacted]
07/12/2010 15:02

[redacted]

cc

Subject
Re: Valproate information as requested at the December 2010 MARC meeting

Hi All

The NZ PI looks better than the UK and US datasheets

With regard to:

June 2010 -- Standing Agenda section -- 2.1.3
Sodium valproate and foetal valproate syndrome, drug exposure during pregnancy (82615)
MARC Recommendation
In December 2009, the Committee recommended that the Precautions section of the Epilim data sheet be revised to ensure that the risk-benefit statement is clear at the beginning of the section. The Committee also recommended that the sponsor be requested to include information in the data sheet from the Meador et al paper.
Outcome
The data sheets are in the process of being updated and published with improved presentation of information regarding the use of sodium valproate in pregnancy.
Discussion
The Committee noted the above.

Have we seen the amended Product Information documents?

Otherwise, it looks like the issue has received adequate discussion at MARC (in the absence of new data being presented)

Regards

David

At 02:19 PM 12/7/2010, [redacted] wrote:

>Dear MARC Members,
>
>As discussed at the MARC meeting on Thursday, please find attached:
> * Copies of reports presented to the MARC on this issue since
> March 2004 -- 10 attachments
> * A collation of sections of MARC minutes in which this issue
> was discussed since March 2004 -- 1 attachment (History of MARC minutes)
> * An analysis of information contained in international
> valproate prescribing documents regarding use in women of
> child-bearing potential and in pregnancy -- 1 attachment
> (International prescribing information)
>
>If you consider further information is needed or that the data sheet
>does not sufficiently describe the risk, please let me know as soon
>as possible so that this topic can be incorporated into the agenda
>for the next MARC meeting.
>
>Kind regards,
>Kimberly Bridgewater
>Advisor Science, Pharmacovigilance,
>MARC Secretary
>

[redacted] 20/12/2010 01:44 p.m.

To: [redacted]

cc:

bcc:

Subject: Re: Valproate information as requested at the December 2010 MARC meeting

Dear MARC Members,

This e-mail follows on from the package of information Kim sent out on 7 December and the subsequent comments made by David. Thank you for your time in reading the information. So far, there has been no expression from the MARC that this issue needs to be reviewed by the Committee in March 2011.

I can confirm that Medsafe will be conducting its own review of the available data in response to the concerns from PTAC. If warranted, Medsafe will approach the committee for expert advice to aid in the review. Otherwise, Medsafe will notify the MARC of the outcome in the subsequent Signal Detection and Evaluation paper (or what ever its new name will be).

Kind regards,
Abby Cutfield
Advisor Science, Pharmacovigilance
Clinical Risk Management
Medsafe
Population Health Directorate
Ministry of Health
[redacted]

http://www.medsafe.govt.nz
[redacted]



----- Document: Re: Fw: Valproate information as requested at the December 2010 MARC meeting, forwarded by [redacted] 2010 01:33 pm -----

Sent By: [redacted]
To: [redacted]

Copy To: [redacted]
Subject: Re: Fw: Valproate information as requested at the December 2010 MARC meeting

Hi David,

Thanks for your comments.

Just to confirm, the data sheet currently published on the Medsafe website (and quoted in the attachment - "International prescribing information") is the up-to-date data sheet which was revised following the MARC recommendation you refer to.

Prior to the MARC recommendation, the wording regarding use in women of child-bearing potential and pregnancy in the NZ data sheet was identical to the current wording of the Australian PI (as quoted in the attachment - "International prescribing information")

I hope this helps,
Abby

Abby Cutfield
Advisor Science, Pharmacovigilance
Clinical Risk Management
Medsafe
Population Health Directorate
Ministry of Health
[redacted]

http://www.medsafe.govt.nz
[redacted]

[redacted]

[redacted]
07/12/2010 03:03 p.m.

To [redacted]
cc
Subject Fw: Valproate information as requested at the December 2010 MARC meeting



Kimberly Bridgewater
Advisor Science, Pharmacovigilance,
MARC Secretary
Clinical Risk Management
Medsafe
Population Health Directorate
Ministry of Health
[redacted]

http://www.medsafe.govt.nz
[redacted]

----- Forwarded by [redacted] 07/12/2010 15:03 -----

[redacted]
07/12/2010 15:02

To [redacted]
cc
Subject Re: Valproate information as requested at the December 2010 MARC meeting

[redacted]

21/10/2014 03:09 p.m.

To: [redacted]

cc:

bcc:

Subject: Re: Peer Review Request - Sodium Valproate in Pregnancy

And here's the attachment, sorry!

Andrea Govender
Advisor - Pharmacovigilance/Editor - Prescriber Update
Clinical Risk Management
Medsafe
Clinical Leadership, Protection, & Regulation
Ministry of Health
[redacted]
http://www.medsafe.govt.nz
[redacted]

sodium valproate in pregnancy.docx

Andrea Govender Hello Everyone, I hope all is we... 21/10/2014 03:04:02 p.m.

From: [redacted]
To: [redacted]
Date: 21/10/2014 03:04 p.m.
Subject: Peer Review Request - Sodium Valproate in Pregnancy

Hello Everyone,

I hope all is well with you.

I would really appreciate it if you would peer review this article for our next edition of Prescriber Update.

Please let me know your comments by **Friday, 24 October 2014.**

Many thanks and kindest regards,

Andrea Govender
Advisor - Pharmacovigilance/Editor - Prescriber Update
Clinical Risk Management
Medsafe

Clinical Leadership, Protection, & Regulation
Ministry of Health
[redacted]

http://www.medsafe.govt.nz
[redacted]

**Use of Sodium Valproate in Pregnancy**

Sodium valproate (Epilim) was first introduced as an anti-epileptic in 1964. [Kini] It is currently indicated for treatment of primary generalised epilepsy, partial (focal) epilepsy, and bipolar disease.

Epilim is contraindicated in pregnancy due to the risk of congenital malformations and developmental effects. In addition the data sheet recommends that Epilim should not be used in women of child-bearing potential unless other treatments are ineffective or not tolerated. Before Epilim is prescribed for use in women who could become pregnant they should receive advice on the benefits and risks of treatment.

*Congenital malformations*

The first report of teratogenic effects of valproate was published in 1980. The term fetal valproate syndrome (FVS) was suggested in 1984. [Kini] A number of different anomalies have been associated with valproate exposure (see table), the clinical presentation varies between affected infants. The variability in clinical presentation may be influenced by a number of factors such as maternal seizures during pregnancy, folic acid intake, dose and timing of exposure of valproate, parental factors such as IQ and socioeconomic status and genetic susceptibility. [Kini]

Anomalies most commonly associated with valproate exposure

| | |
|---|---|
| Neural tube defects | Spina bifida<br>Anencephaly |
| Congenital heart defects | Ventricular septal defect<br>Atrial septal defect<br>Aortic stenosis<br>Patent ductus arteriosus |
| Limb defects | Radial ray defect<br>Polydactyly<br>Split hand<br>Overlapping toes<br>Camptodactyly |
| Genitourinary defects | Hypospadias |
| Skin abnormalities | Capillary haemangioma |
| Dysmorphic features | Trigonocephaly<br>Prominent metopic ridge<br>Thin arched eyebrows<br>Epicanthic folds<br>Infraorbital grooves<br>Broad nasal bridge<br>Short anteverted nose<br>Long philtrum<br>Thin upper lip |

The risk of congenital malformations in exposed infants is higher than the background rate of 2-3%. [Kini] Specific estimates from different pregnancy registries include.

- UK and Ireland Epilepsy and pregnancy registers (includes 1/3 of relevant pregnancies) rate estimate is 6.7% (95% CI 5.5-8.3%). [Campbell]
- North American Anti-Epileptic Drug Pregnancy Registry rate estimate is 9.3%. [Campbell]
- International Registry of antiepileptic drugs and pregnancy rate estimate is 9.7%.[Campbell]
- Australian Pregnancy Registry (includes 1/12 of all relevant pregnancies) the rate estimate is 12.4%. [Vajda]

In contrast the risk of malformations associated with carbamazepine was 2.6% (1.9-3.5%) and 2.3% (1.8-3.1%) with lamotrigine in the UK and Ireland registries. [Campbell]

The risk for some specific malformations associated with valproate exposure has also been estimated. The risk of spina bifida has been estimated at 1-2%; the background rate is 0.2-0.5%. The risk associated with carbamazepine exposure has been estimated at 0.5-1%,. [Kini]

In some registries a dose dependent effect has been seen with valproate exposed pregnancies. [Campbell]. [Vajda] In general a dose of > 1000mg/day has been associated with a higher risk for all of these abnormalities. [Kini] In the Australian Pregnancy Register the mean maternal daily valproate dose in pregnancies associated with fetal malformations was 1,367mg and in unaffected pregnancies was 870mg. [Vajda] In the UK and Ireland registries the mean daily dose of valproate for infants with malformations was 1031.2mg and 897.9mg in those without malformations. [Campbell] The dose of maternal valproate has been decreasing in Australia over the last 5 years and this has been paralleled by a significant decrease in the rate of spina bifida and hypospadias. [Vajda]

The risk of a congenital malformation is increased when women require polytherapy. [Kini]

Other antiepileptics have also been associated with malformations, for example microcephaly has been associated with carbamazepine exposure *in utero*. [Kini]

*CARM Reports*

CARM have received 13 reports of fetal valproate syndrome, the first report was received in 1997 and the most recent report in 2014. The mother's dose of valproate was only available in 2 reports and was greater than 1000mg per day. None of the reports mentioned whether folate was taken at conception. However this was not surprising as the majority of the reports were made at least one year after the birth of the affected child.

*Other birth outcomes*

The occurrence of generalised tonic-clonic seizures in pregnancy is associated with shorter gestational age and reduced birthweight. However, the majority of babies exposed to valproate are of normal weight. [Kini]

A recent study found no association between the use of anti-epileptic medicines in pregnancy and the risk of spontaneous abortion or stillbirth. [Bech]

Babies exposed to valproate *in utero* may exhibit withdrawal symptoms at birth such as feeding difficulties, hypoglycaemia, jitteriness, irritability and hypothermia. [Kini]

*Cognitive impairment and behavioural issues*

Children with fetal valproate syndrome have also been noted to have cognitive impairment. Global developmental delay has been noted in children with severe fetal valproate syndrome. The most frequently affected developmental aspect is speech and language. [Kini] The average full-scale IQ of a child with FVS is in the 80-90 range. However the verbal IQ is significantly lower. [Kini]

Autism, Asperger's syndrome and autistic spectrum disorder have been diagnosed and reported more frequently in FVS, but are also seen in valproate exposed children without FVS. [Kini]

A population based study in Denmark investigated the risk of Autism spectrum disorder and Autism. Children exposed to valproate *in utero* were compared with the whole population and a cohort of children born to women with epilepsy.

- The absolute risk of autism spectrum disorder in children exposed to valproate was 4.4% (95% CI 2.6%-7.5%) for autism spectrum disorder. The absolute risk in the total population was 1.2%. The Hazard Ratio was 2.9 (95% CI 1.7-4.9).
- When the cohort was restricted to children of mothers with epilepsy; the absolute risk of autism spectrum disorder in children exposed to valproate was 4.2%. The risk for the cohort was 2.4%; the HR was 1.7 (95% CI 0.9-3.2).
- The absolute risk of autism in children exposed to valproate was 2.5%. The absolute risk in the total population was 0.5%. The HR was 5.2 (95% CI 2.7-10)
- When the cohort was restricted to children of mothers with epilepsy the absolute risk of autism in children exposed to valproate was 3%. The absolute risk for the cohort was 1%; the HR was 2.9 (95% CI 1.4-6.0). [Christensen]

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study found a significant dose related performance decline in parental ratings of adaptive functioning in children exposed *in utero* to valproate (or phenytoin). Children of mothers who took valproate during pregnancy were at a greater risk for a diagnosis of ADHD. [Cohen]

Measurement of IQ in the NEAD study showed that the mean IQ of children (aged 6 years) exposed to valproate was in the normal range but lower than in children exposed to other anti-epileptics: 97 (95% CI 94-101) compared to 108 (105-110) for lamotrigine.[Meador]

In another small study comparing levetiracetam with valproate, children exposed to valproate scored, on average, 15.8 points below children exposed to levetiracetam on measures of gross motor skills, 6.4 points below on comprehension language abilities and 9.5 points below on expressive language abilities. [Shallcross]

*Management*

As the use of valproate in pregnancy is an unapproved use, under the health and disability code of rights women requiring valproate treatment during pregnancy must be informed about the benefits and risks of treatment and this information must be provided in writing if requested (Consumer Medicine Information is available: **www.medsafe.govt.nz/consumers/CMI/e/Epilim.pdf**).

It should be remembered that none of the anti-epileptic medicines available are completely safe during pregnancy. [Kini] Seizures during pregnancy are also associated with poorer developmental outcomes. Lamotrigine has been found to be less effective than other treatments for seizure control in pregnancy [Campbell]

For women requiring valproate treatment the risk of malformations is reduced when the daily dose is below 1000mg. However any dose adjustments should be made well in advance of pregnancy to ensure that seizures are still controlled. [kini]

High dose folic acid is recommended, starting at least 6 weeks pre-conception. [Kini] Periconceptional use of folic acid has generally been associated with a reduced risk of autism. [Christensen] The NEAD study results provide some support for use of preconception folate. Parents reporting maternal folate use noted fewer physical complaints and atypical behaviours in their children and teachers endorsed lower levels of anxiety in these offspring. [Cohen] IQ was also higher in children whose mothers had taken folate [Meador]

In addition among women exposed to valproate in the UK and Ireland Pregnancy registries neural tube defects were slightly less frequent in their infants if they took folic acid (0.9% compared with 1.2%). [Campbell] Only 40% of women included in these registries and taking valproate reported also taking periconceptual folic acid.

Women should also be encouraged to address any other risk factors for adverse pregnancy outcomes, such as smoking.



**Key Messages**

- Sodium valproate (Epilim) is contraindicated in pregnancy
- Sodium valproate should not be used in women of child bearing potential unless clearly necessary.
- The risk of congenital malformations in infants exposed to sodium valproate *in utero* has been estimated between 6 and 12%.
- The risk of autism spectrum disorder in children exposed to valproate *in utero* has been estimated at around 4%.
- Children exposed to valproate *in utero* have reduced IQ compared to children exposed to other antiepileptic medicines.
- Reducing the dose of valproate below 1000mg/day and using of high dose folate periconceptually reduces the risk of some malformations and cognitive impairment.
- Seizures during pregnancy and use of other anti-epileptic medicines have also been associated with risks of adverse developmental outcomes and malformations.

**References**

Kini U (2006) 'Fetal valproate syndrome: a review' Paediatric and Perinatal Drug Therapy 7: 123-130.

Christensen J, Grønborg TK, Sørensen MJ et al (2013) 'Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism' *JAMA* 309: 1696-1703.

Vajda FJ, O'Brien TJ, Graham JE (2013) 'Dose dependence of fetal malformations associated with valproate' *Neurology* 81: 999-1003.

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Campbell E, Kennedy F, Russell A et al (2014) 'Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers' *J Neurol Neuosurg Psychiatry* 85: 1029-1034.

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Meador KJ, Baker GA, Browning N et al (2013) 'Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study' *Lancet Neurol* 12: 244-52

Sanofi-aventis NZ Ltd. 2014 *Epilim data sheet* 12 June 2014 URL: http://www.medsafe.govt.nz/profs/datasheet/e/Epilimtabsyrliqiv.pdf (accessed 10 October 2014).

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Additional information not for the article -

Spelling of fetus

Pronunciation: /'fi:tas

/(*British* (in non-technical use) also foetus)

**noun (plural fetuses)**

An unborn or unhatched offspring of a mammal, in particular, an unborn human more than eight weeks after conception.

More example sentences

A small subset of fetuses with large lung lesions will become hydropic, deteriorate rapidly, and die in utero.

Feedback is currently being used in a trial of early versus delayed delivery for preterm, growth retarded fetuses.

How well a woman and the fetus do during pregnancy depends upon the type of heart problem.

Synonyms

embryo, fertilized egg, unborn baby, unborn child

**Origin**

late Middle English: from Latin *fetus* 'pregnancy, childbirth, offspring'.

**Usage**

The spelling **foetus** has no etymological basis but is recorded from the 16th century and until recently was the standard British spelling in both technical and non-technical use. In

technical usage **fetus** is now the standard spelling throughout the English-speaking world, but **foetus** is still found in British English outside technical contexts.

PHARMAC
Pharmaceutical Management Agency

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Wellington 6143, New Zealand
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Fax 64-4-460-4995
www.pharmac.govt.nz

31 August 2009

Dr Stewart Jessamine
Manager
Medsafe
P O Box 5013
Wellington

Dear Stewart

**SODIUM VALPROATE AND TERATOGENIC RISK**

I am writing on behalf of the Neurological Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC) requesting that Medsafe strengthen the warning information on the sodium valproate datasheet regarding its teratogenic risk.

The Subcommittee discussed this issue at its most recent meeting on 2 April 2009. The relevant excerpt from the meeting minutes is as follows:

> Members expressed concern about the high incidence of teratogenic effects associated with sodium valproate (10.7% in a recent meta-analysis (Meador et al. Epilepsy Res 2008;81(1):1-13)), noting that sodium valproate produces a higher risk of foetal malformations than other currently used anticonvulsant medications. The Subcommittee noted that the New Zealand Medsafe datasheet states that sodium valproate is contraindicated in pregnancy; however members considered that the datasheet does not appear to fully address the key issues given that, although recommending counselling for women of child-bearing potential and monitoring for women taking sodium valproate during pregnancy and pre-pregnancy, it does not state that sodium valproate should not be prescribed in woman of child-bearing age if there is a suitable alternative. The Subcommittee felt that the Medsafe regulations were inadequate as the risk of teratogenic effects is greatest in the earlier stages of pregnancy and many pregnancies are unplanned. The Subcommittee noted that some international experts consider that sodium valproate should be contraindicated in all women of child-bearing age, and agreed that sodium valproate should be avoided in women of child-bearing age if there was a suitable alternative treatment. The Subcommittee considered that this issue should be raised with Medsafe.

I would be grateful if you could give consideration to this issue. Please feel free to contact me on [redacted] if you have any questions.

Yours sincerely

Dr Sisira Jayathissa
Chair, Neurological Subcommittee of PTAC

A302325 - qA9429

11 May 2010

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www.medsafe.govt.nz

Dr Sisira Jayathissa
Chair
Neurological Subcommittee of PTAC
PHARMAC
PO Box 10-254
WELLINGTON

TT35-07-5-4-5



Dear Dr Jayathissa

**Re: Sodium valproate and teratogenic risk**

Thank you for your letter of 31 August 2009 on behalf of the Neurological Subcommittee of PTAC requesting that Medsafe strengthen the warning information in the Epilim (sodium valproate) data sheet regarding the teratogenic risk.

Please accept my apologies for the delay in this response. A copy of your letter was not received until recently.

Your letter advises that the Neurological Subcommittee discussed the teratogenic risk associated with sodium valproate at its April 2009 meeting. Although sodium valproate is contraindicated in pregnancy the subcommittee considered the current data sheet is inadequate as it does not state that sodium valproate should not be prescribed in women of child-bearing potential if there is a suitable alternative. The subcommittee was concerned that the risk of teratogenic effects is greatest in the earlier stages of pregnancy and many pregnancies are unplanned.

Medsafe has previously noted that in offspring born to mothers with epilepsy receiving *any* anti-epileptic treatment, the overall rate of malformations has been demonstrated to be 2 to 3 times higher than the rate reported in the general population.

There are currently no antiepileptic medicines that do not pose risk to the developing foetus. Although recent studies have suggested that taking sodium valproate in the first trimester carries the highest risk for congenital malformations, phenytoin, phenobarbital and carbamazapine are also teratogenic. Although newer antiepileptic agents may appear safer in pregnancy, this may be due to a lack of data. To date, no antiepileptic medicines have been proven to be safe in pregnancy in terms of teratogenesis and therefore treatments (including the need for medication) must be tailored to the patient.

The evidence that one antiepileptic carries a greater risk than another for *all* women of child-bearing potential, is insufficient to make such firm treatment recommendations in the data sheet.

Medsafe is working with the sponsor of Epilim to improve the clarity of the information contained in the *Use in Pregnancy* section of the data sheet. The revised data sheet which is expected to be published on the Medsafe website by the end of May 2010 will ensure that a clear risk-benefit statement is provided at the beginning of this section. The revised data sheet will also provide clearer treatment advice for use in women of child-bearing potential.

To summarise there is a risk of teratogenesis associated with all antiepileptic medicines with little evidence for a safer alternative over sodium valproate. The data sheet for Epilim contains extensive warnings and advice regarding the use of this medicine in women of child-bearing potential. It is Medsafe's assessment that there is insufficient evidence to require the sponsor to include the Neurological Subcommittee's statement that *sodium valproate should not be prescribed in women of child-bearing potential if there is a suitable alternative* in the data sheet.

As with all medicines, Medsafe continues to monitor any new information that arises regarding sodium valproate and undertakes appropriate action where necessary including seeking expert advice from the Medicines Adverse Reactions Committee.

I hope this response adequately addresses the concerns of the Neurological Subcommittee of PTAC.

Yours sincerely,

Dr Stewart Jessamine
**Group Manager**
**Medsafe**

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11 October 2010

Dr Stewart Jessamine
Manager
Medsafe

Cc Marius Rademaker
Acting Chair
Medicines Adverse Reactions Committee

*By email:* [redacted]



Dear Stewart

**SODIUM VALPROATE AND TERATOGENIC RISK**

Thank you for your letter of 11 May 2010 in response to the request from the Neurological Subcommittee of PTAC for Medsafe to strengthen the warning information on the sodium valproate datasheet regarding its teratogenic risk.

The Subcommittee discussed your response at its most recent meeting on 5 August 2010. The Subcommittee was disappointed that Medsafe has elected not to alter the datasheet to state that sodium valproate should not be prescribed in women of childbearing age if there is a suitable alternative. Members noted that some changes had been made to the datasheet but felt that these did not go far enough.

In particular, Subcommittee members were concerned with the statement in your letter that "there is a risk of teratogenesis associated with all antiepileptic medicines with little evidence for a safer alternative over sodium valproate." The Subcommittee feels very strongly that there is evidence that the risk of teratogenic effects is greater for sodium valproate than for other antiepileptic agents. Please find attached a recent publication in support of this view (Jentink et al. N Engl J Med 2010;362:2185-93).

I would be grateful if you could give further consideration to this issue, as we remain very concerned that female patients of childbearing age may be placed at unnecessarily high risk of congenital malformations where other antiepileptic options are available.

Please feel free to contact me on [redacted] if you have any questions.

Yours sincerely

Dr Sisira Jayathissa
Chair, Neurological Subcommittee of PTAC

A384451 - qA9429

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10 November 2010

Dr Sisira Jayathissa
Chair, Neurological Subcommittee of PTAC
PHARMAC
PO Box 10-254
WELLINGTON



Dear Dr Jayathissa

**Re: Sodium valproate and teratogenic risk**

Thank you for your letter of 11 October 2010 on behalf of the Neurological Subcommittee of PTAC. I can confirm Medsafe has received the recent publication regarding the teratogenic risk associated with sodium valproate and the request for Medsafe to give further consideration to PTAC's concerns regarding this issue.

Your letter advises that the Neurological Subcommittee discussed Medsafe's response from previous correspondence on this matter at its August 2010 meeting. The Subcommittee was disappointed that Medsafe has elected not to alter the data sheet to state that sodium valproate should not be prescribed in women of childbearing age if there is a suitable alternative.

Please note as data sheets are owned and maintained by the sponsor responsible for each medicine, changes to data sheets must be made by the sponsor. When Medsafe identifies possible concerns with a medicine, a review of the available data is undertaken and can result in a request to the sponsor to amend the data sheet. The sponsor may decide that the requested changes are not warranted, providing justification for their position. The Minister of Health may impose data sheet changes only following a statutory review of the risks and benefits under section 36 of the Medicines Act 1981.

Medsafe is in the process of reviewing the publication the Neurological Subcommittee has provided (Jentink et al, 2010). This publication will be carefully considered in the context of the available data including the published literature and internationally approved prescribing information for sodium valproate. Should Medsafe consider that expert advice is required, this issue may be referred to the Medicines Adverse Reactions Committee for their consideration in March 2011.

It is therefore anticipated that the outcome of the review will be available in April 2011, if not earlier.

Please do not hesitate to contact me directly on [redacted] should you have any further questions or concerns.

Yours sincerely,

Dr Joanne Hart
**Manager, Clinical Risk Management**
**Medsafe**

cc. Geraldine MacGibbon
PHARMAC

[redacted]

08/12/2010 02:46 p.m.

To: [redacted]
cc: [redacted]
bcc:

Subject: Re: Fw: Sodium valproate concerns from Neurological Subcommittee of PTAC

Hi Stewart,

As provided in the below e-mail trail, I put together a package for the MARC members on the history of this topic as addressed by the MARC. I also collated an analysis of information contained in international prescribing information for valproate, for comparison. This was in response to a short discussion at Thursday's MARC meeting. We have asked the Committee to advise if they wish to discuss this further at the next meeting.

In Sisira's e-mail below, he has stated that the Neurological Sub-committee of PTAC (of which he is the Chair) strongly feels valproate should be contraindicated in pregnancy. I can confirm that, as already communicated with the sub-committee, the valproate data sheets already clearly contraindicate use in pregnancy. It is therefore my understanding from the letters we have received from Sisira, that the sub-committee wish to see valproate contraindicated in women of child-bearing potential (given that often a women will not know she is pregnant in the first few weeks of pregnancy).

I was requested to perform a preliminary investigation into this issue following the receipt of the 2nd letter from Sisira. This 2nd letter was sent following the initial response signed by you explaining to PTAC why we would not contraindicate valproate in women or request the sponsor to recommend alternative treatments in their data sheet.

Following the responses of the MARC to the data package sent out this week, we will make a decision as to further actions.

I hope this helps,
Abby

Abby Cutfield
Advisor Science, Pharmacovigilance
Clinical Risk Management
Medsafe
Population Health Directorate
Ministry of Health
[redacted]

http://www.medsafe.govt.nz
[redacted]

Joanne Hart/MOH

[redacted]

08/12/2010 01:12 p.m.

To [redacted]
cc

Subject Re: Fw: Sodium valproate concerns from Neurological Subcommittee of PTAC

Hi Stewart

MARC discussed briefly at last meeting and we agreed to send them some information to see if they consider it necessary to re-review (see below) - it was last reviewed in Dec 2009 with updates to the data sheets. PTAC have been advised (twice) that information on comparative risks cannot be included in data sheets and at the MARC meeting the Committee was informed that an assessment of the relative risks and benefits of treatment must be done on an individual patient basis. We are awaiting feedback from the MARC wrt deciding on next steps and whether we should take a review to MARC or just look at internally and respond to PTAC (we are OK either way). PTAC has already been responded to say that the review may take several weeks. As far as I am aware only David Reith has responded and he seems comfortable.

Cheers
Jo

Dear MARC Members,

As discussed at the MARC meeting on Thursday, please find attached:

- Copies of reports presented to the MARC on this issue since March 2004 -- 10 attachments
- A collation of sections of MARC minutes in which this issue was discussed since March 2004 -- 1 attachment (History of MARC minutes)
- An analysis of information contained in international valproate prescribing documents regarding use in women of child-bearing potential and in pregnancy -- 1 attachment (International prescribing information)

If you consider further information is needed or that the data sheet does not sufficiently describe the risk, please let me know as soon as possible so that this topic can be incorporated into the agenda for the next MARC meeting.

Kind regards,

Kimberly Bridgewater
Advisor Science, Pharmacovigilance,
MARC Secretary
[redacted]

http://www.medsafe.govt.nz
[redacted]



MARC Report 1.pdf
MARC Report 1 - Annex 1.pdf
MARC Report 2.pdf
MARC Report 2 - Annex 1.pdf
MARC Report 2 - Annex 2.pdf
MARC Report 2 - Annex 3.pdf
MARC Report 3.pdf
MARC Report 3 - Annex 1.pdf
MARC Report 3 - Annex 2.pdf
MARC Report 3 - Annex 3.pdf
History of MARC minutes.pdf
International prescribing information.pdf

Joanne Hart
Manager
Clinical Risk Management
Medsafe
Ministry of Health
[redacted]

http://www.moh.govt.nz
[redacted]

Stewart Jessamine/MOH

[redacted]

08/12/2010 12:17 p.m.

To J[redacted]
cc
Subject Fw: Sodium valproate concerns from Neurological Subcommittee of PTAC

Jo

I'm not sure where we got to on this issue.

Stewart

Stewart Jessamine
Group Manager
Medsafe
Population Health Directorate
Ministry of Health
[redacted]

http://www.moh.govt.nz
[redacted]

----- Forwarded by Stewart Jessamine/MOH on 08/12/2010 12:17 p.m. -----

[redacted]

08/12/2010 12:14 p.m.

To Stewart Jessamine [redacted]
cc
Subject Fwd: Sodium valproate concerns from Neurological Subcommittee of PTAC

Dear Stewart,

Will you respond appropriately to the neurological subcommittee? (you may already have done so).

Have a great Hogmanay.

Marius
Dr Marius Rademaker BM FRCP FRACP DM
Hon Associate Professor
Dermatology Department, Waikato Hospital
Hamilton, New Zealand

Begin forwarded message:

**From:** "Sisira Jayathissa" <[redacted]>
**Date:** 8 December 2010 11:06:30 AM
**To:** '[redacted]
**Subject: Re: Fwd: Sodium valproate concerns from Neurological Subcommittee of PTAC**



Dear Marius

Now I understand the complexities associated with the process better. From neurologists perspective (I wrote the letter on their behalf) they strongly feel it should be contraindicated in the pregnancy based on the emerging data. To give them a meaningful response it may be reasonable to review the new evidence. I haven't thought about psychiatrists perspective in relation to stable mental health patient on valproate.

Sisira

>>> Marius and Linda Rademaker [redacted] 8/12/2010 8:47 a.m. >>>
Dear Sisira,

Are you happy with the responses, or do you want me to raise it formally at the next meeting?

Kind regards,

Marius

Dr Marius Rademaker BM FRCP FRACP DM
Hon Associate Professor
Dermatology Department, Waikato Hospital
Hamilton, New Zealand

Begin forwarded message:

**From:** [redacted]
**Date:** 12 October 2010 9:20:04 AM
**To:** [redacted]
**Subject: Re: Sodium valproate concerns from Neurological Subcommittee of PTAC**

Hi Marius, in Stewart's absence, I have asked Joanne Hart to look at this. Medsafe will appraise the NEJM paper to see whether it could change our position. We'll then consider whether it warrants taking to the MARC.

Cheers
Deb

Deborah James
Personal Assistant
Medsafe
Population Health Directorate
Ministry of Health
[redacted]

http://www.medsafe.govt.nz
[redacted]

[redacted]

11/10/2010 07:47 p.m.

To Stewart Jessamine [redacted]
cc
Subje Re: Sodium valproate concerns from Neurological
ct Subcommittee of PTAC

Dear Stewart,

Is this something we need to discuss at the next MARC?

Marius

Dr Marius Rademaker BM FRCP FRACP DM
Hon Associate Professor

Dermatology Department, Waikato Hospital
Hamilton, New Zealand

On 11/10/2010, at 9:56 AM, Geraldine MacGibbon wrote:

Dear Stewart

Please find attached a letter from the Neurological Subcommittee of PTAC continuing your correspondence about sodium valproate. I've also attached the previous correspondence between you and the Subcommittee FYI.

<<2010-10-11 to Medsafe from Neurological Subcommittee - sodium valproate.pdf>> <<Jentink et al. Valproic acid in pregnancy & congenital malformations. N Engl J Med 2010;362_2185-93.PDF>> <<2009-08-31 to Medsafe from Neurological Subcommittee - sodium valproate in women of childbearing age.pdf>> <<2010-05-12 Medsafe re Sodium valproate and teratogenic risk.PDF>>

Let me know if you have any questions.

Kind regards
Geraldine

Geraldine MacGibbon, PhD | Therapeutic Group Manager
PHARMAC | Level 9, 40 Mercer Street, Wellington
[redacted] | www.pharmac.govt.nz



<2010-10-11 to Medsafe from Neurological Subcommittee - sodium valproate.pdf><Jentink et al. Valproic acid in pregnancy & congenital malformations. N Engl J Med 2010;362_2185-93.PDF><2009-08-31 to Medsafe from Neurological Subcommittee - sodium valproate in women of childbearing age.pdf><2010-05-12 Medsafe re Sodium valproate and teratogenic risk.PDF>

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18 February 2011

Dr Sisira Jayathissa,
Chair, Neurological Subcommittee of PTAC
PHARMAC
PO Box 10-254
WELLINGTON



Dear Dr Jayathissa

**Re: Sodium valproate and teratogenic risk**

Thank you for your letter of 11 October 2010, on behalf of the Neurological Subcommittee of PTAC. In November 2010 Dr Joanne Hart wrote to you to advise that Medsafe would review the need for a contraindication for valproate treatment in women of child-bearing potential, if there is a suitable alternative. I am now in a position to inform you of the conclusions of Medsafe's review.

Medsafe considers that the available information (including the studies provided by the Subcommittee) is consistent with there being an increased risk of congenital anomalies in association with sodium valproate exposure during pregnancy, compared with healthy women. However, due to the limitations of the studies it is not certain that valproate treatment carries the highest risk. Medsafe notes that there is some discussion in the published literature regarding a dose effect of sodium valproate. It has been proposed that lower doses of valproate (<1000mg/day) do not increase the risk of a congenital anomaly above the expected background rate.

Medsafe notes that the absolute risk associated with sodium valproate treatment is less than that seen for genetic/hereditary factors. The risk of congenital anomalies is also lower than other known teratogenic medicines such as isotretinoin.

In summary, this information could be considered to support a contraindication to sodium valproate treatment in pregnancy, but not in women of child-bearing potential.

To contraindicate sodium valproate treatment in women of child bearing potential different information is needed. The evidence would need to show:

- either that the balance of benefits and risks was unfavourable in women of child bearing potential compared to other women and/or men; or
- that the medicine reduced the efficacy of all contraceptive measures and that the majority of (accidental) pregnancies resulted in a congenital malformation.

To date Medsafe is not aware of any evidence to show that sodium valproate has these effects. In addition, as far as Medsafe is aware, no other country has contraindicated sodium valproate treatment in women of child-bearing potential.

The pregnancy warnings in the sodium valproate data sheet have been reviewed by the Medicines Adverse Reactions Committee (MARC) on several occasions. The most recent review was at the December 2009 meeting; the minutes are published on the Medsafe website. In December 2010 Medsafe asked the MARC members whether, in their opinion, the data sheet pregnancy warnings required further discussion. Overall the MARC members considered that no further discussion was necessary and that the data sheet adequately reflected the known information.

In conclusion it is Medsafe's opinion that a contraindication for sodium valproate treatment in women of child-bearing potential, if there is a suitable alternative, is not supported by the evidence. It should not, therefore, be included in the data sheet. However, this does not preclude the incorporation of this statement into treatment guidelines. The Subcommittee may wish to consider this option.

A summary of Medsafe's review is outlined in the enclosed memo.

I hope that this information addresses the Subcommittee's concerns.

Yours sincerely,

Dr Stewart Jessamine
**Group Manager**
**Medsafe**

cc Peter Moodie, Medical Director, PHARMAC

# Internal Memo
# Ministry Of Health

| | |
|---|---|
| **To:** | ~~Manager, Clinical Risk Management Branch, Medsafe~~<br>General Manager Medsafe |
| **From:** | Susan Kenyon and Abby Cutfield |
| **Subject:** | **PTAC concerns regarding sodium valproate use in women of child-bearing potential** |
| **Date:** | February 2011 |
| **For Your:** | ACTION: DECISION: ☑ INFORMATION: |



**Background**

In August 2009 the neurological subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC) wrote to Medsafe to request that the data sheet for sodium valproate be updated regarding teratogenic risk. Essentially the committee had decided that valproate should be contraindicated in women of childbearing potential (unless there is no suitable alternative).

Medsafe replied stating that the data sheet contained sufficient warnings and contraindications and that the evidence did not warrant contraindication in women of childbearing potential.

In October 2010 PTAC replied to Medsafe reiterating the request to contraindicate valproate in women of childbearing potential. In addition the subcommittee disagreed that there was no evidence to show that valproate was more teratogenic than other antiepileptic medicines.

This memo provides a summary of our assessment of PTAC's concerns regarding the use of sodium valproate in women of childbearing potential.

Epilim is the only valproic acid/sodium valproate-containing medicine with ministerial consent for distribution in New Zealand. There are many dose forms of Epilim approved as identified in Table 1:

The approved indications for Epilim are as follows:

- *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.*

- *For the treatment of manic episodes, maintenance and prophylactic treatment of bipolar disease.*
- *Epilim IV is used for the treatment of patients with epilepsy or bipolar disorder, who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible.*

Table 1: Dose forms of Epilim approved in New Zealand

| Name | Active | Quantity | Approved | Funded |
|---|---|---|---|---|
| Epilim Syrup | Sodium valproate | 200mg/5mL | Oct 1977 | Yes |
| Epilim Liquid | Sodium valproate | 200mg/5mL | Jan 1986 | Yes |
| Epilim Crushable | Sodium valproate | 100mg | Mar 1986 | Yes |
| Epilim CR | Sodium valproate + Valproic acid | 200mg + 100mg | Jan 1992 | No |
| Epilim EC | Sodium valproate | 200mg | Jun 1978 | Yes |
| Epilim EC | Sodium valproate | 500mg | Aug 1998 | Yes |
| Epilim IV | Sodium valproate | 100mg/mL | Sept 1989 | Yes |

The mode of action of Epilim has not been fully established. Its anticonvulsant effect is attributed to the blockade of voltage dependent $Na^+$ channels and increased brain levels of the inhibitory synaptic transmitter, γ-aminobutyric acid (GABA). The GABA-ergic effect is also believed to possibly contribute towards the anti-manic properties of sodium valproate.

It has been suggested that sodium valproate raises GABA levels 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.

Of relevance to teratogenic effects, sodium valproate also has anti-folate activity (as do other anti-epileptics). This is either an effect of increased hepatic metabolism caused by induction of cytochrome P450s by Anti Epileptic Drugs (AEDs) or due to a direct effect on the enzymes involved in folate and methionine metabolism.

## Relevant Information

In support of their proposals the PTAC subcommittee supplied two publications. Medsafe's review of these publications follows:

*Meador et al. (2008). Epilepsy Research. 81(1): 1-13.*
This was a systematic review and meta-analysis designed to quantify the incidence of congenital malformations and other pregnancy outcomes as a function of *in- utero* anti-epileptic drug (AED) exposure.
Following a systematic literature review 59 studies were included; involving 65,533 pregnancies in epileptic patients and 1817,024 in 'healthy' women. The authors noted significant heterogeneity between the studies in design and results.

*Comment*
*Whilst the authors gave some overview data there was no review of patient numbers in individual studies, medicines included, time-scales per study, individual study outcomes, or*

*whether the studies were critically appraised for validity confounding and bias. The authors themselves state that there was significant heterogeneity indicating that the data should not have been pooled. 19 of the 53 studies were cross-sectional and it is debatable if data from these studies should be included in this study. 10 studies were published in the 1970s and 7 studies in the 1980s. The authors provide no reassurance that the conduct of these studies or treatment of epilepsy is comparable with the present day. The authors provided very little information on patient characteristisc and it is unclear to what extent (if at all) any confounding factors were taken into account.*

The authors calculated the incidence of congenital malformations using a random effects model. The main results are outlined in the table below.

| Group | Incidence (percent) | 95%CI |
|---|---|---|
| Healthy women | 2.28 | 1.46-3.10 |
| AED exposure | 7.08 | 5.62-8.54 |
| Polytherapy | 16.78 | 0.51-33.05 |
| Valproate monotherapy | 10.73 | 8.16-13.29 |
| Phenytoin monotherapy | 7.36 | 3.6-11.11 |
| Phenobarbitol monotherapy | 4.91 | 3.22-6.59 |
| Lamotrigine monotherapy | 2.91 | 2.00-3.82 |
| Carbamazpine monotherapy | 4.62 | 3.48-5.76 |

Defects associated with AED in these studies were noted by the authors to be cardiovascular (especially ventricular septal defect), cleft lip and spina bifida.
The authors noted that significant heterogeneity was seen in the analysis and this was likely caused in part by varying definitions of teratogenic outcomes as well as differences in exposure. In addition the authors stated it was difficult to come to firm conclusions with regard to the precise magnitude of the difference between active treatments and non-treatment. Neither could the authors be sure that patients weren't included more than once in the analysis.

*Comments*
*The comparison group was healthy patients, therefore an effect of epilepsy per se on tertatogenic risk could not be excluded. The increase in risk with polytherapy may reflect an increased risk due to additional drug use or be a marker of more severe disease causing more teratogenic effects. Women taking anti-epileptics for indications other than epilepsywould have made a better control group. The authors do not discuss the risk of congenital malformations in untreated epileptics.*
*The authors note an increase in spina bifida and cleft lip – both conditions have been associated with low folate levels and as valproate is an anti-folate drug this lends biological plausibility of an association. The use of folate supplements in pregnancy is therefore an important confounding factor. Routine folate supplementation in pregnancy did not start until the 1990s; this raises questions regarding the validity of including data from studies conducted in the 1970s and 80s.*
*Whilst the increase in incidence with monotherapy was highest with valproate this was not a risk estimate and no comparison of risk was made with other anti-epileptics. Therefore this paper cannot provide evidence of increased risk of congenital malformations with valproate compared to other AEDs.*

*Whilst this paper represents the results of a meta-analysis, such analyses are only as good as the studies they are based on. Since the authors do not clearly discuss the limitations of the included studies it is hard to ascertain the validity of the meta-analysis.*

*Jentink et al. (2010). New England Journal of Medicine. 362(23): 2185-2193.*
The authors of this study combined data from eight published cohort studies in which women were exposed to valproic acid and identified 14 malformations that were significantly more common among the offspring of women treated with valproic acid during pregnancy. The authors then further assessed these associations in a case-control study using the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database. Two control groups were used: one consisting of infants with malformations not previously linked to valproate and one consisting of infants with chromosomal abnormalities.

An overview of studies included in the analysis is provided in the supplementary information, the majority of studies were conducted using data from the mid 1990's. The number of exposed pregnancies in each study ranged from 30-268. Overall a total of 135 births with malformations were noted in 1565 exposed pregnancies.

*Comments*
*The authors do not state how they synthesised the data to get an overall incidence of malformations with valproate treatment of 8.6 % (7.3-10.1).*

The authors state that from the literature review they identified 14 malformations with prevalences that were significantly higher in the studies of maternal exposure to valproic acid than in the EUROCAT reference group. Exposure to valproate monotherapy during the first trimester was compared to no exposure to anti-epileptic medicines and with exposure to AEDs other than valproate.

The authors used logistic-regression analysis to calculate odds ratios. Adjustments were made for: maternal age, child's year of birth and individual registry. For anomalies for which there were fewer than 6 cases with valproate exposure no adjustments were made. No adjustments for multiple comparisons are stated to have been made.

The frequency of exposure to valproate was 3.3 per 1000 registrations compared to 1.1 per 1000 of controls. The results as presented in the paper are shown below.

The authors state that significant associations between valproate exposure (compared to no AED exposure) and six conditions were noted: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly and craniosynostosis.

The authors state that they cannot rule out the possibility of confounding by indication. The authors note the lack of information on potential confounders and the limitations of the choice of control group.

Table 3. Odds Ratios for Malformations with Exposure to Valproic Acid Monotherapy as Compared with No Antiepileptic-Drug (AED) Exposure and with Exposure to Monotherapy with Other Antiepileptic Drugs in Control Groups 1 and 2.*

| Type of Malformation | No. with Malformation† | No. with Malformation Exposed to Valproic Acid Monotherapy | Adjusted Odds Ratio for Valproic Acid Monotherapy vs. No AED (95% CI)‡ | Adjusted Odds Ratio for Valproic Acid Monotherapy vs. Other AED Monotherapy (95% CI)‡ |
|---|---|---|---|---|
| Nervous system | | | | |
| Spina bifida | 2,046 | 27 | | |
| Control group 1 | | | 12.7 (7.7–20.7)§ | 5.7 (2.6–12.3)§ |
| Control group 2 | | | 16.3 (8.0–33.4) | 5.5 (1.2–10.0)§ |
| Macrocephaly¶ | 696 | 2 | | |
| Control group 1 | | | 2.5 (0.5–9.7)§ | 1.6 (0.1–14.7)§ |
| Control group 2 | | | 2.6 (0.5–11.6)§ | 1.0 (0.1–9.8)§ |
| Heart | | | | |
| Ventricular septal defect | 11,711 | 19 | | |
| Control group 1 | | | 1.6 (0.9–2.7) | 2.2 (1.1–4.4)§ |
| Control group 2 | | | 1.3 (0.8–3.9) | 1.5 (0.5–4.2)§ |
| Atrial septal defect | 5,267 | 19 | | |
| Control group 1 | | | 2.5 (1.4–4.4) | 3.2 (1.5–7.0)§ |
| Control group 2 | | | 3.0 (1.1–7.4) | 2.4 (0.6–8.0)§ |
| Tetralogy of Fallot | 980 | 3 | | |
| Control group 1 | | | 2.3 (0.6–8.6)§ | 1.5 (0.2–7.9)§ |
| Control group 2 | | | 2.6 (0.5–10.4)§ | 0.9 (0.1–5.5)§ |
| Pulmonary-valve atresia | 311 | 1 | | |
| Control group 1 | | | 2.6 (0.1–15.7)§ | 2.4 (0.0–193.6)§ |
| Control group 2 | | | 2.9 (0.1–19.5)§ | 1.5 (0.0–130.7)§ |
| Hypoplastic right heart | 80 | 0 | | |
| Control group 1 | | | — | — |
| Control group 2 | | | — | — |
| Cleft palate | 2,244 | 15 | | |
| Control group 1 | | | 3.2 (2.8–9.9) | 3.0 (1.2–7.4)§ |
| Control group 2 | | | 5.2 (2.2–12.3) | 1.9 (0.6–5.9)§ |
| Cleft lip with or without cleft palate | 754 | 2 | | |
| Control group 1 | | | 2.3 (0.3–9.0)§ | 1.2 (0.1–8.9)§ |
| Control group 2 | | | 2.4 (0.3–10.7)§ | 0.7 (0.1–6.1)§ |
| Gastroschisis | 798 | 1 | | |
| Control group 1 | | | 1.1 (0.4–6.5)§ | 1.3 (0.0–24.0)§ |
| Control group 2 | | | 1.1 (0.0–7.6)§ | 0.7 (0.0–15.6)§ |
| Hypospadias (male outcome only) | 5,395 | 32 | | |
| Control group 1 | | | 4.8 (2.8–8.1) | 6.7 (2.9–15.2)§ |
| Control group 2 | | | 6.3 (2.6–15.3) | 4.1 (1.1–15.0)§ |
| Limb | | | | |
| Clubfoot¶ | 3,676 | 6 | | |
| Control group 1 | | | 1.6 (0.7–3.7) | 3.3 (0.5–3.9)§ |
| Control group 2 | | | 2.2 (0.8–6.7) | 1.2 (0.3–4.7)§ |
| Polydactyly | 3,500 | 9 | | |
| Control group 1 | | | 2.2 (1.0–4.5) | 7.1 (1.8–28.4)§ |
| Control group 2 | | | 2.4 (0.9–6.4) | 4.4 (0.8–22.6)§ |
| Craniosynostosis | 520 | 4 | | |
| Control group 1 | | | 6.5 (2.2–18.8)§ | 4.9 (0.7–35.2)§ |
| Control group 2 | | | 7.0 (1.7–22.9)§ | 2.9 (0.4–35.8)§ |

* Control group 1 included registrations without chromosomal abnormalities, and control group 2 registrations with chromosomal abnormalities. For the number of cases with no exposure to valproic acid, see Section 3 in the Supplementary Appendix, available with the full text of this article at NEJM.org.
† A case or control may have been counted in more than one subgroup.
‡ Odds ratios were adjusted for reporting registry, birth year, and maternal age unless otherwise indicated.
§ Odds ratios were adjusted for birth year and maternal age only.
¶ Microcephaly and clubfoot occurred without spina bifida.
‖ Odds ratios were not adjusted because of the small number of exposed cases.

The authors also note that although their results indicated increased relative risks of several malformations, the absolute rates of specific malformations was low and the majority of children born to mothers who take valproate do not have malformations. For example the authors calculate that the absolute risk of having a child with spina bifida after valproate exposure is 0.6%.

*Comments*
*Significant limitations of this study include the possibility of confounding by indication, choice of control group and lack of information on confounding factors.*
*The choice of AED may be determined by the form of epilepsy with valproate being more commonly used in idiopathic generalised epilepsy.*
*Whilst some adjustment was made for individual registry it is not clear that treatment of epileptics and choice of treatment is comparable throughout Europe.*
*It is noted that the confidence intervals are wide for most of the estimates reflecting the low number of valproate exposed cases. These estimates would be expected to decrease if confounding factors had been taken into account.*
*As stated by the authors the absolute risk of a congenital anomaly in a foetus exposed to valproate was low.*
*For comparison, the risk of having a second child with spina bifida after having had a child with spina bifida, is 3%. High dose folate taken before and during pregnancy reduces this risk to 1%.*

In response to this article Vajda F and O'Brien T[1] report that in the Australian pregnancy register the risk of teratogenic effects of low dose valproate (<1000mg) was not significantly higher. They also note that seizure control was better with valproate than lamotrigine or carbamazepine. Jentink et al refute this argument stating that the number of pregnancies in the Australian register is too low and other published information has shown an increased risk with low dose valproate.

*Comments*
*This debate suggests that the evidence relating to valporate and congenital anomalies is not entirely clear and the possibility exists that there is a dose dependent effect. The effect of high-dose folate supplementation was not discussed in these papers, but may also be relevant.*
*It should also be borne in mind that it may not be possible to switch from valproate for some patients.* There are a number of additional papers investigating this issue. Some of the limitations mentioned above apply equally to these papers. The data for effects in different medicines overlap and it is difficult to identify which medicine may be associated with least risk. Valporate does appear to be consistently found to be associated with the greatest risk. However, given the lack of information on confounding factors and differences in prescribing due to epilepsy type or previous failure of other medicines an increased risk with valproate treatment cannot be seen as a secure outcome of this research

[1] Vajda F and O'Brien T. 2010 'Valproic acid monotherapy in pregnancy and major congenital malformations' NEJM 363: 1771

## Medsafe and MARC review of the data sheet

Epilim is contraindicated in pregnancy in New Zealand and Australia, but not in the UK or the US. The information including warning re use in women of child bearing potential in the NZ data sheet is consistent with that in other countries. The MARC have been asked to comment on the data sheet information both before and after PTAC raised concerns and have concluded that the data sheet accurately reflects the information on use in pregnancy at the present time.

## Regulatory considerations

There are a number of considerations that are taken into account by regulators when approving indications, contraindications, precautions and adverse effects of medicines.

Of relevance to this issue is the need to maintain access to appropriate epilepsy treatment for patients.

No evidence has been presented by PTAC to show, that when women reach child-bearing age, the benefit risk profile for valproate treatment changes. No evidence has been provided to show that sodium valproate reduces the effectiveness of all contraceptive measures resulting in an increased risk of pregnancy. Either scenario could be a justification for the proposed indication. Therefore, PTAC appear to be requesting that sodium valproate is contraindicated in women of childbearing age purely because they might become pregnant whilst taking valproate and, as a result, have a baby with congenital anomalies.

Since no evidence has been provided that there is a change in the benefit risk profile for women of child bearing age, the only possible reasons for a contraindication in this population would be that the majority of (accidental) pregnancies would result in a foetus with a congenital abnormality *and* that there is an alternative treatment without risk. The evidence provided does not support these assertions. The majority of women exposed to valproate in pregnancy have a normal baby. Indeed as outlined above, the increase in absolute risk of a baby with spina bifida (for example) is less than the risk associated with hereditary/genetic factors. The other treatments also appear to be associated with a risk of congenital anomalies that is higher than the background rate. No information on predisposing factors associated with an increased risk of congenital anomalies when taking AEDs was found during this review. This is in part due to the fact that these papers did not examine or adjust for confounding factors. There appears to be some evidence to show that there is a dose dependent effect or a dose (<1000mg per day) below which no there is effect of valproate detectable above the background rate of congenital anomalies.

It should also be noted that PTAC's proposal is inconsistent with actions taken for other teratogenic medicines such as isotetinoin where up to 30% of exposed pregnancies result in a congenital anomaly of the foetus.

Sodium valproate is not contraindicated in pregnancy in other jurisdictions other than Australia, and is not contraindicated in women of childbearing potential in any jurisdiction.

The proposed wording from PTAC was that 'sodium valproate should be contraindicated in women of child bearing potential if there is a suitable alternative'. This wording is open to interpretation. It is not clear what age range child bearing potential would encompass and a better definition of a suitable alternative would be needed e.g. failed on therapy with x other anti-epileptic medicines.

In these situations it is normal for the regulator to ensure that the product information contains as much information as possible regarding the issue to facilitate discussion between prescriber and patient. The relationship between prescriber and patient should be robust enough to discuss the benefits and risks of valproate treatment.

## Conclusions

The available evidence is consistent with there being an increased risk of congenital anomalies in association with sodium valproate exposure during pregnancy. In a number of studies valproate is identified as having the highest risk. However, the statistical comparison is not always made and the risk estimates tend to overlap with those for other AEDs. Therefore it is not *certain* that valproate treatment carries the highest risk. Since all these studies are by necessity observational they are subject to a number of limitations and the evidence provided has not accounted for or adjusted for these limitations. For example the lack of adjustment for confounding factors in the studies mentioned here is a serious drawback and probably inflates the risk estimate.

The absolute increase in risk associated with sodium valproate treatment is small, less than is seen for genetic/hereditary factors. From a regulatory point of view the contraindication of sodium valproate in pregnancy is not strongly supported by the available evidence. This appears to have occurred in 2006 and have been the decision of the company (no recommendation from MARC found or Prescriber Update article). The data provided by PTAC and reviewed here does not support a contraindication to valproate treatment in women of child-bearing potential at this time.

## Recommendations

It is recommended that you:

a. Agree that no further changes to the data sheets should be requested from the company — YES / NO

b. Agree that a letter outlining the conclusions of this memo should be sent to PTAC neurological subcommittee from the General Manager of Medsafe. — YES / NO

Signed: [signature]

Date: 15/2/2011

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11Th August 2013

Dr Stewart Jessamine
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Dear Stewart

**SODIUM VALPROATE AND TERATOGENIC RISK**

In response to the latest response letter from Medsafe, I am writing on behalf of the Neurological Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC) requesting that Medsafe strengthens the warning information on the sodium valproate datasheet regarding its teratogenic risk.

The Subcommittee discussed this issue at its most recent meeting on the 24 July 2012. The relevant excerpt from the meeting minutes is as follows:

> The Subcommittee noted the response letter from Medsafe in relation to the teratogenicity of sodium valproate and members disagree with the statement that there is insufficient evidence to require the sponsor to include the statement that 'sodium valproate should not be prescribed in women of child bearing potential if there is a suitable alternative'. The Subcommittee considered that the datasheet be amended to read 'sodium valproate is contraindicated in women of child bearing age, unless there is no other suitable alternative'. The Subcommittee considered that there is a fundamental difference between this phrasing.
>
> The Subcommittee considered that the proposed amendment is necessary because many pregnancies are unplanned and once a woman who is taking sodium valproate falls pregnant, it is likely that the damage to the foetus is done. The Subcommittee considered that there are other alternative treatments which are usually equally effective and have a lower teratogenicity.
>
> The Subcommittee noted a recently published observational study of pregnant women enrolled in the North American anti-epilepsy drugs (AED) Pregnancy Registry between 1997 and 2011, published by Hernandez-Diaz et al (Neurology 2012; 78:1692-1699). The authors calculated the risk of major malformations among infants exposed to specific AEDs in monotherapy during the first trimester of pregnancy and

among an unexposed group. The Subcommittee noted that the risk of major malformations in the exposed group ranged from 9.3% for valproate to 2.0% for lamotrigine. The Subcommittee considered that there is a dose relationship between the rate of major malformations and increasing doses of sodium valproate.

In view of results of the study noted above, I would be grateful if you could give further consideration to this issue. Please feel free to contact me if you have any questions.

Yours sincerely

Dr Peter Moodie
Medical Director

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH
www.medsafe.govt.nz

23 September 2013

Dr Peter Moodie
Medical Director
PHARMAC
PO Box 10-254
Wellington 6143

Dear Dr Moodie

**Sodium valproate and teratogenic risk**

Medsafe notes PHARMAC's continuing correspondence on behalf of the neurological subcommittee of PTAC and the latest letter dated 11 August 2013 that was received 12 September 2013.

The Subcommittee continues to request that sodium valproate be contraindicated in women of childbearing potential (24 July 2012).

Medsafe notes that the Subcommittee has provided no evidence to justify the requested change to the data sheet.

The data sheet for sodium valproate already contraindicates use in pregnancy. Medsafe notes that this is not consistent with other jurisdictions: sodium valproate is not contraindicated in pregnancy in the United States or the UK. In addition, the New Zealand data sheet contains the following warning:

*Women of child bearing potential:*

*This medicine should not be used in women of child-bearing potential unless clearly necessary (i.e. in situations where other treatments are ineffective or not tolerated). This assessment is to be made before sodium valproate is prescribed for the first time, or when a woman of child bearing potential treated with sodium valproate plans a pregnancy. Women of child-bearing potential must use effective contraception during treatment.*

Should the Subcommittee be concerned that prescribers are not following the advice in the data sheet they should contact the professional college(s) to address this issue.

Medsafe notes that the Subcommittee has identified a further observational study showing a higher incidence of congenital malformations with sodium valproate than other antiepileptics. Medsafe reiterates that this paper does not provide sufficient evidence to contraindicate use of sodium valproate in women of childbearing potential. In addition, Medsafe notes the following limitations of this study.

- Women were self-enrolled into the study at any point during pregnancy, including after prenatal testing; meaning the study was subject to significant bias.
- Study characteristics of the groups were not comparable, for example more women taking valproate were smokers compared with women taking lamotrigine or those unexposed (25.7% cf 8.8% and 6.1%).
- Only crude relative risks were presented because the authors stated that confounders did not change the results. However, the effect or non-effect of confounders on valproate risks were not presented. Neither was a fully adjusted relative risk presented.

- The authors did not provide information on other potential confounders such as family history of abnormalities or use of other medicines.

Medsafe reiterates, as the medicine regulator in New Zealand, that there is insufficient evidence to justify contraindicating this medicine from all women of child-bearing potential. The need to consider the use of alternative antiepileptics before using sodium valproate in this population is clearly outlined in the data sheet.

Yours sincerely

Sarah Reader
**Acting Group Manager**
**Medsafe**

# Comparative safety of antiepileptic drugs during pregnancy

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ABSTRACT

**Objective:** To assess the safety of the newer antiepileptic drugs (AEDs) during pregnancy.

**Methods:** The study population was pregnant women who enrolled in the North American AED Pregnancy Registry between 1997 and 2011. Data on AED use and maternal characteristics were collected through phone interviews at enrollment, at 7 months' gestation, and postpartum. Malformations were confirmed by medical records. The risk of major malformations was calculated among infants exposed to specific AEDs in monotherapy during the first trimester of pregnancy and among an unexposed group. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated with logistic regression.

**Results:** The risk of major malformations was 9.3% (30 of 323) for valproate, 5.5% (11 of 199) for phenobarbital, 4.2% (15 of 359) for topiramate, 3.0% (31 of 1,033) for carbamazepine, 2.9% (12 of 416) for phenytoin, 2.4% (11 of 450) for levetiracetam, and 2.0% (31 of 1,562) for lamotrigine. Compared with lamotrigine, the RR was 5.1 (95% CI 3.0–8.5) for valproate, 2.9 (1.4–5.8) for phenobarbital, and 2.2 (1.2–4.0) for topiramate. The proportion of women with epilepsy who had seizures during pregnancy ranged from 23% for valproate to 31% for lamotrigine. Valproate was associated with a higher risk of neural tube defects, hypospadias, cardiac defects, and oral clefts and phenobarbital with a higher risk of cardiac defects and oral clefts; 5 infants exposed to topiramate (1.4%) had a cleft lip.

**Conclusions:** AEDs such as valproate and phenobarbital were associated with a higher risk of major malformations than newer AEDs such as lamotrigine and levetiracetam. Topiramate was associated with an increased risk of cleft lip compared with that of a reference population. *Neurology*® 2012;78:1692–1699

GLOSSARY

AED = antiepileptic drug; CI = confidence interval; RR = relative risk.

Prenatal exposure to traditional antiepileptic drugs (AEDs) has been associated with an increased risk of congenital malformations and deficits in IQ.[1,2] However, the magnitude of the risks and the specific abnormalities has varied for each drug: it is widely accepted that valproate increases the risk of spina bifida, phenytoin of digit hypoplasia, phenobarbital of oral clefts, and carbamazepine of neural tube defects.[3–5]

Less is known about the safety of newer AEDs during pregnancy.[6] The relatively low risk of specific major malformations together with the few pregnant women exposed to each drug in the population have made it difficult to obtain valid, precise, and timely estimates of the teratogenic effects of recently introduced AEDs. Cohorts of women taking a variety of thera-

Supplemental data at www.neurology.org

Supplemental Data

CME

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North American AED Pregnancy Registry Coinvestigators are listed on the *Neurology*® Web site at www.neurology.org.

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Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this article.

pies with shared indications, enrolled early in pregnancy, and followed throughout gestation and postpartum can be used to assess the relative safety of individual AEDs.

We present the findings in the North American AED Pregnancy Registry. The objective was to estimate the risk of major malformations in infants whose mothers had taken specific AEDs as monotherapy during the first trimester of pregnancy and to assess whether exposure to each AED is associated with an increased risk of specific major malformations.

**METHODS Study design.** The North American AED Pregnancy Registry is an ongoing surveillance system of pregnant women who are taking an AED for any reason.[5,7,8] Women self-enrolled by calling a toll-free telephone number. To be eligible, a woman must be pregnant and have taken AEDs at some point during her pregnancy.

Women are interviewed at enrollment, at 7 months' gestation and at 8–12 weeks after the expected date of delivery. The computer-assisted interviews include questions on start and stop dates of each AED taken, dose, frequency, changes in medication, indication, and, if epilepsy, number and type of seizures during pregnancy; demographic characteristics; habits, such as cigarette smoking, alcohol intake, and use of illicit drugs; medical conditions; use of other medications; family history; and results of any prenatal testing.

**Study population.** Women were eligible for analysis if they had a liveborn infant, a stillborn infant, or a pregnancy terminated because of a fetal abnormality and were ineligible if they had a spontaneous abortion, withdrew from the Registry, or were lost to follow-up. The units of analysis were pregnancies, and malformations in one or more fetuses in twins were considered as one outcome.

Although women are encouraged to enroll before they have had any prenatal testing, they are enrolled throughout pregnancy. Enrollment is considered pure prospective if subjects enroll without having had a nuchal translucency screening test or chorionic villus sampling at 11–13 weeks' gestation, an amniocentesis, maternal serum screening, or an ultrasound after 15 weeks' gestation. The traditional enrollees might have some knowledge of the status of the fetus.

We present below findings for the first trimester monotherapy-exposed groups with 50 or more women eligible for analysis.

**Exposure definition.** Women were considered exposed if they used any AED, as monotherapy, during the first 4 lunar months after the last menstrual period. Women could have added or switched to different AEDs after the first trimester.

**Outcome definitions.** The outcomes of interest were major congenital malformations diagnosed before 12 completed weeks after birth. A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance.[9] The physical features excluded were minor anomalies, birth marks, deformations, anatomic findings by ultrasound studies in pregnancy that were not identified by the examining pediatrician, complications of prematurity, genetic disorders, and chromosome abnormalities.[9] In the postnatal interview, the mother is asked about the birth status of the infant, including any health problems, and she is asked to sign and return a medical record release form. The infant's doctors are asked to return copies of their examination findings through the first 12 weeks of life. Medical records are requested also from the infant's cardiologist or urologist or other specialist who has evaluated the infant. The written descriptions in the pediatricians' examinations are reviewed by the teratologist (L.B.H.), blinded to exposure status, to determine inclusion or exclusion.

**Reference groups.** Our primary reference group was women exposed to lamotrigine because it was the most commonly reported AED in the Registry. The rationale for the primary active reference group was 2-fold. First, this comparison responds to the most clinically relevant question: which AED is safest? Second, it minimizes confounding by indication, because most subjects in the groups compared (i.e., specific AEDs vs lamotrigine) will have epilepsy. A secondary internal reference group was pregnant women not taking an AED and without epilepsy who had been recruited, since 2003, among the friends and relatives of AED-exposed participants and followed with the same methodology.

In addition, to estimate the expected risk of specific malformations, we considered an external reference group of 206,224 infants born at Brigham and Women's Hospital in Boston and captured by a surveillance system that used the same inclusion/exclusion criteria for outcome definition, but followed infants only up to 5 days after birth.[10] For analyses using this reference, malformations identified in the Registry after 5 days of life had to be excluded.

**Analysis.** We evaluated the sociodemographic and clinical characteristics of women exposed to specific drugs. The risk of major congenital malformations in each exposed group was compared with the risk in the internal reference groups. We estimated both crude and adjusted relative risks (RRs) and their 95% confidence intervals (CIs) using multivariate logistic regression. Potential confounders considered included maternal age, race, education, alcohol use, cigarette smoking, periconceptional folic acid supplementation, illicit drug use, chronic diseases (e.g., insulin-dependent diabetes), and calendar year. We added one potential confounder at a time to each model; because RR estimates remained similar, we present the crude RRs as the main analysis. Within women with epilepsy, we compared the risk of seizures during pregnancy among AED-exposed groups.

We conducted a number of sensitivity analyses. To assess the role of indication, we restricted the comparisons to women with epilepsy. To assess the impact of gestational time at enrollment, we restricted the analysis to pure prospective subjects. To assess the accuracy of maternal AED report, we repeated the analyses using only AED use information from medical records.

**Standard protocol approvals, registrations, and patient consents.** Informed consent is obtained verbally at enrollment. The study has been approved annually by the Human Studies Committee of the Massachusetts General Hospital and Partners HealthCare.

**RESULTS** From February 1, 1997, through June 1, 2011, a total of 7,370 AED-exposed and 479 AED-unexposed women (internal comparison group) were enrolled. Of 5,667 women taking an AED as mono-

Table 2 Risk of major malformations identified among infants who had been exposed to a specific AED in monotherapy during the first trimester and among the internal comparison group of unexposed infants and relative risk of major malformations compared withto both unexposed and lamotrigine groups: North America AED Pregnancy Registry 1997–2011

| | Unexposed (n = 442)[b] | Lamotrigine (n = 1,562) | Carbamazepine (n = 1,033) | Phenytoin (n = 416) | Levetiracetam (n = 450) | Topiramate (n = 359) | Valproate (n = 323) | Phenobarbital (n = 199) | Oxcarbazepine (n = 182) | Gabapentin (n = 145) | Zonisamide (n = 90) | Clonazepam (n = 64) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Major congenital malformations[a] | | | | | | | | | | | | |
| No. (%) | 5 (1.1) | 31 (2.0) | 31 (3.0) | 12 (2.9) | 11 (2.4) | 15 (4.2) | 30 (9.3) | 11 (5.5) | 4 (2.2) | 1 (0.7) | 0 (0) | 2 (3.1) |
| 95% CI | (0.37–2.6) | (1.4–2.8) | (2.1–4.2) | (1.5–5.0) | (1.2–4.3) | (2.4–6.8) | (6.4–13.0) | (2.8–9.7) | (0.6–5.5) | (0.02–3.8) | (0.0–3.3) | (0.4–10.8) |
| Unexposed reference | | | | | | | | | | | | |
| Relative risk | Reference | 1.8 | 2.7 | 2.6 | 2.2 | 3.8 | 9.0 | 5.1 | 2.0 | 0.6 | NA | 2.8 |
| 95% CI | | (0.7–4.6) | (1.0–7.0) | (0.9–7.4) | (0.8–6.4) | (1.4–10.6) | (3.4–23.3) | (1.8–14.9) | (0.5–7.4) | (0.07–5.2) | | (0.5–14.8) |
| Exposed reference | | | | | | | | | | | | |
| Relative risk | | Reference | 1.5 | 1.5 | 1.2 | 2.2 | 5.1 | 2.9 | 1.1 | 0.3 | NA | 1.6 |
| 95% CI | | | (0.9–2.5) | (0.7–2.9) | (0.6–2.8) | (1.2–4.0) | (3.0–8.5) | (1.4–5.8) | (0.4–3.2) | (0.05–2.5) | | (0.4–6.8) |
| Exposed reference restricted to pure prospective participants | | | | | | | | | | | | |
| Relative risk | | Reference | 1.1 | 1.4 | 0.8 | 2.6 | 4.2 | 2.5 | 1.5 | 0.5 | NA | 1.3 |
| 95% CI | | | (0.6–2.2) | (0.6–3.4) | (0.3–2.1) | (1.2–5.2) | (2.1–8.3) | (0.9–6.8) | (0.5–4.6) | (0.07–4.1) | | (0.2–10.1) |

Abbreviations: AED = antiepileptic drug; CI = confidence interval.
[a] Diagnosed during pregnancy or before 12 weeks after birth. Confirmed by review of medical records.
[b] The unexposed internal comparison group were pregnant women not taking an AED, who were recruited from among the friends and family members of the enrolled women taking an AED.

therapy during the first trimester, 4,899 were eligible for analysis (figure e-1 on the *Neurology*® Web site at www.neurology.org). From the unexposed internal comparison group, 442 subjects were eligible for analysis.

In 2011, the most commonly reported AED monotherapies during the first trimester were lamotrigine, levetiracetam, and topiramate (figure e-2). AEDs were used for epilepsy (92%), mood disorders (6%), migraine (1%), and other conditions. Of note, the AED pregnancy registry does not reflect the indications in the general population because it targets women with epilepsy. Demographic characteristics are presented in table 1.

**Major malformations.** Compared with lamotrigine, the RR of major malformations was 1.2 (95% CI 0.6–2.5) for levetiracetam and 2.2 (1.2–4.0) for topiramate (table 2). Neither restriction to pure prospective enrollees, nor adjustment for potential confounders, nor restriction to women with epilepsy, nor use of AED information from medical records (data not shown) changed the results significantly. For example, compared with lamotrigine, the RR for topiramate was 2.5 (1.2–5.2) after restriction to pure prospective enrollees, 2.2 (1.2–4.2) after adjustment for potential confounders, 2.4 (1.2–4.6) after restriction to nonsmokers, 3.1 (1.6–5.9) after restriction to women with epilepsy, and 2.2 (1.2–4.1) based on AED information from medical records. Compared with the unexposed reference group, the RR of major malformations was 2.2 (0.8–6.4) for levetiracetam and 3.8 (1.4–10.6) for topiramate.

**Dose.** The risk of major malformations increased with valproate dose (figure 1); the median average daily dose during the first trimester was 1,000 mg for pregnancies with malformations and 750 mg for those without malformations. There was no apparent dose trend for other AEDs; the median average dose was identical for malformed and nonmalformed infants exposed to phenobarbital (120 mg), topiramate (200 mg), or lamotrigine (300 mg).

**Seizures.** The proportion of women with epilepsy who reported seizures during pregnancy varied among AEDs (table 1). AED groups with a higher frequency of seizures tended to have a lower risk of major malformations (figure 2). Exclusively within valproate and phenobarbital users, women without seizures during pregnancy had a numerically higher risk of malformations (10.6% and 6.3%, respectively) than women with seizures (7.3% and 2.5%), and such a difference was not explained by AED dose. However, these analyses were based on small numbers and should be considered exploratory.

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Table 1 Characteristics of the study subjects either unexposed or exposed to AEDs in monotherapy during the first trimester: North America AED Pregnancy Registry 1997–2011

| Categories[a] | Unexposed (n = 442)[b] | Lamotrigine (n = 1,562) | Carbamazepine (n = 1,033) | Levetiracetam (n = 450) | Phenytoin (n = 416) | Topiramate (n = 359) | Valproate (n = 323) | Phenobarbital (n = 199) | Oxcarbazepine (n = 182) | Gabapentin (n = 145) | Zonisamide (n = 90) | Clonazepam (n = 64) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Maternal age, y, mean (SD) | 31.5 (4.2) | 30.24 (5.0) | 29.9 (5.5) | 29.6 (5.1) | 29.8 (5.3) | 28.81 (5.5) | 28.6 (6.0) | 31.1 (5.2) | 30.4 (5.5) | 31.12 (5.4) | 27.4 (5.5) | 33.4 (4.4) |
| Mother's education, n (%) | | | | | | | | | | | | |
| < Grade 12 | 17 (3.9) | 181 (12.6) | 81 (16.1) | 73 (16.3) | 30 (13.4) | 98 (28.7) | 37 (23.1) | 7 (8.2) | 21 (11.6) | 17 (20.5) | 19 (21.1) | 0 (0.0) |
| Junior college graduate (2-y) | 59 (13.4) | 284 (19.7) | 109 (21.7) | 100 (22.3) | 46 (28.2) | 98 (28.7) | 46 (28.8) | 20 (23.5) | 50 (27.6) | 18 (21.7) | 22 (24.4) | 9 (24.3) |
| College graduate (4-y) | 177 (40.2) | 582 (40.4) | 193 (38.5) | 170 (37.9) | 56 (34.4) | 99 (29.0) | 50 (31.3) | 32 (37.7) | 67 (37.0) | 23 (27.7) | 32 (35.6) | 16 (43.2) |
| Postcollege | 187 (42.5) | 393 (27.3) | 119 (23.7) | 106 (23.6) | 31 (19.0) | 47 (13.7) | 27 (16.9) | 26 (30.6) | 43 (23.8) | 25 (30.1) | 17 (18.9) | 12 (32.4) |
| Married, n (%) | 417 (94.8) | 1,289 (89.5) | 414 (83.1) | 375 (83.9) | 133 (81.6) | 252 (73.9) | 108 (67.9) | 78 (92.9) | 155 (85.2) | 69 (83.1) | 64 (71.1) | 27 (73.0) |
| Mother Caucasian, n (%) | 401 (90.9) | 1,381 (88.4) | 903 (87.4) | 377 (83.8) | 344 (82.7) | 325 (90.5) | 277 (85.8) | 176 (88.4) | 155 (85.2) | 136 (93.8) | 76 (84.4) | 60 (93.8) |
| Father Caucasian, n (%) | 394 (89.3) | 1,330 (85.3) | 882 (85.6) | 366 (81.5) | 336 (80.5) | 295 (82.2) | 258 (80.1) | 171 (85.9) | 149 (81.9) | 124 (85.5) | 68 (75.6) | 59 (92.2) |
| Primiparity, n (%) | 146 (33.0) | 663 (42.5) | 374 (36.2) | 180 (40.0) | 135 (32.5) | 151 (42.0) | 124 (38.4) | 51 (25.6) | 81 (44.5) | 55 (37.9) | 50 (55.6) | 25 (39.1) |
| Folic acid supplement at LMP, n (%) | 305 (69.0) | 1,229 (78.7) | 684 (66.2) | 358 (79.6) | 232 (55.8) | 216 (60.2) | 209 (64.7) | 126 (63.3) | 142 (78.0) | 82 (56.6) | 57 (63.3) | 27 (42.2) |
| Cigarette smoking, n (%) | | | | | | | | | | | | |
| None | 414 (93.9) | 1,422 (91.2) | 904 (87.8) | 403 (89.6) | 352 (85.0) | 297 (82.7) | 240 (74.3) | 174 (87.4) | 168 (92.8) | 114 (78.6) | 78 (88.6) | 47 (73.4) |
| > None, <[1/2] pack | 16 (3.6) | 57 (3.7) | 48 (4.7) | 26 (5.8) | 19 (4.6) | 20 (5.6) | 35 (10.8) | 10 (5.0) | 5 (2.8) | 7 (4.8) | 4 (4.6) | 5 (7.8) |
| >[1/2] pack, <1 pack | 6 (1.4) | 37 (2.4) | 27 (2.6) | 13 (2.9) | 16 (3.9) | 22 (6.1) | 20 (6.2) | 5 (2.5) | 5 (2.8) | 12 (8.3) | 4 (4.6) | 5 (7.8) |
| >1 pack | 3 (0.7) | 34 (2.2) | 41 (4.0) | 7 (1.6) | 24 (5.8) | 15 (4.2) | 22 (6.8) | 10 (5.0) | 2 (1.1) | 10 (6.9) | 2 (2.3) | 6 (9.4) |
| Yes, but unknown | 2 (0.5) | 9 (0.6) | 10 (1.0) | 1 (0.2) | 3 (0.7) | 5 (1.4) | 6 (1.9) | 0 (0.0) | 1 (0.6) | 2 (1.4) | 0 (0.0) | 1 (1.6) |
| Alcohol, n (%) | | | | | | | | | | | | |
| None | 308 (70.0) | 1,186 (76.2) | 726 (70.4) | 347 (77.1) | 299 (72.2) | 283 (79.1) | 222 (68.7) | 132 (67.0) | 147 (80.8) | 102 (70.3) | 75 (83.3) | 39 (60.9) |
| Moderate (1–5 drinks/wk) | 103 (24.4) | 323 (20.8) | 265 (25.7) | 80 (17.8) | 99 (23.9) | 62 (17.3) | 81 (25.1) | 58 (29.4) | 29 (15.9) | 38 (26.2) | 13 (14.4) | 23 (35.9) |
| >5 drinks/wk | 20 (4.6) | 24 (1.5) | 17 (1.7) | 16 (3.6) | 3 (0.7) | 7 (2.0) | 8 (2.5) | 4 (2.0) | 3 (1.7) | 1 (0.7) | 1 (1.1) | 1 (1.6) |
| Yes, but unknown | 9 (2.1) | 23 (1.5) | 23 (2.2) | 7 (1.6) | 13 (3.1) | 6 (1.7) | 12 (3.7) | 3 (1.5) | 3 (1.7) | 4 (2.8) | 1 (1.1) | 1 (1.6) |
| Indication epilepsy, n (%) | NA | 1,366 (87.5) | 1,021 (98.8) | 447 (99.3) | 416 (100) | 302 (84.1) | 296 (91.6) | 198 (99.5) | 179 (98.4) | 105 (72.4) | 89 (98.9) | 19 (29.7) |
| Age first seizure, y, mean (SD)[c] | NA | 17.9 (8.5) | 16.6 (8.7) | 18.1 (8.7) | 18.2 (8.6) | 17.09 (8.6) | 13.3 (6.3) | 14.7 (8.2) | 18.8 (9.1) | 19.1 (10.0) | 13.4 (8.0) | 12.4 (6.6) |
| Seizures during pregnancy, n (%)[c] | NA | 424 (31.0) | 283 (27.7) | 138 (30.9) | 113 (27.2) | 100 (33.1) | 69 (23.3) | 40 (20.2) | 78 (43.6) | 47 (44.8) | 21 (23.6) | 5 (26.3) |

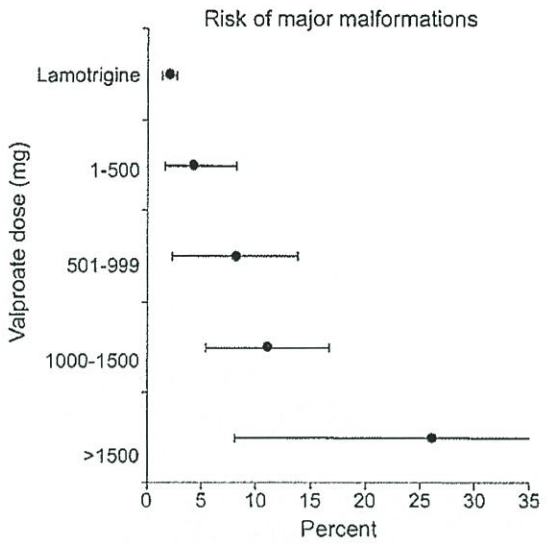
Abbreviations: AED = antiepileptic drug; LMP = last menstrual period.

[a] Numbers in columns might not add to the total because of missing values.

[b] The unexposed internal comparison group were pregnant women, not taking an AED, who were recruited from among the friends and family members of the enrolled women taking an AED.

[c] Among subjects with epilepsy.

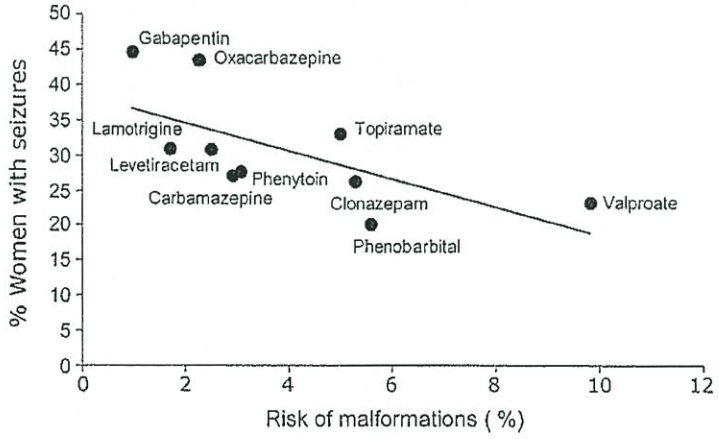
Figure 1 Risk of major malformations by average valproate dose (mg) during the first trimester




North American AED Pregnancy Registry 1997–2011.

**Specific malformations.** The frequency of specific malformations for each AED is described in tables 3 and e-1. In a comparison of the lower bound of the risk estimates with the risk in the external reference population,[10] valproate was associated with an increased risk of neural tube defects, hypospadias, and cardiovascular malformations, and phenobarbital was associated with a higher risk of cardiovascular malformations. The risk of oral clefts was higher among infants exposed to phenobarbital, valproate, and topiramate. Among the topiramate-exposed infants, there were 5 infants with cleft lip.

Figure 2 Risk of major malformations by proportion of women having at least one seizure during their pregnancy within each antiepileptic drug group among women with epilepsy




North American AED Pregnancy Registry 1997–2011.

**DISCUSSION** The risk of major malformations overall associated with first-trimester exposure to specific AEDs ranged from 9.3% for valproate to 2.0% for lamotrigine. The risk of oral clefts was more than 10 per 1,000 for infants exposed to phenobarbital, valproate, and topiramate users, which is higher than expected based on any reference population (approximately 1 per 1,000 births).[10]

The teratogenicity of valproic acid is well established.[11] Although the risk of malformations has been shown to be dose dependent,[12–14] low doses (<1,000 mg) seem to be associated with an increased risk.[15] It is widely accepted that first-trimester exposure to valproic acid increases the risk of neural tube defects from approximately 1 per 1,000 to 10 per 1,000 births.[1,12,13,16,17] Some studies have also suggested an association with hypospadias,[1,13,14,16,17] oral clefts,[1,13,16] cardiac septal defects,[1,14,16,17] and limb defects.[1,17] Our findings are consistent with these literature reports. Moreover, prenatal exposure to valproic acid has been associated with neurodevelopmental delay and autism.[18] Despite the overwhelming evidence for fetal toxicity, valproic acid is still prescribed to pregnant women because it is an effective drug in the treatment of idiopathic generalized epilepsy and, specifically, juvenile myoclonic epilepsy.

Previous studies had suggested that other traditional AEDs may increase the risk of malformations 2–3 times. Phenobarbital has been associated with oral clefts and cardiovascular and urogenital defects.[19] Although less common, oral clefts, cardiovascular defects, and urogenital defects have also been reported after phenytoin therapy.[20,21] Exposure to carbamazepine during pregnancy has been associated with cleft palate,[22] neural tube defects,[20,22,23] hypospadias, and cardiovascular defects.[22]

The use of lamotrigine, topiramate, and levetiracetam has increased in the last decade and, therefore, assessing their safety is critical.[6] Studies consistently show a lower risk of malformations overall for lamotrigine than for traditional AEDs,[6,24] and in most studies the risk does not increase with dose.[6,13,25,26] We published a risk of oral clefts of 7.3 per 1,000 among users of lamotrigine monotherapy.[8] With a larger sample size, the estimate is now 4.5 per 1,000 (95% CI 2.0–8.8). Other studies have reported lower risks of oral clefts after first-trimester lamotrigine exposure: 1–2.5 per 1,000.[6,13,26]

For topiramate, based on 359 women exposed in monotherapy during the first trimester, we found a risk of cleft lip of 14 per 1,000. The lower bound of the 95% CI was 5.1 per 1,000, which is still higher than the expected risk in the population. Another registry from the United Kingdom has reported a risk of oral clefts of 29 (95% CI 5–91)[27] per 1,000

Table 3 Prevalence of most common specific malformations diagnosed before 5 days of age among infants exposed to the AED monotherapies most commonly reported in the North America AED Pregnancy Registry 1997–2011 and among an external reference population from Brigham and Women's Hospital in Boston

| Major congenital anomaly[a] | Lamotrigine (n = 1,562) | Carbamazepine (n = 1,033) | Phenytoin (n = 416) | Levetiracetam (n = 450) | Topiramate (n = 359) | Valproate (n = 323) | Phenobarbital (n = 199) | External reference, %[b] |
|---|---|---|---|---|---|---|---|---|
| Hypospadias[c] | | | | | | | | |
| No. (%) | 0 | 1 (0.19) | 0 | 0 | 2 (1.1) | 5 (3.1) | 1 (0.97) | 0.04 |
| 95% CI | | (0.01–0.93) | | | (0.19–3.6) | (1.1–6.7) | (0.05–4.7) | |
| Neural tube defects | | | | | | | | |
| No. (%) | 2 (0.13) | 3 (0.29) | 0 | 1 (0.22) | 0 | 4 (1.2) | 0 | 0.12 |
| 95% CI | (0.02–0.42) | (0.07–0.79) | | (0.01–1.1) | | (0.39–3.0) | | |
| Cardiovascular anomalies | | | | | | | | |
| No. (%) | 3 (0.19) | 3 (0.29) | 4 (0.96) | 1 (0.22) | 1 (0.28) | 8 (2.5) | 5 (2.8) | 0.33 |
| 95% CI | (0.05–0.52) | (0.07–0.79) | (0.31–2.4) | (0.01–1.1) | (0.01–1.4) | (0.12–4.6) | (0.93–5.5) | |
| Oral clefts | | | | | | | | |
| No. (%) | 7 (0.45) | 5 (0.48) | 2 (0.48) | 0 | 5 (1.4) | 4 (1.2) | 4 (2.0) | 0.11 |
| 95% CI | (0.20–0.88) | (0.18–1.1) | (0.08–1.6) | | (0.51–3.1) | (0.39–3.0) | (0.64–4.8) | |

Abbreviations: AED = antiepileptic drug; CI = confidence interval.
[a] Restricted for malformations diagnosed before 5 days of age, including elective terminations, to be comparable with the external reference population. Confirmed by review of medical records. Some infants had more than one defect.
[b] Prevalence among 206,224 births, including stillbirths and elective terminations surveyed for anomalies at Brigham and Women's Hospital in Boston.
[c] Excludes mild glandular hypospadias. Restricted to male infants.



among 70 topiramate monotherapy users, more than 10 times their background risk. A recent study from Denmark has reported 1 case among 108 women exposed during the first trimester, corresponding to a risk of 9.3 cases (95% CI 0.5–45) per 1,000 compared with 1.7 per 1,000 in their unexposed population.[6]

For levetiracetam, one study found no malformed infants among 39 exposed prenatally to monotherapy,[28] and another reported no malformed infants among 58 exposed during the first trimester.[6] In the current study, the risk of major malformations in 450 infants exposed during the first trimester to levetiracetam monotherapy was 2.4% (95% CI 1.2–4.3%).

A few studies have evaluated the teratogenicity of oxcarbazepine; the numbers of malformations after pregnancy exposure were 1 in 55,[29] 2 in 37,[24] 3 in 130,[30] and 11 in 393,[6] each study having too small a sample to assess the risk for specific malformations. The risk associated with oxcarbazepine monotherapy in the current study was 2.2% (95% CI 0.6–5.5%). Likewise, the risk estimates of major congenital malformations for gabapentin and zonisamide had very wide confidence intervals and, therefore, were uninformative.

The evaluation of the teratogenic effects of AEDs is complicated by the fact that epilepsy itself could potentially increase the risk of birth defects.[31] However, several lines of evidence suggest drug effects: the type of epilepsy and the number of seizures during pregnancy do not appear to affect the risk of malformations.[25,32–35] In addition, the risk of malformations is higher in the offspring of women taking AEDs than in those with untreated epilepsy during pregnancy,[3,32,33] and women with a history of epilepsy but taking no AED do not have an increased risk of having children with major malformations.[36] However, the latter observations might also reflect an effect of disease severity, because epilepsy can seldom remain untreated, and untreated women might not be comparable to women taking AEDs. Comparative safety research methods minimize this bias by comparing different AEDs among women with epilepsy.

In addition to the lamotrigine-exposed reference group, we used 2 unexposed comparison groups, one external and the other internal. It was reassuring to see that there was no qualitative difference in the main conclusions from either of these comparisons. Results were also similar when restricting the sample to pure prospective enrollees, when using evidence of AED prescriptions in medical records, when adjusting for potential confounders, or when restricting the sample to women with epilepsy. The limited role of confounding in the assessment of AED teratogenicity had been reported previously.[6,13,30,37]

More than 70% of the enrolled mothers provided medical records release forms. Medical records were received from the neurologist or psychiatrist who prescribed the AED for 65% of the mothers and from the pediatrician for 59% of the infants. In a

validation study, there was a 99% agreement between the mother's verbal report and the doctors' records for the infants whose mothers had provided permission.[8] However, the sensitivity of maternal report might be lower for women who did not provide permission. The low risk of malformations in this study, relative to that in other reports, is probably due to the strict outcome inclusion criteria.[9] In addition, registries rely on volunteers to participate; this population might have a lower risk of malformations. We can only assume that the teratogenic effects of AEDs would be similar in the population of exposed pregnant women from whom the sample was drawn.

In exploratory analyses, AEDs associated with the largest risk of major malformations in the fetus were also associated with the lowest risk of seizures in the mother. Other studies had suggested a higher frequency of seizures during pregnancy in lamotrigine users than in valproate users.[38] In the absence of randomization, the differences in effectiveness observed among the drugs may be due to the underlying indication. Clinicians might continue valproate or phenobarbital treatment for women of childbearing age when their epilepsy is well controlled and they are reluctant to switch drugs and risk seizure recurrence. Conversely, newer AEDs could have been prescribed to patients whose epilepsy was not responding to traditional drugs. Another important factor is the pharmacokinetic changes during pregnancy due to increased clearance, which may be particularly pronounced for specific AEDs and can increase the risk of seizures. Whatever the explanation might be, it is intriguing that less effective seizure control during pregnancy seemed safer for fetal development.

Most traditional AEDs have been associated with relatively specific defects (i.e., oral clefts, neural tube defects, cardiac defects, and urogenital defects) to different degrees. Whether lamotrigine and topiramate also increase the risk of oral clefts is still under investigation. The etiology of all of these malformations might involve alterations in the fusion of embryonic folds. Embryonic cell adhesion involves cellular communication processes that might share mechanisms with neuronal signaling.[39] Neurotransmitters that participate in embryologic cell-cell interactions may be later involved in synaptic transmission.[40] Because AEDs affect neuronal transmissions through various means, one could speculate that more successful inhibition of neurotransmission might lead to both better seizure control in the mother and stronger alteration of cell-cell adhesion processes in the embryo. This hypothesis would be compatible with the lower risk of seizures during pregnancy found for those AED groups associated with a higher risk of malformations.

Because women with epilepsy often need to continue their AEDs during pregnancy for seizure control, we need to know which AEDs are safer for the mother and the fetus. Overall, traditional AEDs such as valproate and phenobarbital were associated with a higher risk of major malformations in the fetus than newer AEDs like lamotrigine and levetiracetam. The observed association of topiramate with an increased risk of cleft lip was based on small numbers and would need to be confirmed by others.

## AUTHOR CONTRIBUTIONS

The authors had substantial contributions to the intellectual content of the paper. Dr. Holmes was responsible for the conception and design of the study and for obtaining funding. Dr. Hernández-Díaz was responsible for the analysis of the data and, together with Dr. Holmes, for the interpretation of data and drafting of the manuscript. C.R. Smith and A. Shen participated in the acquisition of data and provided administrative support. Dr. Mittendorf, Dr. Hauser, and Dr. Yerby supervised the study and provided critical revisions of the manuscript.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## DISCLOSURE

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[redacted]

To: [redacted]
cc:
bcc:

28/02/2017 03:39 p.m. Subject: sodium valproate - pregnancy [SEC=UNCLASSIFIED]

Hi Susan

As per our pregnancy database (https://www.tga.gov.au/prescribing-medicines-pregnancy-database ), sodium valproate is Category D and the additional information is as follows:

"If taken in the first trimester of pregnancy, sodium valproate (valproic acid) is associated with a one to two percent risk of neural tube defects (especially spina bifida) in the exposed fetus. Women taking sodium valproate (valproic acid) who become pregnant should be encouraged to consider detailed mid-trimester morphology ultrasound for prenatal diagnosis of such abnormalities. The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and fetus of uncontrolled epilepsy. It is recommended that: women on antiepileptic drugs (AEDs) receive prepregnancy counselling with regard to the risk of fetal abnormalities; AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication; folic acid supplementation (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception; Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered."

Even though the PI says that it is contraindicated in pregnancy, it also refers to read all the info under Precautions – which is 2 pages of risk/benefits and the above paragraph from the pregnancy database. (So technically, it is not an absolute contraindication provided the prescriber informs the patient all the risks/benefits etc...)

All the info in the PI had been evaluated by the tox and clinical sections of the pre-market and considered by the (then) ADEC (Adverse Drug Evaluations Committee) and ADRAC (Adverse Drug Reactions Committee) in the early 1990s with subsequent updates when new info were available.

Hope this helps.

Cheers

[redacted]

**Therapeutic Goods Administration**
Department of Health

[redacted]

02/03/2017 12:29 p.m.

To: [redacted]
cc: [redacted]
bcc:

Subject: RE: Valproate and pregnancy

That's great, thanks Rowan,
We will wait to hear more in due course.

[redacted]

**From:** [redacted]
**Sent:** 01 March 2017 21:28
**To:** [redacted]
**Cc:** [redacted]
**Subject:** RE: Valproate and pregnancy

Hi [redacted]

The information is collected here at the Ministry of Health through national collections, so will be requesting internally rather than from PHARMAC.
I'll request from 2012 to 2016 inclusive and will get those 5 year increments as it may give some indication if it is older or younger women who are being prescribed valproate.

Kind regards
Rowan

**Rowan Pollock** | Manager | Clinical Risk Management | Medsafe | Ministry of Health | [redacted]



From: [redacted]
To:
Cc: [redacted]
Date: 02/03/2017 10:18 a.m.
Subject: RE: Valproate and pregnancy

Hi Rowan
Thanks for your reply and for your agreement to look at NZ dispensing data for valproate – will you request this from Pharmac? ( For Sarah's information, Pharmac data is for all funded scripts in NZ and this will cover the vast majority of valproate scripts as this medicine has been funded for some years).

I agree that looking at dispensings over the last 5 years may help us see any impact of the pregnancy contraindication. Perhaps we should look at 2 years prior to 2014 and 2 years after 2014 (as we are not far into 2017 yet) so 2012-2016 inclusive which is five complete years?

It's probably sufficient (and simpler) to just request data for adult women age 16-55 (exclude children and the elderly) because we are only interested in how this regulatory action may have affected prescriptions to women of reproductive age. Breaking these data down into 5 year increments may help, but it's not essential.

(I'm happy if you want to copy me into emails making the data request as I have some experience of analysing prescription data and could perhaps help answer any questions from their side).

If you have any other suggestions as to how we might assess the impact of the valproate contraindication in NZ, please let me know. Did Medsafe consult with specialists/professional bodies in 2014? Was there any feedback to Medsafe after the action?

Thanks for your help with this interesting issue,
[redacted]

**From:** [redacted]
**Sent:** 01 March 2017 20:28
**To:** [redacted]
**Subject:** Fw: Valproate and pregnancy

Hi [redacted]

Chris forwarded this to me to respond.
I will request dispensing data, which will give an idea of numbers of prescriptions for valproate.

This is what I suggest, but please let me know if you'd like any amendments.
Monthly dispensing numbers for valproate over the last 5 years for women in 5 year increments (eg, 15-19 years, 20-24 years etc.)
It may take up to 7-10 days to receive this information. It comes in an excel spreadsheet so it can be reviewed for any trends.

Let me know if this is what you're after.

Kind regards
Rowan

**Rowan Pollock** | Manager | Clinical Risk Management | Medsafe | Ministry of Health | [redacted]
MEDSAFE [redacted]

----- Forwarded by Chris James/MOH on 02/03/2017 08:55 a.m. -----

From: [redacted]
To: [redacted]
Date: 01/03/2017 06:06 p.m.
Subject: RE: Valproate and pregnancy

Thank Chris – I appreciate it. I had another thought, that maybe we could request Pharmhouse data to get an idea of exposure in NZ women of reproductive age, but we'll wait to hear from Rowan first.

I'm glad to see you are still a member of ISoP – are you planning to go to Liverpool in October? Hope to see you there!

Now that I'm ISoP Secretary General, I've handed over the leadership of the Western Pacific Chapter to [redacted] so you may hear from him soon regarding whether there may be anyone else at Medsafe who would like to join ISoP (maybe Gendy or other assessors?). We are hoping to develop the WPC during this next year and are even discussing the prospect of a chapter meeting in our region in early 2018. Do let me know if you would like to be involved.

All the best,
[redacted]

**From:** [redacted]
**Sent:** 28 February 2017 22:42
**To:** [redacted]
**Cc:** [redacted]
**Subject:** Re: Valproate and pregnancy

Hi [redacted]

Thanks for the email. Happy to help. I've asked Rowan Pollock (Manager Clinical Risk) to provide some information.

This is an issue we are working on with ACC, experts in this areas, and consumer groups also.

Chris

Chris James | Group Manager | Medsafe | Ministry of Health | [redacted]

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A business unit of the Ministry of Health

[redacted]

From: [redacted]
To: [redacted]
Cc: [redacted]
Date: 01/03/2017 11:07 a.m.
Subject: Valproate and pregnancy

Hi Chris,

My colleague [redacted] at MHRA has asked if I can help find out more about issues relating to the use of sodium valproate in pregnancy in New Zealand.

We note that in 2014 Medsafe issued a notification http://www.medsafe.govt.nz/profs/PUArticles/December2014SodiumValproate.htm to contraindicate in pregnancy for all indications and we also note in the Australian SmPCs (PIs) pregnancy is a contraindication – all indications.

Can you advise how we could find out more about what impact the contraindication has had in NZ? Would Medsafe or any other body have conducted an impact assessment? Or perhaps you could advise if Medsafe received any correspondence from specialists or GPs (or women themselves) following the 2014 contraindication?

I discussed the issues with my husband [redacted]. He thinks that few women aged 18-50 are now prescribed sodium valproate (he is trying to get us some data from his practice to support this) and that women of reproductive age with epilepsy will usually be prescribed other medicines. So his view from a primary care perspective is that the contraindication in NZ has not really affected clinical practice. He will discuss further with his colleagues, but perhaps we also need to ask specialists who manage pregnant women with epilepsy – can you recommend anyone? Perhaps you consulted with experts in 2014 prior to the contraindication?

Many thanks for your help,

[redacted]

[redacted]

24/03/2017 01:23 p.m.

To: "EMA International" [redacted]
cc:
bcc:

Subject: Response re: EMA Request for Information: Sodium valproate use in pregnancy

Dear [redacted]

Please find attached the response to the EMA Request for Information: Sodium valproate use in pregnancy.

Response EMA request for information - sodium valproate use in pregnancy.pdf

Kind regards,
Chris

**Chris James** | Group Manager | Medsafe | Ministry of Health | [redacted]

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A BUSINESS UNIT OF THE MINISTRY OF HEALTH

133 Molesworth Street
PO Box 5013
Wellington 6145, New Zealand
T +64 4 496 2000

24 March 2017

[redacted]
European Medicines Agency
[redacted]

Dear [redacted]

**Re: EMA Request for Information: Sodium valproate use in pregnancy**

Thank you for your email of 15 March 2017 seeking further information about the pregnancy contraindication for sodium valproate.

**Addition of contraindication**

Legislation controlling medicines was first introduced in 1962. The earliest sodium valproate-containing product (Epilim) was approved in New Zealand in October 1977. Currently, Epilim is the main approved brand of sodium valproate. An additional solution for injection dose form is also approved, but is not funded. There are two different Epilim data sheets available (New Zealand equivalent of the summary of product characteristics). There is one data sheet for the powder for injection dose form and a combined data sheet for the other dosage forms (enteric coated tablets, crushable tablets, syrup and oral solution).

A notification to harmonise the data sheet information with the Australian product information was received by Medsafe in 2005. The contraindication for use in pregnancy was added at this time.

The contraindication was added during a harmonisation of safety information with the Australian product information. TGA-approved product information is an acceptable source document for the preparation of, or updates to, a New Zealand data sheet. The Australian product information already included pregnancy as a contraindication. This update was submitted to Medsafe as a self-assessable change notification (SACN).

Data sheets amended via a SACN are not routinely assessed by Medsafe. Approval is granted on the basis of the sponsor's signed declaration that the data sheet has been prepared in compliance with New Zealand guidelines. The relevant guideline in 2005 was the New Zealand Regulatory Guidelines for Medicines 5th Edition (Section 13). This has now been superseded by the Guideline on the Regulation of Therapeutic Products in New Zealand Part 10: Requirements for information for prescribers and consumers - www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/Part10.pdf

Please note that under section 25 of the Medicines Act 1981, an authorised prescriber may prescribe, administer or arrange for the administration of a medicine for the treatment of a

patient in his or her care. The Medicines Act puts no restriction on the use of a medicine, even in a situation in which it is contraindicated. However, the authorised prescriber must provide care of an adequate professional and ethical standard and ensure the patient is fully informed of the benefits and risks.

## Usage information

The below table provides an overview of the number of sodium valproate prescriptions dispensed in a community pharmacy from 2010 until 2016. Sodium valproate is generally dispensed on a monthly basis, therefore the average number of people taking sodium valproate is an estimate based on the yearly number divided by 12 months.

| Year | Number of Dispensings | Average Number of People |
|---|---|---|
| 2010 | 121808 | 10151 |
| 2011 | 121776 | 10148 |
| 2012 | 120649 | 10054 |
| 2013 | 118614 | 9885 |
| 2014 | 116655 | 9721 |
| 2015 | 115441 | 9620 |
| 2016 | 113290 | 9441 |

It is currently not possible to breakdown usage by indication. However, it is estimated to be approximately 50% for use in epilepsy and 50% for use in bipolar disorder.

The below table shows the number of females under 50 years of age dispensed (in a community pharmacy) sodium valproate by quarter and age group in five year increments from 2014 to 2016.

Number of female clients under 50 years old dispensed Sodium Valproate, by quarter, gender and age group.
Source: MoH Pharms collection extracted March 2017

| Female - only | 2014 | | | | 2015 | | | | 2016 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age group | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| 0 to 4 | 127 | 118 | 127 | 120 | 99 | 89 | 99 | 97 | 87 | 81 | 73 | 73 |
| 5 to 9 | 149 | 149 | 148 | 147 | 130 | 147 | 150 | 142 | 132 | 136 | 140 | 140 |
| 10 to 14 | 193 | 187 | 191 | 205 | 194 | 202 | 180 | 177 | 194 | 184 | 183 | 184 |
| 15 to 19 | 310 | 321 | 323 | 324 | 317 | 313 | 326 | 307 | 287 | 297 | 287 | 288 |
| 20 to 24 | 421 | 407 | 396 | 382 | 392 | 371 | 372 | 382 | 365 | 360 | 385 | 370 |
| 25 to 29 | 457 | 458 | 464 | 450 | 437 | 440 | 435 | 425 | 430 | 404 | 423 | 430 |
| 30 to 34 | 558 | 542 | 551 | 547 | 534 | 535 | 530 | 540 | 515 | 503 | 536 | 533 |
| 35 to 39 | 838 | 826 | 838 | 833 | 799 | 797 | 817 | 788 | 749 | 727 | 742 | 741 |
| 40 to 44 | 918 | 926 | 969 | 982 | 921 | 937 | 940 | 937 | 935 | 966 | 998 | 1,002 |
| 45 to 49 | 163 | 163 | 169 | 149 | 151 | 163 | 169 | 166 | 165 | 171 | 177 | 167 |

The following table shows the percentage of people dispensed sodium valproate that were female, by age group in five year increments for 2014 and 2015.

**Percentage of clients under 50 years old dispensed Sodium Valporate that were female by quarter, gender and age group.**
Source: MoH Pharms collection extracted April 2016

| % Female | 2014 | | | | 2015 | | | |
|---|---|---|---|---|---|---|---|---|
| Age group | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| 0 to 4 | 52% | 50% | 53% | 52% | 51% | 47% | 50% | 53% |
| 5 to 9 | 45% | 42% | 46% | 42% | 44% | 44% | 44% | 45% |
| 10 to 14 | 40% | 38% | 37% | 36% | 36% | 36% | 37% | 35% |
| 15 to 19 | 34% | 35% | 34% | 35% | 35% | 36% | 33% | 32% |
| 20 to 24 | 35% | 36% | 35% | 35% | 36% | 35% | 35% | 34% |
| 25 to 29 | 39% | 38% | 36% | 35% | 36% | 35% | 35% | 36% |
| 30 to 34 | 39% | 40% | 41% | 39% | 40% | 39% | 39% | 38% |
| 35 to 39 | 43% | 41% | 42% | 41% | 42% | 42% | 42% | 43% |
| 40 to 44 | 45% | 45% | 46% | 46% | 46% | 45% | 46% | 45% |
| 45 to 49 | 47% | 47% | 48% | 48% | 47% | 47% | 47% | 47% |

The below tables show the number of live births and pregnancies where mothers were dispensed (in a community pharmacy) sodium valproate during pregnancy, by quarter from 2013 to 2015. The numbers for 2016 are not yet available.

Number of live births to mothers who were dispensed specified anticonvulsants during preganacy, by year and type of drug.
Source Ministry of Health Pharmaceutical and Maternity collections, extracted 30/05/2016

| | 2013Q1 | 2013Q2 | 2013Q3 | 2013Q4 | 2014Q1 | 2014Q2 | 2014Q3 | 2014Q4 | 2015Q1 | 2015Q2 | 2015Q3 | 2015Q4 | Grand Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Valproate | 21 | 19 | 11 | 12 | 13 | 11 | 15 | 13 | 12 | 19 | 13 | 14 | 173 |

Number of pregnancies where the mother was dispensed specified anticonvulsants during pregnancy, by year and type of drug.
Source Ministry of Health Pharmaceutical and Maternity collections, extracted 30/05/2016

| | 2013Q1 | 2013Q2 | 2013Q3 | 2013Q4 | 2014Q1 | 2014Q2 | 2014Q3 | 2014Q4 | 2015Q1 | 2015Q2 | 2015Q3 | 2015Q4 | Grand Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Valproate | 21 | 19 | 10 | 12 | 13 | 12 | 14 | 13 | 13 | 19 | 12 | 14 | 172 |



## Monitoring of sodium valproate

The table above shows that the number of live births and pregnancies in which the mother was dispensed sodium valproate remains relatively low (63 live births in 2013, 51 in 2014 and 58 in 2015; 62 pregnancies in 2013, 52 in 2014 and 58 in 2015). Although the numbers appear steady, given the increase in births each year this represents a relative decrease in numbers. In general, the number of women being dispensed sodium valproate is steady or reducing in each age group.

Medsafe is not specifically monitoring the use of sodium valproate in women of childbearing potential. However, Medsafe regularly informs healthcare professionals and consumers about different medicine related safety issues. Issues that are communicated include emerging safety signals, regulatory action that has taken place or reminders of known adverse reactions.

Due to a number of factors it was determined that further communication was required, hence the *Prescriber Update* article in December 2014 and alert communication in September 2015. The intention of these communications was not to have an immediate

decrease in sodium valproate use, particularly if patients were adequately controlled on this medicine, but to inform healthcare professionals and consumers of the risks and to aid the decision making process.

In addition, the Accident Compensation Corporation (ACC), who provides comprehensive, no-fault personal injury cover for all New Zealanders, is also undertaking a project to educate prescribers and patients about the risks of taking sodium valproate while pregnant. ACC's aim for this project is to prevent further cases of fetal anticonvulsant (antiepileptic) syndrome. The project team includes a number of stakeholders, including a Medsafe representative.

I trust this information is of assistance.

Yours sincerely

Chris James
Group Manager
Medsafe

[redacted]

24/03/2017 01:25 p.m.

To: [redacted]
cc:
bcc:

Subject: Response re: MHRA Request for Information: Sodium valproate use in pregnancy

Dear [redacted]

Please find attached the response to the MHRA Request for Information: Sodium valproate use in pregnancy.

Response MHRA request for information - sodium valproate use in pregnancy.pdf

Kind regards,
Chris

**Chris James** | Group Manager | Medsafe | Ministry of Health | [redacted]

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY

133 Molesworth Street
PO Box 5013
Wellington 6145, New Zealand
T +64 4 496 2000

24 March 2017

[redacted]
Medicines and Healthcare products Regulatory Agency
[redacted]

Dear [redacted]

**Re: MHRA Request for Information: Sodium valproate use in pregnancy**

Thank you for your letter of 6 March 2017 seeking further information about the pregnancy contraindication for sodium valproate.

Please find below the responses to your questions.

1. **What date was the contraindication for use of sodium valproate in pregnancy introduced?**

Legislation controlling medicines was first introduced in 1962. The earliest sodium valproate-containing product (Epilim) was approved in New Zealand in October 1977. Currently, Epilim is the main approved brand of sodium valproate. An additional solution for injection dose form is also approved, but is not funded. There are two different Epilim data sheets available (New Zealand equivalent of the summary of product characteristics). There is one data sheet for the powder for injection dose form and a combined data sheet for the other dosage forms (enteric coated tablets, crushable tablets, syrup and oral solution).

A notification to harmonise the data sheet information with the Australian product information was received by Medsafe in 2005. The contraindication for use in pregnancy was added at this time.

2. **What data formed the basis of the contraindication?**

The contraindication was added during a harmonisation of safety information with the Australian product information. TGA-approved product information is an acceptable source document for the preparation of, or updates to, a New Zealand data sheet. The Australian product information already included pregnancy as a contraindication. This update was submitted to Medsafe as a self-assessable change notification (SACN).

Data sheets amended via a SACN are not routinely assessed by Medsafe. Approval is granted on the basis of the sponsor's signed declaration that the data sheet has been prepared in compliance with New Zealand guidelines. The relevant guideline in 2005 was the New Zealand Regulatory Guidelines for Medicines 5th Edition (Section 13). This has now been superseded by the Guideline on the Regulation of Therapeutic Products in New Zealand Part 10: Requirements for information for prescribers and consumers - www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/Part10.pdf

Please note that under section 25 of the Medicines Act 1981, an authorised prescriber may prescribe, administer or arrange for the administration of a medicine for the treatment of a patient in his or her care. The Medicines Act puts no restriction on the use of a medicine, even in a situation in which it is contraindicated. However, the authorised prescriber must provide care of an adequate professional and ethical standard and ensure the patient is fully informed of the benefits and risks.

3. **What is the level of usage of valproate in New Zealand in the last 3 years:**

The below table provides an overview of the number of sodium valproate prescriptions dispensed in a community pharmacy from 2010 until 2016. Sodium valproate is generally dispensed on a monthly basis, therefore the average number of people taking sodium valproate is an estimate based on the yearly number divided by 12 months.

| Year | Number of Dispensings | Average Number of People |
|---|---|---|
| 2010 | 121808 | 10151 |
| 2011 | 121776 | 10148 |
| 2012 | 120649 | 10054 |
| 2013 | 118614 | 9885 |
| 2014 | 116655 | 9721 |
| 2015 | 115441 | 9620 |
| 2016 | 113290 | 9441 |

a. **Is it possible to breakdown usage by indication?**

It is currently not possible to breakdown usage by indication. However, it is estimated to be approximately 50% for use in epilepsy and 50% for use in bipolar disorder.

b. **Is it possible to provide an estimate of the proportion of women of childbearing potential receiving valproate in that time period?**

The below table shows the number of females under 50 years of age dispensed (in a community pharmacy) sodium valproate by quarter and age group in five year increments from 2014 to 2016.

**Number of female clients under 50 years old dispensed Sodium Valproate, by quarter, gender and age group.**
Source: MoH Pharms collection extracted March 2017

| Female - only | 2014 | | | | 2015 | | | | 2016 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age group | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| 0 to 4 | 127 | 118 | 127 | 120 | 99 | 89 | 99 | 97 | 87 | 81 | 73 | 73 |
| 5 to 9 | 149 | 149 | 148 | 147 | 130 | 147 | 150 | 142 | 132 | 136 | 140 | 140 |
| 10 to 14 | 193 | 187 | 191 | 205 | 194 | 202 | 180 | 177 | 194 | 184 | 183 | 184 |
| 15 to 19 | 310 | 321 | 323 | 324 | 317 | 313 | 326 | 307 | 287 | 297 | 287 | 288 |
| 20 to 24 | 421 | 407 | 396 | 382 | 392 | 371 | 372 | 382 | 365 | 360 | 385 | 370 |
| 25 to 29 | 457 | 458 | 464 | 450 | 437 | 440 | 435 | 425 | 430 | 404 | 423 | 430 |
| 30 to 34 | 558 | 542 | 551 | 547 | 534 | 535 | 530 | 540 | 515 | 503 | 536 | 533 |
| 35 to 39 | 838 | 826 | 838 | 833 | 799 | 797 | 817 | 788 | 749 | 727 | 742 | 741 |
| 40 to 44 | 918 | 926 | 969 | 982 | 921 | 937 | 940 | 937 | 935 | 966 | 998 | 1,002 |
| 45 to 49 | 163 | 163 | 169 | 149 | 151 | 163 | 169 | 166 | 165 | 171 | 177 | 167 |

The following table shows the percentage of people dispensed sodium valproate that were female, by age group in five year increments for 2014 and 2015.

**Percentage of clients under 50 years old dispensed Sodium Valporate that were female by quarter, gender and age group.**
Source: MoH Pharms collection extracted April 2016

| % Female | 2014 | | | | 2015 | | | |
|---|---|---|---|---|---|---|---|---|
| Age group | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| 0 to 4 | 52% | 50% | 53% | 52% | 51% | 47% | 50% | 53% |
| 5 to 9 | 45% | 42% | 46% | 42% | 44% | 44% | 44% | 45% |
| 10 to 14 | 40% | 38% | 37% | 36% | 36% | 36% | 37% | 35% |
| 15 to 19 | 34% | 35% | 34% | 35% | 35% | 36% | 33% | 32% |
| 20 to 24 | 35% | 36% | 35% | 35% | 36% | 35% | 35% | 34% |
| 25 to 29 | 39% | 38% | 36% | 35% | 36% | 35% | 35% | 36% |
| 30 to 34 | 39% | 40% | 41% | 39% | 40% | 39% | 39% | 38% |
| 35 to 39 | 43% | 41% | 42% | 41% | 42% | 42% | 42% | 43% |
| 40 to 44 | 45% | 45% | 46% | 46% | 46% | 45% | 46% | 45% |
| 45 to 49 | 47% | 47% | 48% | 48% | 47% | 47% | 47% | 47% |

c. Is it possible to provide data on the level of prescribing during pregnancy?

The below tables show the number of live births and pregnancies where mothers were dispensed (in a community pharmacy) sodium valproate during pregnancy, by quarter from 2013 to 2015. The numbers for 2016 are not yet available.

Number of live births to mothers who were dispensed specified anticonvulsants during preganacy, by year and type of drug.
Source Ministry of Health Pharmaceutical and Maternity collections, extracted 30/05/2016

| | 2013Q1 | 2013Q2 | 2013Q3 | 2013Q4 | 2014Q1 | 2014Q2 | 2014Q3 | 2014Q4 | 2015Q1 | 2015Q2 | 2015Q3 | 2015Q4 | Grand Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Valproate | 21 | 19 | 11 | 12 | 13 | 11 | 15 | 13 | 12 | 19 | 13 | 14 | 173 |

Number of pregnancies where the mother was dispensed specified anticonvulsants during pregnancy, by year and type of drug.
Source Ministry of Health Pharmaceutical and Maternity collections, extracted 30/05/2016

| | 2013Q1 | 2013Q2 | 2013Q3 | 2013Q4 | 2014Q1 | 2014Q2 | 2014Q3 | 2014Q4 | 2015Q1 | 2015Q2 | 2015Q3 | 2015Q4 | Grand Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Valproate | 21 | 19 | 10 | 12 | 13 | 12 | 14 | 13 | 13 | 19 | 12 | 14 | 172 |

4. Is Medsafe monitoring the use of sodium valproate in women of childbearing potential and if so what impact has the contraindication had on the usage of sodium valproate in women of childbearing potential in New Zealand?

The table above shows that the number of live births and pregnancies in which the mother was dispensed sodium valproate remains relatively low (63 live births in 2013, 51 in 2014 and 58 in 2015; 62 pregnancies in 2013, 52 in 2014 and 58 in 2015). Although the numbers appear steady, given the increase in births each year this represents a relative decrease in numbers. In general, the number of women being dispensed sodium valproate is steady or reducing in each age group.

Medsafe is not specifically monitoring the use of sodium valproate in women of childbearing potential. However, Medsafe regularly informs healthcare professionals and consumers about different medicine related safety issues. Issues that are communicated include emerging safety signals, regulatory action that has taken place or reminders of known adverse reactions.

Due to a number of factors it was determined that further communication was required, hence the *Prescriber Update* article in December 2014 and alert communication in September 2015. The intention of these communications was not to have an immediate decrease in sodium valproate use, particularly if patients were adequately controlled on this medicine, but to inform healthcare professionals and consumers of the risks and to aid the decision making process.

In addition, the Accident Compensation Corporation (ACC), who provides comprehensive, no-fault personal injury cover for all New Zealanders, is also undertaking a project to educate prescribers and patients about the risks of taking sodium valproate while pregnant. ACC's aim for this project is to prevent further cases of fetal anticonvulsant (antiepileptic) syndrome. The project team includes a number of stakeholders, including a Medsafe representative.

I trust this information is of assistance.

Yours sincerely

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Medsafe