[redacted]

15/09/2014 03:21 p.m.

To: [redacted]
cc:
bcc:

Subject: Sunday Star Times Epilan questions

Hello Stewart / Chris.

[redacted] is a freelancer writing about Epilan, and judging by the questions below, also a wider issue of efficacy of current labelling - she's an experienced reporter.

Would you be interested in doing an interview rather than a written response?

Kevin McCarthy
Senior Media Advisor
Media Relations
Communications & HR
Corporate Services
Ministry of Health
[redacted]

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

----- [redacted] on 15/09/2014 03:17 p.m. -----

From: [redacted]
To:
Cc:
Date: 15/09/2014 03:07 p.m.
Subject: SS Times medication questions

Hi Kevin McCarthy

I am writing a feature article for the Sunday Star Times. My deadline is Tues 23 September. I would like to interview someone from Medsafe.

Sodium Valproate - Epilim - is used primarily to treat epilepsy and has also been used for neuropathic pain and mood disorders. It has a risk of birth defects and some children are on ACC after being diagnosed with a syndrome caused by this medication. A number of parents claim they were not fully informed about the high risk of defects it may cause their babies. They also want a warning on every medication pack, as well as potentially a simple and brief patient information sheet inside.

This is different from the current sheet that is detailed and in small print. Some medical specialists agree that more simple warnings would work better than the current system of prescribers warnings. They say research shows only about a third of what they tell patients goes in. And some drs describe the current information in drug packets as 'useless'. They support warnings like the ones on cigarette packets. They don't believe referring patients to MedSafe is working.

Line of questions as follows.

1. Medsafe currently provides patient information about Epilim on its website. Is this enough? Why?

2. When was it last updated and why?

3. Prescribers say they do all they can to warn patients but that more is needed so support a simple info sheet being provided with the medication, and a very blunt warning on packets - like cigarettes. How does Medsafe feel about this?

4. Yes it is the prescribers responsibility to warn patients but it appears not to be working as well as it could. What can Medsafe do to improve this?

5. There is no legislation in NZ saying this needs to happen - but how would Medsafe feel about getting it happening anyway as the emotional and financial cost of looking after these disabled kids is huge?

6. Some parents with children who have birth defects caused by Epilim are also wanting more warnings on packets. What have you got to say to them?

7. There is a claim that hundreds of babies have been born in NZ with defects due to Epilim and that it will continue to rise. How concerning is this for MedSafe?

These are the basic questions. I would like to actually talk to someone.. maybe Stuart Jessamine?

Many thanks

[redacted]

[redacted]

15/09/2014 04:19 p.m.

To: C[redacted]
cc:
bcc:

Subject: Re: Sunday Star Times Epilan questions

Yes please.

It would be good if we could get some sort of feeling for the number of potentially affected children from ACC or CARM.

It would also be good to know what pharmacy labelling is required for this medicine as it is a Class D in pregnancy. I would have thought that each bottle (either dispensed or otherwise would be required to carry a specific pregnancy warning anyway.

Stewart Jessamine
Group Manager
Medsafe
Clinical Leadership
Protection & Regulation
Ministry of Health
[redacted]
http://www.health.govt.nz
[redacted]

Chris James Thanks Kevin. Stewart - irrespectiv... 15/09/2014 03:42:36 p.m.

From: [redacted]
To:
Cc:
Date: 15/09/2014 03:42 p.m.
Subject: Re: Sunday Star Times Epilan questions

Thanks Kevin.

Stewart - irrespective of an interview, would you like us to put together some information in response to the questions. This can then be used either as a written response or as a briefing for you prior to an interview?

Thanks

Chris

Chris James
Manager
Clinical Risk Management
Medsafe
Ministry of Health
[redacted]
http://www.medsafe.govt.nz
[redacted]

Kevin McCarthy Hello Stewart / Chris. [redacted] 15/09/2014 03:21:06 p.m.

[redacted]

16/09/2014 04:25 p.m.

To: [redacted]
cc:
bcc:

Subject: Info for interview/response about Epilim

Hi Stewart

Attached is info put together for either a direct response to the SST or for an interview. As discussed this response requires some background education as well as detailed information to cover off information access vs patients being informed.

Chris

Sunday Star Times Epilim.docx

Chris James
Manager
Clinical Risk Management
Medsafe
Ministry of Health
[redacted]
http://www.medsafe.govt.nz
[redacted]

I am writing a feature article for the Sunday Star Times. My deadline is Tues 23 September. I would like to interview someone from Medsafe.

Sodium Valproate - Epilim - is used primarily to treat epilepsy and has also been used for neuropathic pain and mood disorders. It has a risk of birth defects and some children are on ACC after being diagnosed with a syndrome caused by this medication. A number of parents claim they were not fully informed about the high risk of defects it may cause their babies. They also want a warning on every medication pack, as well as potentially a simple and brief patient information sheet inside.

This is different from the current sheet that is detailed and in small print. Some medical specialists agree that more simple warnings would work better than the current system of prescribers warnings. They say research shows only about a third of what they tell patients goes in. And some drs describe the current information in drug packets as 'useless'. They support warnings like the ones on cigarette packets. They don't believe referring patients to MedSafe is working.

Line of questions as follows.

1. Medsafe currently provides patient information about Epilim on its website. Is this enough? Why?

2. When was it last updated and why?

3. Prescribers say they do all they can to warn patients but that more is needed so support a simple info sheet being provided with the medication, and a very blunt warning on packets - like cigarettes. How does Medsafe feel about this?

4. Yes it is the prescribers responsibility to warn patients but it appears not to be working as well as it could. What can Medsafe do to improve this?

5. There is no legislation in NZ saying this needs to happen - but how would Medsafe feel about getting it happening anyway as the emotional and financial cost of looking after these disabled kids is huge?

6. Some parents with children who have birth defects caused by Epilim are also wanting more warnings on packets. What have you got to say to them?

7. There is a claim that hundreds of babies have been born in NZ with defects due to Epilim and that it will continue to rise. How concerning is this for MedSafe?

These are the basic questions. I would like to actually talk to someone.. maybe Stuart Jessamine?

Medsafe is sorry to hear that babies have been affected by birth defects following exposure to sodium valproate taken by their mothers.

Role of Medsafe

Medsafe is the New Zealand regulator for medicines and medical devices. Medsafe is bound by and administers legislation relevant to the provision of medicines and medical devices in New Zealand.

In addition as part of these activities Medsafe provides advice about the safe use of medicines and medical devices. The responsibility for the medicine/ medical device remains with the manufacturer and/ or New Zealand sponsor.

Medsafe does not regulate the practice of healthcare professionals. This is the responsibility for example of the Medical council and Pharmacy Council. In addition the HQSC work with healthcare professionals patients and consumers to help improve the quality and safety of care.

Medicines Information

Data sheets are mandatory for all prescription and restricted medicines. These are provided by the manufacturer (sponsor) of the medicine and remain their responsibility. Data sheets are published on the Medsafe website as a service, to ensure that they are freely available in New Zealand.

Provision of Consumer Medicine Information is voluntary in New Zealand. These are provided by the manufacturer (sponsor) and are published on the Medsafe website, as a service. The date of the last update of a CMI or data sheet is published on the leaflet at the end of the leaflet. The company provides the CMI and is responsible for its maintenance and will be able to state why they decided to update the leaflet.

This information (CMI) is provided as an addition, not a substitute to the information provided to the patient by their healthcare professionals. The patient's doctor, pharmacist and/or nurse may also use this information to help them explain some of the difficult health concepts relating to the use of various medicines. The leaflet is provided in a ready-to-print format for healthcare professionals to use during their day-to-day practice. It is Medsafe's expectation that healthcare professionals discuss the benefits and risks of all treatments with their patients so that the patient can make an informed decision regarding their treatment. Medsafe publishes information to help healthcare professionals understand these expectations.

http://www.medsafe.govt.nz/profs/RIss/unapp.asp

Medsafe has also published a Prescriber Update on anticonvulsants and congenital malformations http://www.medsafe.govt.nz/profs/PUArticles/Anticonvulsants-Feb09.htm

Provision of information in 'drug packets' is voluntary. Healthcare professionals may make a complaint to Medsafe if they believe the information provided is incorrect.

Additional information on the risks of taking medicines is also available from the New Zealand formulary http://nzf.org.nz/search (this is funded by the Ministry of Health).

Prescribers may produce their own leaflets if they feel that this will help them in their practice. Some DHB's already publish additional information on medicines, some of these leaflets are available through the NZF.

Information on best practice and use of medicines is provided by BPAC which also publishes the Best Practice Journal. BPAC have published information on treating women with epilepsy http://www.bpac.org.nz/BPJ/2009/November/anticonvulsants.aspx

ACC also publish treatment injury case studies to help inform prescribers about the safe use of medicines. A study on foetal valproate syndrome was published in June this year.

Medicines labelling requirements

There are statutory requirements for medicine package labels. However most prescribed medicines are not provided to patients in the original pack, but are dispensed by pharmacists into pharmacy packs with pharmacy labels attached. Medsafe does not regulate dispensing practice or the pharmacy label requirements.

Safety monitoring of medicines

Medsafe monitors the safety of all medicines available in New Zealand through a contract with the Centre for Adverse Reactions Monitoring (CARM). Healthcare professionals and consumers can send a report of any suspected reaction to any medicine to the Centre. CARM then alerts Medsafe to any safety concerns with medicines used in New Zealand. Reporting suspected adverse reactions is the official method of alerting CARM and Medsafe to safety concerns with medicines. If no reports are received it is assumed that there is no safety concern. CARM and Medsafe actively promote the scheme and encourage healthcare professionals and consumers to report. Reports can be made on paper, fax, telephone call, email, GP software, on-line and via an i-phone app.

To date CARM have received 13 reports of foetal valproate syndrome; 7 of these were from ACC, 4 from DHBs, one from a GP and one from the company. This is a very low number of reports considering sodium valproate has been in use since the start of data collection in 1964.

If there are further cases of birth defects due to sodium valproate these should be reported to CARM. In that way Medsafe can review the information and take appropriate action.

Medsafe can also seek advice on medicines safety concerns from the Medicines Adverse Reactions Monitoring Committee (MARC). The MARC have considered the use of sodium valproate in pregnancy on several occasions. The minutes are published on the Medsafe website, for example:

http://www.medsafe.govt.nz/profs/adverse/Minutes149.htm

http://www.medsafe.govt.nz/profs/adverse/Minutes138.htm

http://www.medsafe.govt.nz/profs/adverse/Minutes124.htm#3.1.16

Benefits and Risks of Medicines including Epilim (sodium valproate)

All medicines have benefits and risks. Medsafe approves a medicine for use in New Zealand if the medicine has acceptable benefits, quality and risks; that is if the benefits outweigh the risks.

Medsafe determines the balance of benefits and risks for the population overall, however there may be some people for whom the benefits do not outweigh the risks. Healthcare professionals need to use the information in the data sheet to determine whether the benefits outweigh the risks for their individual patients. For example the use of Epilim is contraindicated in pregnancy, that is the benefits are not considered to outweigh the risks. However the prescriber may disagree with this assessment, for example if all other anti-epileptics have been tried and sodium valproate is the only effective medicine for that woman.

In general it is considered that the benefits of epilepsy treatment for a pregnant women and her fetus outweighs the risk of a congenital abnormality in the infant. A convulsive/tonic clonic seizure during pregnancy risks trauma to the abdomen and hence the baby. Also the temporary interruption of breathing, rarely of any significance to the mother can lead to oxygen deprivation for the fetus. Prolonged or repetitive tonic clonic seizure can seriously impair the supply of oxygen to the fetus.
http://epilepsy.med.nyu.edu/epilepsy/epilesy-and-women/effects-seizure-fetus

The data sheet contains the following recommendation:

...women of child-bearing potential taking sodium valproate should:

- receive counselling with regard to the risk of foetal abnormalities;
- 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;
- undergo routine ultrasound and amniocenteses for specialist prenatal diagnosis of such abnormalities;
- 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.

It is recommended that in bipolar disorders indication, cessation of valproate therapy should be considered.

The CMI contains the following text (part in bold on the first page).

If you are a female patient of child-bearing age, make sure that you talk to your doctor about the risks associated with taking Epilim during pregnancy.

Tell your doctor if you are pregnant or intend to become pregnant.

Like most medicines of this kind, Epilim may affect your developing baby if taken in the first trimester of pregnancy, as it is suspected of causing an increased risk of malformations in the exposed foetus. Also, children born to mothers who take Epilim throughout their pregnancy may be at risk of impaired cognitive development or withdrawal syndrome. However, do not stop taking Epilim unless your doctor says so as there are risks to the mother and child from uncontrolled epilepsy or uncontrolled mania episodes.

Congenital abnormalities

Around 3% or 1 in 33 infants are born with a congenital anomaly for no apparent reason (this is the background rate). WHO states that this means that around 3.2 million infants are born with an abnormality worldwide every year.
http://www.who.int/mediacentre/factsheets/fs370/en/

In general the risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. The contribution to this increase in risk from the use of medicines or the disease itself is unknown.

Fetal Valproate syndrome

http://rarediseases.info.nih.gov/gard/5447/fetal-valproate-syndrome/case/25731/case-questions

Signs and symptoms of fetal valproate syndrome can vary greatly from person to person. There are certain subtle facial features that are more commonly (but not always) associated with this syndrome. These features include thin arched eyebrows that may be spaced far apart, a wide nasal bridge, short nose with anteverted nostrils, thin upper lip, and smooth long philtrum (space between nose and lip).

The symptoms are generally considered to include:

- Trigonocephaly (triangular shaped head)
- Flat nasal bridge
- Thin upper lip
- Smaller than average mouth
- Cleft palate or cleft lip
- Eyebrow deformations
- Anteverted nostils
- Thick lower lip
- Spina bifida
- Other musculoskeletal malformations

- Neurological problems
- Congenital heart defects

Symptom and symptom severity varies from person to person. Risks for harmful effects due to prenatal exposure to valproic acid are likely influenced by a variety of factors, including drug dosage, multiple drug or drug combination, timing of drug exposure, severity of seizure disorder in the mother, predisposing genes, and folic acid intake. In general, children of women with a seizure disorder also are at an increased risk for having a seizure disorder themselves. Parental factors such as IQ and socio-economic status may also play a role in symptom and symptom severity.

Some children with fetal valproate syndrome show delays in development, autistic features, and/or intellectual disability. In general, the most commonly affected developmental aspect is speech and language. In addition some children have motor delays which may cause clumsiness and impair daily living skills, such as getting dressed, handwriting, riding a bike and swimming. Toilet-training may also be delayed, however most children do achieve this milestone. Lastly, some children with fetal valproate syndrome have difficulty with social interaction, which may prompt investigation for autistic spectrum disorder.

The NIH in the US state that the incidence is 6-9% of infants exposed to sodium valproate. (other sources quote higher rates).

Neural tube defects

The main malformation commonly associated with sodium valproate is a neural tube defect. The risk has been estimated at 1-2% of all pregnancies exposed to sodium valproate.

Couples with a family history of neural tube defects also have an increased risk. A couple with one child with an NTD has a 4% chance of having another baby with a NTD.

Other risk factors for NTDs include obesity and smoking.

http://www.marchofdimes.org/baby/neural-tube-defects.aspx

The background rate of NTD is about 3.5 per 10,000; decreased from 5 per 10,000 since the introduction of folic acid supplementation in pregnancy.

Impaired cognitive function

Children born to mothers using valproate have significantly lower IQ scores (8-9 points)[1].

Observational studies have found increased rates of autism among children exposed to sodium valproate before birth. The normal incidence for autism in the general population is estimated at less than one percent, incidence associated with valproate estimated at 4-8% depending on the study.[2]

Risk with other anti-epileptic medicines

Phenytoin has the same pregnancy category as sodium valproate (D). Birth defects associated with phenytoin include fetal anticonvulsant syndrome, cleft palate, microcephaly and ventricular septal defect.

Ethosuximide is also category D, no specific syndrome or defect has been associated with this medicine.

Phenobarbitol is also category D and has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability.

---

[1] 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: 244-8-52

[2] Christensen J, Groenborg TK, Sorensen MJ et al 2013 'prenatal valproate exposure and risk of autism spectrum disorders and childhood autism' JAMA 309: 1696-703

Vigabatrin is category D, no specific syndrome or defect has been associated with this medicine.

Other medicines contain precautionary statements in their data sheets but have a lower category of risk.

Effect of dose and using multiple medicines

There is some evidence that taking a dose lower than 1000mg sodium valproate per day is less risky. Observational studies indicate that the risk of birth defects is greater for infants born to women taking more than one anti-epileptic medicine[3]

Support for people with epilepsy

No medicine is without risk, Medsafe strongly advises everyone to make sure that any medicine they take is right for them. This may involve them asking questions about the expected benefits and risks. These questions may be directed to their doctor, nurse, pharmacist or to charitable organisations such as the Epilepsy foundation.

[3] Meador K, Reynolds MW, Crean S et al 2008 'pregnancy outcomes in women with epilepsy: A systematic review and meta-analysis of published pregnancy registries and cohorts' Epilepsy Res 81: 1-13

[redacted]

02/10/2014 01:39 p.m.

To: [redacted]
cc:
bcc:

Subject: Epilim update response

Is this a fair precis?

The datasheet for Epilim was revised after a 2009 recommendation from the Medicines Advisory Review Committee, an expert body, to strengthen the precautions around use of Epilim during pregnancy, after new overseas findings.

Kevin McCarthy
Senior Media Advisor
Media Relations
Communications & HR
Corporate Services
Ministry of Health
[redacted]

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

Chris James Hi Kevin - minutes from the last MA... 02/10/2014 01:32:32 p.m.

From: [redacted]
To:
Cc:
Date: 02/10/2014 01:32 p.m.
Subject:

Hi Kevin - minutes from the last MARC review of sodium valproate that resulted in changes to the DS being recommended.

Chris

2.1.25 Sodium valproate and foetal valproate syndrome, drug exposure during pregnancy (82615)

September 2009 minute item 2.1.20, June 2009 minute item 4.1.6.1

References

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.

Medsafe. (2009). Anticonvulsants and congenital malformations. Prescriber Update. 30(1): 4.

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.

Chris James
Manager
Clinical Risk Management
Medsafe
Ministry of Health

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

[redacted] 02/10/2014 05:18 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: Fw: Epilim updates query

We can find out but not quickly. We will have to order the file from archives and review its contents to identify the changes. According to our database there appear to have been six changes to the data sheet since 2010. Obtaining the file and reviewing datasheets for changes could take a couple of days. Alternatively they could always exercise their own intelligence and speak to the product sponsor to get this information i.e. the data sheets and work it out for themselves..

Stewart

Stewart Jessamine
Group Manager
Medsafe
Clinical Leadership
Protection & Regulation
Ministry of Health
[redacted]

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

Kevin McCarthy I have explained and explained bu... 02/10/2014 05:05:43 p.m.

From: [redacted]
To:
Date: 02/10/2014 05:05 p.m.
Subject: Fw: Epilim updates query

I have explained and explained but the reporter appears stuck with an editor who is stuck on this topic.

Do we know what the differences are between the 2014 data sheet and the 2013 datasheet (or when the last previous Epilim datasheet was).

Kevin McCarthy
Senior Media Advisor
Media Relations
Communications & HR
Corporate Services
Ministry of Health
[redacted]

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

----- Forwarded by Kevin McCarthy/MOH on 02/10/2014 05:03 p.m. -----

From: [redacted]
To:
Date: 02/10/2014 05:02 p.m.
Subject: Epilim updates query

Hi Kevin

[redacted] still wants to know what the changes were that were put on medsafe site about Epilim.

From my recorded iv with Stewart he said the CMI part was updated in July, and the Data sheet in June.

Can you please try and find out what those changes were.. and we can wait til tomorrow but need it in the morning.

Thanks

[redacted]

[redacted] 02/10/2014 05:25 p.m.

To: [redacted]
cc:
bcc:

Subject: Fw: Epilim updates query

FYI my response to the reporter.

Is there not some assurance we can give that any substantive change like that undertaken in 2009/10 to strengthen a warning would be known to Medsafe and MARC, and that there has been no similar changes made to the datasheets for Epilim.

Kevin McCarthy
Senior Media Advisor
Media Relations
Communications & HR
Corporate Services
Ministry of Health
[redacted]

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

----- Forwarded by Kevin McCarthy/MOH on 02/10/2014 05:23 p.m. -----

From: [redacted]
To:
Date: 02/10/2014 05:21 p.m.
Subject: Re: Epilim updates query

It will take several days to go through past datasheets. You will find it quicker by talking to Sanofi. Please advise tomorrow how you want to proceed.

Kevin McCarthy
Senior Media Advisor
Media Relations
Communications & HR
Corporate Services
Ministry of Health
[redacted]

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

[redacted] Hi Kevin [redacted] still wants to kno... 02/10/2014 05:02:12 p.m.

From: [redacted]
To:
Date: 02/10/2014 05:02 p.m.
Subject: Epilim updates query

Hi Kevin
[redacted] still wants to know what the changes were that were put on medsafe site about Epilim.

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Can you please try and find out what those changes were.. and we can wait til tomorrow but need it in the morning.
Thanks

[redacted]

[redacted] 03/10/2014 10:11 a.m.

To: [redacted]
cc:
bcc:

Subject: Re: Fw: Epilim updates query

HI

Following a quick look through our database, it appears that most of the changes to the data sheets have occurred following a company decision to amalgamate the data sheets across a range of different formulations, strengths and doses e.g. having a single data sheet for IV and Oral Epilim. The only major safety change I can find is the one that followed the MARC request to add more info re pregnancy in 2009/10. As each change was accepted the data sheet published on the website was updated to the latest approved version.

Stewart

Stewart Jessamine
Group Manager
Medsafe
Clinical Leadership
Protection & Regulation
Ministry of Health
[redacted]

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

Kevin McCarthy FYI my response to the reporter. I... 02/10/2014 05:25:42 p.m.

From: [redacted]
To:
Date: 02/10/2014 05:25 p.m.
Subject: Fw: Epilim updates query

FYI my response to the reporter.

Is there not some assurance we can give that any substantive change like that undertaken in 2009/10 to strengthen a warning would be known to Medsafe and MARC, and that there has been no similar changes made to the datasheets for Epilim.

Kevin McCarthy
Senior Media Advisor
Media Relations
Communications & HR
Corporate Services
Ministry of Health
[redacted]

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

----- Forwarded by [redacted] 02/10/2014 05:23 p.m. -----

From: [redacted]
To:
Date: 02/10/2014 05:21 p.m.
Subject: Re: Epilim updates query

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Please advise tomorrow how you want to proceed.

Kevin McCarthy
Senior Media Advisor
Media Relations
Communications & HR
Corporate Services
Ministry of Health
[redacted]

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

[redacted]

[redacted] 21/10/2014 03:43 p.m.

To: [redacted]
cc:
bcc:

Subject: Fw: Epilim warning upgrade

Thanks

Chris

Chris James
Manager
Clinical Risk Management
Medsafe
Ministry of Health

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

[redacted] 21/10/2014 03:43 p.m. -----

From: [redacted]
To:
Cc:
Date: 21/10/2014 03:04 p.m.
Subject: Fw: Epilim warning upgrade

Hello, this is a query from a reporter who did a Sunday newspaper feature recently on Epilim. Is this correct?

Kevin McCarthy
Senior Media Advisor
Media Relations
Communications & HR
Corporate Services
Ministry of Health
[redacted]

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

----- Forwarded by Kevin McCarthy/MOH on 21/10/2014 03:03 p.m. -----

From: [redacted]
To:
Date: 21/10/2014 09:59 a.m.
Subject: Epilim warning upgrade

Hi Kevin.

There has been a new recommendation for sodium valproate from the European Medicine Agency. It says to not prescribe it to women and girls who may become pregnant. Can you find out if MedSafe is going to send this information out to doctors, and will there be a warning change on the website etc?

Thanks

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/10/WC500175208.pdf

[redacted]

[redacted] 21/10/2014 05:08 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: Fw: Epilim warning upgrade

Thanks Chris, will have a look and get back to you tomorrow.

Kevin McCarthy
Senior Media Advisor
Media Relations
Communications & HR
Corporate Services
Ministry of Health
[redacted]

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

Chris James Hi Kevin Proposed response: 21/10/2014 03:59:08 p.m.

From: [redacted]
To:
Cc:
Date: 21/10/2014 03:59 p.m.
Subject: Re: Fw: Epilim warning upgrade

Hi Kevin

Proposed response:

In New Zealand, 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. This advice appears to be consistent with the information published by the European Medicines Agency. Before Epilim is prescribed for use in women who could become pregnant they should receive advice on the benefits and risks of treatment.

Medsafe published an article on anticonvulsants and congenital malformations in Prescriber Update 30(1): 1 February 2009; an update on sodium valproate will be included in the next edition (due December 2014).

Thanks

Chris

Chris James
Manager
Clinical Risk Management
Medsafe
Ministry of Health

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

Kevin McCarthy Hello, this is a query from a report... 21/10/2014 03:04:10 p.m.

[redacted]

23/10/2014 05:45 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: Epilim response to freelance writer

Thanks
I think the key issue is that we are providing an update in the Dec 2014 Prescriber Update.

Stewart

Stewart Jessamine
Group Manager
Medsafe
Clinical Leadership
Protection & Regulation
Ministry of Health
[redacted]

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

Kevin McCarthy Stewart, sorry this has taken so lo... 23/10/2014 05:26:00 p.m.

From: [redacted]
To:
Date: 23/10/2014 05:26 p.m.
Subject: Epilim response to freelance writer

Stewart, sorry this has taken so long to get back to you. I've made those tweaks we discussed yesterday morning after your interview on psychoactives at Medsafe. Chris, are you happy with this tweaked version - I would attribute to Stewart.

QUERY - [redacted] for Sunday Star-Times

There has been a new recommendation for sodium valproate from the European Medicine Agency. It says to not prescribe it to women and girls who may become pregnant. Can you find out if MedSafe is going to send this information out to doctors, and will there be a warning change on the website etc?

Thanks

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/10/WC500175208.pdf

RESPONSE - Dr Stewart Jessamine, Group Manager, Medsafe

In New Zealand, 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.

This advice is consistent with the information published by the European Medicines Agency. The agency statement notes that "women currently taking valproate who have any questions about their treatment should speak with their doctor". Medsafe strongly supports this approach.

Before Epilim is prescribed for use in women who could become pregnant, they should receive advice on the benefits and risks of treatment.

Medsafe published an article on anticonvulsants and congenital malformations in its regular Prescriber Update in February 2009; an update on sodium valproate will be included in the next edition (due December 2014).

Kevin McCarthy
Senior Media Advisor
Media Relations
Communications & HR
Corporate Services
Ministry of Health
[redacted]

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

[redacted] 08/12/2015 09:19 a.m.

To: [redacted]
cc:
bcc:

Subject: Re: Fw: One News Query

Hi Peter
recent actions on use of Epilim in pregnancy
Alert:
http://www.medsafe.govt.nz/safety/EWS/alert-communications.asp
this was pushed out to email subscribers
PU article
http://www.medsafe.govt.nz/profs/PUArticles/December2014SodiumValproate.htm
Data sheet was updated to include more info
CMI clearly states that should speak to Dr before pregnancy and asap if pregnant

This was also discussed at MARC last week
consumer rep was satisfied with the CMI wording
and the MARC did not consider any further communication necessary at this point
thanks
Susan
Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health [redacted]

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY

[redacted]

Peter Abernethy Hi I will call you about this, Peter 08/12/2015 08:47:24 a.m.

From: [redacted]
To:
Date: 08/12/2015 08:47 a.m.
Subject: Fw: One News Query

Hi I will call you about this, Peter

Peter Abernethy
Media Relations Manager
Ministry of Health
[redacted]
When an urgent response is required please copy to [redacted]

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

----- Forwarded by Peter Abernethy/MOH on 08/12/2015 08:46 a.m. -----

From: [redacted]
To:
Date: 07/12/2015 03:59 p.m.
Subject: RE: One News Query

Hi Peter

I am talking to a neurologist.
Re the MOH - I'm interested in whether Medsafe has upped its advice to the public/gp's/medical fraternity in light of recent publicity about the risks to pregnant women.
Also, whether Medsafe is considering putting warnings on Epilim packets?
Also, Medsafe's view, if any, of overseas lawsuits against Sanofi?
Thanks
[redacted]

From: [redacted]
Sent: Monday, 7 December 2015 2:36 p.m.
To: [redacted]
Subject: Re: One News Query

Hi [redacted] the Consumer Medicine Information sheet for Epilim on the Medsafe website is here:
http://www.medsafe.govt.nz/consumers/cmi/e/Epilim.pdf
Which has information about pregnancy.
It may pay to talk to a neurologist, as it looks as if there is risks to the baby from epilepsy and from anticonvulsants.
Regards

Peter Abernethy
Media Relations Manager
Ministry of Health
[redacted]

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

From: [redacted]
To:
Date: 07/12/2015 02:26 p.m.
Subject: One News Query

I have some questions about anti epilepsy medication, Epilim – specifically the risk information given to pregnant women.
Look forward to hearing from you.
Regards
[redacted]

[redacted]

[redacted] 08/12/2015 12:17 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: Stronger and more information on Sodium Valproate - Link

Hi Peter

Best time for briefing is 8.30am at Stewart's desk, level 1 The Terrace.

Best time for possible interview is 2.00 -3.00pm Wednesday 9 December.

Cheers
Bridie

Bridie Richardson
Executive Assistant to the Director of Public Health
Office of the Director of Public Health
Public Health
Clinical Leadership, Protection & Regulation
Ministry of Health
[redacted]

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

Peter Abernethy Hi Chris, Yes please for a briefing... 08/12/2015 12:05:05 p.m.

From: [redacted]
To:
Cc:
Date: 08/12/2015 12:05 p.m.
Subject: Re: Stronger and more information on Sodium Valproate - Link

Hi Chris,
Yes please for a briefing, and talking points for Stewart for tomorrow morning please (aim for 9.30ish).
Bridie can we get a time with Stewart please Wed am.
In particular it would be good to have the details of the tooing and froing. And responses like an update from PHARMAC about moving to original pack dispensing etc,
Regards Peter

Peter Abernethy
Media Relations Manager
Ministry of Health
[redacted]

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

Chris James Hi Peter Some info: 08/12/2015 11:32:37 a.m.

[redacted] 08/12/2015 01:51 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: Stronger and more information on Sodium Valproate - Link

No timeline from psnz - forms part of a bigger project of additianol cautionary labels for pharmacy dispensing as they don't have a pregnancy label yet. If and once adopted they will be considering if sod Valp needs that label (and probably will).

Chris

Sent from my BlackBerry 10 smartphone.

From: [redacted]
Sent: Tuesday, 8 December 2015 13:49
To: [redacted]
Cc:
Subject: Re: Stronger and more information on Sodium Valproate - Link

Hi Chris. GPNZ comms confirm no subsequent meeting. Pharmac comms checking any contact.
PSNZ can we please check for timeline please (if they bring in will sodium valproate be covered?)
Peter

Peter Abernethy
Media Relations Manager
Ministry of Health
[redacted]

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

Chris James---08/12/2015 11:32:37 a.m.---Hi Peter Some info:

From: [redacted]
To:
Cc:
Date: 08/12/2015 11:32 a.m.
Subject: Re: Stronger and more information on Sodium Valproate - Link

Hi Peter

Some info:

PSNZ does not have a pregnancy advisory label that they ask pharmcists to put on

dispensing labels but are considering this (I don't have a timeline - best to ask PSNZ direct). They agree that there is little point putting a warning on the medicine box as the pharmacist has to dispense into a pharmacy skillet and put their label on it (unless PHARMAC moves to original pack dispensing in the future).

Email below re royal college of GPs - not sure if a meeting happened subsequently. Reporter needs to talk to college direct in terms of advice GPs are giving

In addition to Susan's email - the New Zealand formularly has clear advice for GPs also in terms of risks in pregnancy and what to inform patients. So there is plenty of informaiton available for HCPs and consumers.

If Stewart needs a list of talking points prior to interview please let us know - Rowan if he does can you please organise so Stewart is fully briefed.

Thanks

Chris

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

[redacted]

MEDSAFE

	Date	Author	Title
[ ]	15/02/2015	Denise Astill	Re: Stronger and more information on Sodium Valproate

[Link]

Chris James
Acting Group Manager
Medsafe
Clinical Leadership, Protection & Regulation
Ministry of Health
[redacted]

[redacted]

08/12/2015 04:39 p.m.

To: [redacted]
cc:
bcc:

Subject: Valproate

Hi - I found this based on what we sent for the SST article last year.

Chris

Sunday Star Times Epilim.docx

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

I am writing a feature article for the Sunday Star Times. My deadline is Tues 23 September. I would like to interview someone from Medsafe.

Sodium Valproate - Epilim - is used primarily to treat epilepsy and has also been used for neuropathic pain and mood disorders. It has a risk of birth defects and some children are on ACC after being diagnosed with a syndrome caused by this medication. A number of parents claim they were not fully informed about the high risk of defects it may cause their babies. They also want a warning on every medication pack, as well as potentially a simple and brief patient information sheet inside.

This is different from the current sheet that is detailed and in small print. Some medical specialists agree that more simple warnings would work better than the current system of prescribers warnings. They say research shows only about a third of what they tell patients goes in. And some drs describe the current information in drug packets as 'useless'. They support warnings like the ones on cigarette packets. They don't believe referring patients to MedSafe is working.

Line of questions as follows.

1. Medsafe currently provides patient information about Epilim on its website. Is this enough? Why?

2. When was it last updated and why?

3. Prescribers say they do all they can to warn patients but that more is needed so support a simple info sheet being provided with the medication, and a very blunt warning on packets - like cigarettes. How does Medsafe feel about this?

4. Yes it is the prescribers responsibility to warn patients but it appears not to be working as well as it could. What can Medsafe do to improve this?

5. There is no legislation in NZ saying this needs to happen - but how would Medsafe feel about getting it happening anyway as the emotional and financial cost of looking after these disabled kids is huge?

6. Some parents with children who have birth defects caused by Epilim are also wanting more warnings on packets. What have you got to say to them?

7. There is a claim that hundreds of babies have been born in NZ with defects due to Epilim and that it will continue to rise. How concerning is this for MedSafe?

These are the basic questions. I would like to actually talk to someone.. maybe Stuart Jessamine?

Medsafe is sorry to hear that babies have been affected by birth defects following exposure to sodium valproate taken by their mothers.

Role of Medsafe

Medsafe is the New Zealand regulator for medicines and medical devices. Medsafe is bound by and administers legislation relevant to the provision of medicines and medical devices in New Zealand.

In addition as part of these activities Medsafe provides advice about the safe use of medicines and medical devices. The responsibility for the medicine/ medical device remains with the manufacturer and/ or New Zealand sponsor.

Medsafe does not regulate the practice of healthcare professionals. This is the responsibility for example of the Medical council and Pharmacy Council. In addition the HQSC work with healthcare professionals patients and consumers to help improve the quality and safety of care.

Medicines Information

Data sheets are mandatory for all prescription and restricted medicines. These are provided by the manufacturer (sponsor) of the medicine and remain their responsibility. Data sheets are published on the Medsafe website as a service, to ensure that they are freely available in New Zealand.

Provision of Consumer Medicine Information is voluntary in New Zealand. These are provided by the manufacturer (sponsor) and are published on the Medsafe website, as a service. The date of the last update of a CMI or data sheet is published on the leaflet at the end of the leaflet. The company provides the CMI and is responsible for its maintenance and will be able to state why they decided to update the leaflet.

This information (CMI) is provided as an addition, not a substitute to the information provided to the patient by their healthcare professionals. The patient's doctor, pharmacist and/or nurse may also use this information to help them explain some of the difficult health concepts relating to the use of various medicines. The leaflet is provided in a ready-to-print format for healthcare professionals to use during their day-to-day practice. It is Medsafe's expectation that healthcare professionals discuss the benefits and risks of all treatments with their patients so that the patient can make an informed decision regarding their treatment. Medsafe publishes information to help healthcare professionals understand these expectations.

http://www.medsafe.govt.nz/profs/RIss/unapp.asp

Medsafe has also published a Prescriber Update on anticonvulsants and congenital malformations http://www.medsafe.govt.nz/profs/PUArticles/Anticonvulsants-Feb09.htm

Provision of information in 'drug packets' is voluntary. Healthcare professionals may make a complaint to Medsafe if they believe the information provided is incorrect.

Additional information on the risks of taking medicines is also available from the New Zealand formulary http://nzf.org.nz/search (this is funded by the Ministry of Health).

Prescribers may produce their own leaflets if they feel that this will help them in their practice. Some DHB's already publish additional information on medicines, some of these leaflets are available through the NZF.

Information on best practice and use of medicines is provided by BPAC which also publishes the Best Practice Journal. BPAC have published information on treating women with epilepsy http://www.bpac.org.nz/BPJ/2009/November/anticonvulsants.aspx

ACC also publish treatment injury case studies to help inform prescribers about the safe use of medicines. A study on foetal valproate syndrome was published in June this year.

Medicines labelling requirements

There are statutory requirements for medicine package labels. However most prescribed medicines are not provided to patients in the original pack, but are dispensed by pharmacists into pharmacy packs with pharmacy labels attached. Medsafe does not regulate dispensing practice or the pharmacy label requirements.

Safety monitoring of medicines

Medsafe monitors the safety of all medicines available in New Zealand through a contract with the Centre for Adverse Reactions Monitoring (CARM). Healthcare professionals and consumers can send a report of any suspected reaction to any medicine to the Centre. CARM then alerts Medsafe to any safety concerns with medicines used in New Zealand. Reporting suspected adverse reactions is the official method of alerting CARM and Medsafe to safety concerns with medicines. If no reports are received it is assumed that there is no safety concern. CARM and Medsafe actively promote the scheme and encourage healthcare professionals and consumers to report. Reports can be made on paper, fax, telephone call, email, GP software, on-line and via an i-phone app.

To date CARM have received 13 reports of foetal valproate syndrome; 7 of these were from ACC, 4 from DHBs, one from a GP and one from the company. This is a very low number of reports considering sodium valproate has been in use since the start of data collection in 1964.

If there are further cases of birth defects due to sodium valproate these should be reported to CARM. In that way Medsafe can review the information and take appropriate action.

Medsafe can also seek advice on medicines safety concerns from the Medicines Adverse Reactions Monitoring Committee (MARC). The MARC have considered the use of sodium valproate in pregnancy on several occasions. The minutes are published on the Medsafe website, for example:

http://www.medsafe.govt.nz/profs/adverse/Minutes149.htm

http://www.medsafe.govt.nz/profs/adverse/Minutes138.htm

http://www.medsafe.govt.nz/profs/adverse/Minutes124.htm#3.1.16

Benefits and Risks of Medicines including Epilim (sodium valproate)

All medicines have benefits and risks. Medsafe approves a medicine for use in New Zealand if the medicine has acceptable benefits, quality and risks; that is if the benefits outweigh the risks.

Medsafe determines the balance of benefits and risks for the population overall, however there may be some people for whom the benefits do not outweigh the risks. Healthcare professionals need to use the information in the data sheet to determine whether the benefits outweigh the risks for their individual patients. For example the use of Epilim is contraindicated in pregnancy, that is the benefits are not considered to outweigh the risks. However the prescriber may disagree with this assessment, for example if all other anti-epileptics have been tried and sodium valproate is the only effective medicine for that woman.

In general it is considered that the benefits of epilepsy treatment for a pregnant women and her fetus outweighs the risk of a congenital abnormality in the infant. A convulsive/tonic clonic seizure during pregnancy risks trauma to the abdomen and hence the baby. Also the temporary interruption of breathing, rarely of any significance to the mother can lead to oxygen deprivation for the fetus. Prolonged or repetitive tonic clonic seizure can seriously impair the supply of oxygen to the fetus.
http://epilepsy.med.nyu.edu/epilepsy/epilesy-and-women/effects-seizure-fetus

The data sheet contains the following recommendation:

...women of child-bearing potential taking sodium valproate should:

- receive counselling with regard to the risk of foetal abnormalities;
- 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;
- undergo routine ultrasound and amniocenteses for specialist prenatal diagnosis of such abnormalities;
- 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.

It is recommended that in bipolar disorders indication, cessation of valproate therapy should be considered.

The CMI contains the following text (part in bold on the first page).

If you are a female patient of child-bearing age, make sure that you talk to your doctor about the risks associated with taking Epilim during pregnancy.

Tell your doctor if you are pregnant or intend to become pregnant.

Like most medicines of this kind, Epilim may affect your developing baby if taken in the first trimester of pregnancy, as it is suspected of causing an increased risk of malformations in the exposed foetus. Also, children born to mothers who take Epilim throughout their pregnancy may be at risk of impaired cognitive development or withdrawal syndrome. However, do not stop taking Epilim unless your doctor says so as there are risks to the mother and child from uncontrolled epilepsy or uncontrolled mania episodes.

Congenital abnormalities

Around 3% or 1 in 33 infants are born with a congenital anomaly for no apparent reason (this is the background rate). WHO states that this means that around 3.2 million infants are born with an abnormality worldwide every year.
http://www.who.int/mediacentre/factsheets/fs370/en/

In general the risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. The contribution to this increase in risk from the use of medicines or the disease itself is unknown.

Fetal Valproate syndrome

http://rarediseases.info.nih.gov/gard/5447/fetal-valproate-syndrome/case/25731/case-questions

Signs and symptoms of fetal valproate syndrome can vary greatly from person to person. There are certain subtle facial features that are more commonly (but not always) associated with this syndrome. These features include thin arched eyebrows that may be spaced far apart, a wide nasal bridge, short nose with anteverted nostrils, thin upper lip, and smooth long philtrum (space between nose and lip).

The symptoms are generally considered to include:

- Trigonocephaly (triangular shaped head)
- Flat nasal bridge
- Thin upper lip
- Smaller than average mouth
- Cleft palate or cleft lip
- Eyebrow deformations
- Anteverted nostils
- Thick lower lip
- Spina bifida
- Other musculoskeletal malformations

- Neurological problems
- Congenital heart defects

Symptom and symptom severity varies from person to person. Risks for harmful effects due to prenatal exposure to valproic acid are likely influenced by a variety of factors, including drug dosage, multiple drug or drug combination, timing of drug exposure, severity of seizure disorder in the mother, predisposing genes, and folic acid intake. In general, children of women with a seizure disorder also are at an increased risk for having a seizure disorder themselves. Parental factors such as IQ and socio-economic status may also play a role in symptom and symptom severity.

Some children with fetal valproate syndrome show delays in development, autistic features, and/or intellectual disability. In general, the most commonly affected developmental aspect is speech and language. In addition some children have motor delays which may cause clumsiness and impair daily living skills, such as getting dressed, handwriting, riding a bike and swimming. Toilet-training may also be delayed, however most children do achieve this milestone. Lastly, some children with fetal valproate syndrome have difficulty with social interaction, which may prompt investigation for autistic spectrum disorder.

The NIH in the US state that the incidence is 6-9% of infants exposed to sodium valproate. (other sources quote higher rates).

Neural tube defects

The main malformation commonly associated with sodium valproate is a neural tube defect. The risk has been estimated at 1-2% of all pregnancies exposed to sodium valproate.

Couples with a family history of neural tube defects also have an increased risk. A couple with one child with an NTD has a 4% chance of having another baby with a NTD.

Other risk factors for NTDs include obesity and smoking.

http://www.marchofdimes.org/baby/neural-tube-defects.aspx

The background rate of NTD is about 3.5 per 10,000; decreased from 5 per 10,000 since the introduction of folic acid supplementation in pregnancy.

Impaired cognitive function

Children born to mothers using valproate have significantly lower IQ scores (8-9 points)[1].

Observational studies have found increased rates of autism among children exposed to sodium valproate before birth. The normal incidence for autism in the general population is estimated at less than one percent, incidence associated with valproate estimated at 4-8% depending on the study.[2]

Risk with other anti-epileptic medicines

Phenytoin has the same pregnancy category as sodium valproate (D). Birth defects associated with phenytoin include fetal anticonvulsant syndrome, cleft palate, microcephaly and ventricular septal defect.

Ethosuximide is also category D, no specific syndrome or defect has been associated with this medicine.

Phenobarbitol is also category D and has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability.

---

[1] 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: 244-8-52

[2] Christensen J, Groenborg TK, Sorensen MJ et al 2013 'prenatal valproate exposure and risk of autism spectrum disorders and childhood autism' JAMA 309: 1696-703

Vigabatrin is category D, no specific syndrome or defect has been associated with this medicine.

Other medicines contain precautionary statements in their data sheets but have a lower category of risk.

Effect of dose and using multiple medicines

There is some evidence that taking a dose lower than 1000mg sodium valproate per day is less risky. Observational studies indicate that the risk of birth defects is greater for infants born to women taking more than one anti-epileptic medicine[3]

Support for people with epilepsy

No medicine is without risk, Medsafe strongly advises everyone to make sure that any medicine they take is right for them. This may involve them asking questions about the expected benefits and risks. These questions may be directed to their doctor, nurse, pharmacist or to charitable organisations such as the Epilepsy foundation.

[3] Meador K, Reynolds MW, Crean S et al 2008 'pregnancy outcomes in women with epilepsy: A systematic review and meta-analysis of published pregnancy registries and cohorts' Epilepsy Res 81: 1-13

[redacted]

08/12/2015 05:13 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: Valproate

Hi

Here are some dot points and a bit more detailed information

Epilim dot points.docx Sodium Valproate Information.docx

Will bring along some copies tomorrow.

Thanks

Rowan

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

MEDSAFE [redacted]

Chris James Hi - I found this based on what we s... 08/12/2015 04:39:15 p.m.

From: [redacted]
To:
Date: 08/12/2015 04:39 p.m.
Subject: Valproate

Hi - I found this based on what we sent for the SST article last year.

Chris

[attachment "Sunday Star Times Epilim.docx" deleted by Rowan Pollock/MOH]

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

MEDSAFE [redacted]

1. **Alert Communication** – Use of sodium valproate (Epilim) in pregnancy

Published 28 September 2015 www.medsafe.govt.nz/safety/EWS/2015/sodiumvalproate.asp

The use of Sodium valproate (Epilim) is contraindicated in pregnancy due to the risk to the unborn baby (fetus). Congenital malformations have been estimated to affect between 6.7% and 12.4% of children exposed to Epilim in the womb. The rate of malformations in the general population is 2-3%.

The most common types of malformations in children exposed to Epilim are:

- neural tube defects,
- cleft lip and palate,
- heart defects,
- limb defects and
- unusual facial features.

Developmental delay is also common (30-40%) in children exposed to Epilim in the womb. The IQ of Epilim exposed children is 7-10 points lower than the IQ of children exposed to other anti-epileptics. The risk of autism in children exposed to Epilim has been estimated at 2.5%. This is about five times higher than the rate in the general population.

Epilim should not be used in female children or in women of child-bearing age, unless other treatments are ineffective or not tolerated. It is important that girls (and their caregivers) and women of child-bearing age taking Epilim are aware of these risks.

Information for consumers and caregivers:

Female children and their caregivers

- Make sure you understand the risks to an unborn child when taking Epilim (sodium valproate) and the need for effective contraception, when this becomes appropriate.

Women of childbearing age

- Make sure you understand the risks to an unborn child when taking Epilim
- Ensure you are using effective contraception (if required).
- If you decide to try for a baby, discuss this with your doctor first
- Tell your doctor as soon as you are pregnant, or think you may be pregnant.
- It is important to keep taking your medicine. There is a risk to your baby if you have a seizure during pregnancy.
- Make sure you take any recommended supplements like folic acid and attend all your pregnancy screening and monitoring visits.
- If you have any questions speak to your doctor.

Information for healthcare professionals:

- Ensure that all other treatments have been tried and failed before using Epilim (sodium valproate) in female children or women of childbearing age.
- Discuss the risks to the fetus of exposure to Epilim in pregnancy before use with all female patients and regularly during use with women of childbearing age.
- Discuss the need to use effective contraception with women of childbearing age taking Epilim.
- Ensure that your patient and her caregivers (if appropriate) have understood the potential consequences of pregnancy whilst taking Epilim.

- Advise women considering trying for a baby that they should discuss this with you.
- Consider referring women thinking of becoming pregnant for specialist pre-conception advice.
- Advise women trying for a baby to take recommended supplements such as folic acid prior to becoming pregnant.
- Advise women that if they think they might be pregnant they should contact you immediately.
- Ensure that any pregnant women taking sodium valproate receive appropriate pregnancy monitoring and tests to detect neural tube defects and other malformations.

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2. **Prescriber Update Article** – Use of Sodium Valproate in Pregnancy

December 2014 - www.medsafe.govt.nz/profs/PUArticles/December2014SodiumValproate.htm

Key Messages:

- Sodium valproate (Epilim) is contraindicated in pregnancy.
- Sodium valproate should not be used in women of child bearing potential unless other treatments are ineffective or not tolerated.
- 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 a reduced IQ compared to children exposed to other anti-epileptic medicines.
- Reducing the dose of valproate below 1000mg/day and using high-dose folate periconceptually reduces the risk of some malformations and cognitive impairment.
- Seizures during pregnancy and other anti-epileptic drugs have also been associated with risks of adverse developmental outcomes and malformations.

---

3. **Data Sheet – Epilim**

Most recent update February 2015 www.medsafe.govt.nz/profs/Datasheet/e/Epilimtabsyrliqiv.pdf

Contraindications:

- Pregnancy

Precautions:
Women of Child Bearing Potential:

This medicine should not be used in female children, in female adolescents, in women of child-bearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of this high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate, The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of child bearing potential treated with Epilim plans a pregnancy or if she becomes pregnant. 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.

Epilim should be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Treatment should only be initiated if other treatments are ineffective or not

tolerated, and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Epilim should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses during pregnancy.

Women of child-bearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Epilim during pregnancy. The prescriber must ensure that the patient is provided with comprehensive information on the risks.

In particular the prescriber must ensure the patient understands

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.
- The need to use effective contraception
- The need for regular review of treatment
- The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to an appropriate alternate treatment prior to conception, if possible.
Epilim therapy should only be continued after a reassessment of the benefits and risks of the treatment with Epilim for the patient by a physician experienced in the management of epilepsy or bipolar disorder.

Use in Pregnancy (Category D)
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.

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.

Notwithstanding the potential risks, no sudden discontinuation of antiepileptic therapy should be undertaken, without reassessment of the risks and benefits, as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus. If after careful evaluation of the risks and benefits, sodium valproate treatment is to be continued during pregnancy, it is recommended to use sodium valproate in divided doses over the day at the lowest effective dose. The use of a prolonged release formulation may be preferable to any other treatment form.

In bipolar disorder, cessation of sodium valproate should be considered.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia carry a particular risk of death for mother and for the unborn child.

In animals, teratogenic effects have been demonstrated in mice, rats and rabbits,

Congenital malformations:
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,

hypospadias and multiple anomalies involving various body systems has been reported in children born to mothers treated with valproate, when compared to the incidence for certain other antiepileptic drugs. Data has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate monotherapy during pregnancy. This is a greater risk of major malformations than for the general population. Women treated with Epilim IV have a potentially increased risk of giving birth to a baby with an abnormality due to the higher C_{max} of the intravenous formulation compared with the oral formulation.

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%.

This risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Developmental disorders:
Data has shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that some children may experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

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. IQ measured in school aged children with a history of valproate exposure in utero, was lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There is limited data on the long term outcomes.

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.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.

In view of this data, the following recommendation should be taken into consideration:

This medicine should not be used during pregnancy and in women of child-bearing potential unless clearly necessary, that is, 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.

Women of child-bearing potential should be informed of the risks and benefits of the use of valproate during pregnancy.

Treatment advice:

It is recommended that women of child-bearing potential taking sodium valproate should:

- receive counselling with regard to the risk of foetal abnormalities;
- 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;
- undergo routine ultrasound and amniocenteses for specialist prenatal diagnosis of such abnormalities;
- 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.

It is recommended that in bipolar disorders indication, cessation of valproate therapy should be considered.

There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This syndrome is related to thrombocytopenia, hypofibrinaemia and/or to a decrease in other coagulation factors. 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 as they decrease the vitamin-K factors. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of the pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitterness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of pregnancy.

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4. Consumer Medicine Information

Most recent update February 2015 www.medsafe.govt.nz/Consumers/cmi/e/Epilim.pdf

Before you start to take it

If you are a female patient of child-bearing age, make sure that you talk to your doctor about the risks associated with taking Epilim during pregnancy.

Tell your doctor if you are pregnant or intend to become pregnant.

Like most medicines of this kind, Epilim may affect your developing baby if taken in the first trimester of pregnancy, as it is suspected of causing an increased risk of malformations in the exposed foetus. Also, children born to mothers who take Epilim throughout their pregnancy may be at risk of impaired cognitive development or withdrawal syndrome. However, do not stop taking Epilim unless your doctor says so as there are risks to the mother and child from uncontrolled epilepsy or uncontrolled mania episodes.

Your doctor may want to adapt your treatment and/or prescribe dietary supplements of folate.

Your doctor will discuss the risks and benefits of taking it if you are pregnant.

While you are taking it
Things you must do
If you become pregnant while you are taking this medicine, tell your doctor immediately.

What do I need to consider about contraception?
Unplanned pregnancy may not be desirable in patients receiving medicines for epilepsy or mania. You should use an effective method of contraception and consult your doctor before planning pregnancy; for example, your doctor may want you to start taking folate tablets.

Epilim should have little effect on the oral contraceptive pill, however, you should let your doctor know that you are taking it.

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5. **Sanofi – Valproate Educations Materials – Risk in Pregnancy**

Updated June 2015 www.sanofi.com.au/f/au/en/layout.jsp?cnt=613DE812-F0B4-42F1-AE18-D9A0B9B86DF8

Educational materials consist of
- Valproate Guide for Prescribers
- Valproate Patient Information Booklet

Must also consider pregnancy categorisation – Category D

It is not Category X such as isotretinoin as there is no benefit to using isotretinoin during pregnancy. Cannot stop sodium valproate immediately (as can do with isotretinoin) due to seizure risk (must also remember that there is a risk to the fetus of uncontrolled seizures). Reducing the dose of valproate below 1000 mg/day and using high-dose folate periconceptually reduces the risk of some malformations and cognitive impairment.

[redacted] 09/12/2015 07:55 a.m.

To: [redacted]
cc:
bcc:

Subject: Re: Valproate

Hi Rowan

Dotpoints look good. One thing Stewart might ask is if we've had reports - are you able to do a quick check?

Also if you have time can you check that the updated cmi has been published as per discussion with facs. Also an email from susan about this said something about company educational material - would be helpfulk if we could say this was also avail to HCPs but need to check with sponsor.

Will be in shortly

Chris

Sent from my BlackBerry 10 smartphone.

From: [redacted]
Sent: Tuesday, 8 December 2015 17:13
To: [redacted]
Subject: Re: Valproate

Hi

Here are some dot points and a bit more detailed information

(See attached file: Epilim dot points.docx)(See attached file: Sodium Valproate Information.docx)

Will bring along some copies tomorrow.

Thanks

Rowan

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

MEDSAFE [redacted]

Chris James---08/12/2015 04:39:15 p.m.---Hi - I found this based on what we sent for the SST article last year. Chris

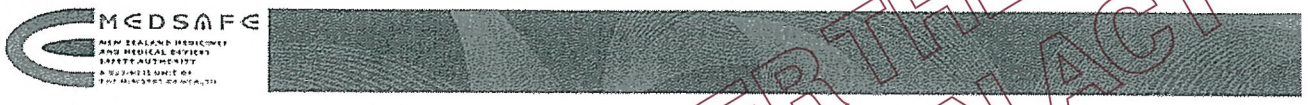
From: [redacted]
To: [redacted]
Date: 08/12/2015 04:39 p.m.
Subject: Valproate

Hi - I found this based on what we sent for the SST article last year.

Chris

[attachment "Sunday Star Times Epilim.docx" deleted by Rowan Pollock/MOH]

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



[redacted] 09/12/2015 09:40 a.m.

To: [redacted]
cc:
bcc:

Subject: Re: strong talking points on epilim

Hi Charlotte

Please find attached the dot points relating to sodium valproate use in pregnancy. I've changed the figure to 1000.

Both the Prescriber Update article and Alert Communication provide some information on the frequency of malformations, estimated from different pregnancy registries around the world. The estimates range from 6.7% to 12.4%. Those with developmental problems is much higher (up to 30 to 40%).

The links for these articles are:

Alert Communication - www.medsafe.govt.nz/safety/EWS/2015/sodiumvalproate.asp
Prescriber Update - www.medsafe.govt.nz/profs/PUArticles/December2014SodiumValproate.htm

Let me know if you need any further information.

Epilim dot points.docx

Thanks
Rowan

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

Charlotte Gendall Hi Rowan Very good to meet yo... 09/12/2015 09:30:45 a.m.

From: [redacted]
To:
Cc:
Date: 09/12/2015 09:30 a.m.
Subject: strong talking points on epilim

Hi Rowan

Very good to meet you guys. Can you please email me a copy of the one page "Information available ..." document you brought along today? We would like to forward these to the reporter ahead of the interview. I have noted from Peter that there is a change to the 100mg day figure to 1000

Also the larger Alert Communication would be useful for background although we may / not send that.

Rgds etc

Charlotte Gendall
Senior Media Advisor
Ministry of Health
[redacted]

http://www.health.govt.nz

Information available on the use of sodium valproate (Epilim) in pregnancy:

- Use is contraindicated in pregnancy due to the risk to the unborn baby.
- Risks include congenital malformations as well as development delays in children exposed in utero.
- Valproate should not be used in female children or in women of childbearing age, unless other treatments are ineffective or not tolerated.
- It is important that women (or female children and their caregivers) understand the risks. There should be discussion of the risks before use with all female patients and regularly during use in women of childbearing age.
- If a woman is considering trying for a baby then they should discuss this with their doctor first.
- If a women is pregnant or thinks she may be pregnant then they should discuss this with their doctor immediately.
- It is important for women to keep taking their medicine. There is a risk to the baby if the woman has seizure during pregnancy. Seizures during pregnancy and other anti-epileptic medicines have also been associated with risks of adverse developmental outcomes and malformations.
- Reducing the dose of valproate below 1000 mg/day and using high-dose folate prior to conception and during pregnancy reduces the risk of some malformations and cognitive impairment.

These messages have been communicated via an alert communication on the Medsafe website (September 2015) and a Prescriber Update article (December 2014).

The sponsor (Sanofi) has also produced education materials on the risks of using sodium valproate in pregnancy. These include a guide for prescribers and a patient information booklet

This issue was presented to the Medicines Adverse Reactions Committee (MARC) in December 2005. By the beginning of 2013 the New Zealand data sheet for Epilim included a contraindication to use in pregnancy and a detailed warning statement about the risk of congenital malformations and developmental delay in children exposed to valproate in utero.

[redacted]

09/12/2015 09:42 a.m.

To: [redacted]
cc:
bcc:

Subject: Re: strong talking points on epilim

Thanks Rowan.

Charlotte Gendall
Senior Media Advisor
Ministry of Health
[redacted]

http://www.health.govt.nz

Rowan Pollock Hi Charlotte Please find attached t... 09/12/2015 09:40:42 a.m.

From: [redacted]
To:
Cc:
Date: 09/12/2015 09:40 a.m.
Subject: Re: strong talking points on epilim

Hi Charlotte

Please find attached the dot points relating to sodium valproate use in pregnancy. I've changed the figure to 1000.

Both the Prescriber Update article and Alert Communication provide some information on the frequency of malformations, estimated from different pregnancy registries around the world. The estimates range from 6.7% to 12.4%. Those with developmental problems is much higher (up to 30 to 40%).

The links for these articles are:

Alert Communication - www.medsafe.govt.nz/safety/EWS/2015/sodiumvalproate.asp
Prescriber Update - www.medsafe.govt.nz/profs/PUArticles/December2014SodiumValproate.htm

Let me know if you need any further information.

[attachment "Epilim dot points.docx" deleted by Charlotte Gendall/MOH]

Thanks
Rowan

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

Charlotte Gendall Hi Rowan Very good to meet yo... 09/12/2015 09:30:45 a.m.

[redacted] 09/12/2015 01:40 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: contact from tvnz [redacted]

Hi Charlotte

We don't hold any packaging as such - there is only a mock-up of the packaging in the product file. It would be better to go into a pharmacy and look at the packaging of Epilim as well as the skillets (boxes) that are used for repackaging.
If you want me to bring up a picture of the US packaging to show that there isn't anything on the actual box there then happy to do so.

Thanks
Rowan

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

MEDSAFE [redacted]

Charlotte Gendall I just had a call from Nicole Bre... 09/12/2015 01:11:59 p.m.

From: [redacted]
To:
Date: 09/12/2015 01:11 p.m.
Subject: contact from tvnz [redacted]

I just had a call from [redacted]

She says "there won't be anything Stewart hasn't been asked before ..."

She also asked if there was any way we could help her with filming the "boxes that Epilim comes in."

My initial reaction was that this wasn't something we could assist with but as a holding response I told her that I would check with Medsafe.

Can you confirm that my initial reaction was correct as I don't believe we would hold any packaging, nor would it be appropriate to provide it for filming?

Charlotte

Charlotte Gendall
Senior Media Advisor
Ministry of Health
[redacted]

http://www.health.govt.nz

[redacted] 09/12/2015 01:45 p.m.

To: [redacted]
cc:
bcc:
Subject: Re: contact from tvnz [redacted]

Many thanks Rowan. Chris suggested you may have a contact with the Lambton Quay Pharmacy, if One News wish to try filming there? Is it possible for you to give the pharmacy a call and then let me know if they would allow TVNZ access?

Don't worry about bringing the photo of the US packaging.

Rgds

Charlotte

Charlotte Gendall
Senior Media Advisor
Ministry of Health
[redacted]

http://www.health.govt.nz

Rowan Pollock Hi Charlotte We don't hold any pac... 09/12/2015 01:40:13 p.m.

From: [redacted]
To:
Cc:
Date: 09/12/2015 01:40 p.m.
Subject: Re: contact from tvnz [redacted]

Hi Charlotte

We don't hold any packaging as such - there is only a mock-up of the packaging in the product file. It would be better to go into a pharmacy and look at the packaging of Epilim as well as the skillets (boxes) that are used for repackaging.
If you want me to bring up a picture of the US packaging to show that there isn't anything on the actual box there then happy to do so.

Thanks
Rowan

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

Charlotte Gendall I just had a call from [redacted] 09/12/2015 01:11:59 p.m.

[redacted]

21/04/2017 11:19 a.m.

To: [redacted]
cc:
bcc:

Subject: re media query on Epilim

Hi Chris

We have had two media requests today about a French study into Epilim, saying pregnant women at four times more likely to have a deformed child. RNZ is keen to have a line for its midday report today and TVNZ is keen to have a response by 2pm. Are you able to help me with this please? Stewart has handled in the past but he is away, as is Andy Simpson. I've also asked whether it is something that Caroline McElnay would handle as deputy director of Public Health, but haven't heard back from her yet.

We did a response on this issue in January 2016 as follows. Do you think we need to say a brief statement to this saying something like "The Ministry is aware of this new research into Epilim and will review it in due course to assess whether its advice to people taking Epilim needs to be altered in anyway."

Kind regards

Deidre

Epilim (statement given in Jan 2016)

TVNZ will be running a story over the break about the anticonvulsant Sodium valproate (Epilim). The statement below has been developed for reactive use, if other media follow up on the story. It has been signed off by Stewart Jessamine. If provided to media, an FYI will first need to be sent as usual.

(may be attributed to Dr Stewart Jessamine, Director of Public Health)

Epilepsy is treatable and manageable when approached with good knowledge, good advice and good medication. Uncontrolled, it can be a difficult condition which presents additional complications for pregnant women, or women hoping to become pregnant.

The Ministry has been asked whether current warnings surrounding Epilim and pregnancy are sufficient.

Anytime a condition requires ongoing medication, good advice should be sought before pregnancy. In this situation, the first and best discussion will between a well-informed woman and her GP.

Sodium valproate is a drug of longstanding which for many patients with epilepsy continues to be an effective treatment. However advice can change over time and as better information becomes available, there may be new options for women of childbearing age.

New Zealand has consistently provided advice ahead of overseas timelines. Early in 2013, the New Zealand data sheet for Epilim included a contraindication for use in pregnancy and a detailed warning statement about the risk of congenital malformation. This preceded similar advice from Europe in 2014.

Practically, there are limits about how much information can go on a label and updated alerts have consistently been provided to health practitioners, while the manufacturer Sanofi has also produced educational material.

For more detailed advice about treatment options, a patient could speak to a neurologist. That discussion could include whether the risk of not taking sodium valproate would outweigh the potential risk of foetal malformation.

If any patient is on an anticonvulsant and becomes concerned about the possible effects, they should talk to a doctor before making any change to medication.

ENDS

The media queries are:

TVNZ:

I am currently looking into a new French study which has proven the epilepsy drug valproate to cause "serious malfunctions" in up to 4100 children. http://www.bbc.com/news/world-europe-39657139

This is a story we have covered in the past- (Jan 2016) with a campaigner in NZ.

Today, we were wanting to touch base and see what the Ministry of Health has recommended for medical professionals in NZ in terms of what warning, if any, they should be giving to patients of childbearing age, or patients who are pregnant.

RNZ:

In light of the French study - that found the drug known as valproate or epilim given to pregnant women for epilepsy and bipolar disorder caused "serious malformations" in over 4000 children – I want to know if the Ministry of Health thinks the warnings it has in place now (http://www.medsafe.govt.nz/profs/datasheet/e/Epilimtabsyrligiv.pdf - bottom of page 8 and top of 9) are sufficient or if there will be any changes made?
Would be good to get a response as soon as possible – I was hoping to get a line in before midday bulletin.

Deidre Mussen
Senior Media Advisor
Ministry of Health
[redacted]
www.health.govt.nz

[redacted] 21/04/2017 01:51 p.m.

To: [redacted]
cc:
bcc:

Subject: Re: 1News Query

That is great - thank you so much.
I will send this on too.

Many thanks

Deidre

Deidre Mussen
Senior Media Advisor
Ministry of Health
[redacted]
www.health.govt.nz

Chris James ==========... 21/04/2017 01:38:07 p.m.

From: [redacted]
To:
Cc:
Date: 21/04/2017 01:38 p.m.
Subject: Re: 1News Query

Thanks Amanda.
Is that enough for you Deidre?
Chris

On 21/04/2017, at 1:23 PM, [redacted] wrote:

Hi Chris and Deidre

Susan has sent through the labels of the Epilim syrup and the tablet to Chris. Both contain the following warning.

WARNING FOR WOMEN AND GIRLS
This medicine can seriously harm an unborn baby. Always use effective contraception during treatment. If you are thinking about becoming pregnant or you become pregnant, talk to your doctor straight away.

Cheers
Amanda

Amanda Taylor | Senior Advisor Pharmacovigilance (Part-time: Wednesday, Thursday, Friday) | Clinical Risk Management | Medsafe | Ministry of Health | [redacted]
<0.46C.gif>

Chris James---21/04/2017 01:01:54 p.m.----------

From: [redacted]
To: [redacted]
Date: 21/04/2017 01:01 p.m.
Subject: Re: 1News Query

I understand sanofi is or has updated their label as per U.K. Amanda can you confirm? This is something Denise Astil fought for and I think got through.

Chris

On 21/04/2017, at 12:41 PM, [redacted] wrote:

Hi Chris

I've sent off your response to TV and RNZ, and TV has come back asking what warning are on the packaging.
Previously we said in Jan 2016 in a media response to TV, which Stewart was quoted:

"Practically, there are limits about how much information can go on a label and updated alerts have consistently been provided to health practitioners, while the manufacturer Sanofi has also produced educational material."

I've suggested the journalist checks with a pharmacy but do you know what warnings are given to people on or in or with their Epilim - ie on the packaging or inside.

Cheers

Deidre :-)

Deidre Mussen
Senior Media Advisor
Ministry of Health
[redacted]
www.health.govt.nz

----- Forwarded by [redacted] 04/2017 12:37 p.m. -----

From: [redacted]
To: "D[redacted]
Date: 21/04/2017 12:22 p.m.
Subject: RE: 1News Query

Thanks Deidre- are you able to confirm that there is a warning on the packaging of the drug?

From: [redacted]
Sent: Friday, 21 April 2017 12:20 p.m.
To: [redacted]
Subject: RE: 1News Query

Hi [redacted]

Here is a response from the Ministry of Health to your query about this new study into Epilim. Please attribute this statement to Chris James, Medsafe Group Manager, Ministry of Health:

Sodium valproate is contraindicated in pregnancy in New Zealand.

This medicine should also not be used in women of child bearing potential (as per Medsafe's medicine data sheet http://www.medsafe.govt.nz/profs/datasheet/e/Epilimtabsyrliqiv.pdf) unless the benefits clearly outweigh the risks. For example, a lack of alternative effective treatment for epilepsy.

This new study may provide further information about the known risks associated with use of Sodium valproate and Medsafe will review it to assess if product information needs to be updated in New Zealand.

Ends

Kind regards
Deidre

Deidre Mussen
Senior Media Advisor
Ministry of Health
[redacted]
www.health.govt.nz

From: [redacted]
To: "[redacted]
Date: 21/04/2017 10:08 a.m.
Subject: RE: 1News Query

Hi Deidre,

Working for the 6pm bulletin so would need to start putting together our story by 2pm if possible.

Thanks.

From: [redacted]

Sent: Friday, 21 April 2017 10:08 a.m.
To: [redacted]
Subject: Re: 1News Query

Hi [redacted]

Thanks for your query. I'll look into this and get back to you. What is your deadline for this?

Kind regards

Deidre

Deidre Mussen
Senior Media Advisor
Ministry of Health
[redacted]
www.health.govt.nz

From: [redacted]
To: [redacted]
Date: 21/04/2017 09:55 a.m.
Subject: 1News Query

Hi there,

I am currently looking into a new French study which has proven the epilepsy drug valproate to cause "serious malfunctions" in up to 4100 children.
http://www.bbc.com/news/world-europe-39657139

This is a story we have covered in the past- (Jan 2016) with a campaigner in NZ.

Today, we were wanting to touch base and see what the Ministry of Health has recommended for medical professionals in NZ in terms of what warning, if any, they should be giving to patients of childbearing age, or patients who are pregnant.

I look forward to hearing back from you,

Kind Regards,
[redacted]

[redacted]
1News Reporter
[redacted]

<0.2CB4.jpeg>