MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

133 Molesworth Street
PO Box 5013
Wellington 6140
New Zealand
T+64 4 496 2000

[redacted]

Ref: H201701543, H201701544 and H201701545

Dear [redacted]

Response to your request for official information

Thank you for your requests of 4 May 2017 under the Official Information Act 1982 (the Act). Four separate requests were made; the request to the Minister of Health has been completed separately. This response provides information relating to the remaining three requests (reference H201701543-5). The scope of your requests was clarified on 8 May 2017 to:

> "What year did the Ministry of Health/Medsafe become aware of the teratogenic effects of sodium valproate?
>
> What advice was provided to prescribers and consumers from the date this was known?
>
> What communication has there been between the UK and NZ with regards to sodium valproate? (eg, discussion between different committees)
>
> What other communications has there been? (eg, internal emails). I would like the correspondence of the ACC working group omitted from this request, after the date that the first meeting commenced on 20 May 2016. I would not like omitted communications had in between where the whole FACS prevention team was not privy to.
>
> How many females have been dispensed sodium valproate during 2014-current date? Please put them into 5 year age bands – start of 2014 to end of 2016 (3 year period)
>
> How many possible children since 1975 have been affected due to exposure to sodium valproate during pregnancy?
>
> Copy of minutes from relevant MARC meetings?"

I will respond to each of your questions in turn.

Year in which the Ministry of Health/Medsafe became aware of the teratogenic effects of sodium valproate

Medsafe is the medicines and medical device regulator for New Zealand and came into being in 1997. Prior to this, legislation relating to medicines was administered by the therapeutics section of the Ministry of Health. Before this, the therapeutics and utilisation section of the Department of Health was responsible for medicines regulation. I have taken your request to include these departments.

Sodium valproate was first approved in New Zealand by the Drug Assessment Advisory Committee (DAAC) in 1975. However, this particular sodium valproate product is no longer available. The legislation regulating the use of medicines at the time was the Food and Drug Act 1969. The amount and type of data required from the sponsor wishing to distribute a new medicine in New Zealand was considerably less than is required now. At this time medical practitioners could supply their patients with any therapeutic drug required by them. Sodium valproate was first approved internationally in 1967, therefore it is possible that it was available in New Zealand prior to first approval.

There was concern in New Zealand about the teratogenic effects of anti-convulsant (antiepileptic) medicines in the 1970s (see 8th meeting of DAAC and MARC meeting minutes prior to 1975 in the documents provided).

There was no mention in the DAAC minutes of a concern regarding sodium valproate teratogenicity when the medicine was recommended for approval. However, in the Clinical Services Letter 165 (1977), it was stated that
'distribution of Epilim was restricted to appropriate specialists. This restriction was based on the desire for further long-term clinical data and in particular, the possible dangers of a link between sodium valproate and teratogenicity in humans'.

Data sheets were not required for medicines until the Medicines Act 1981 came into effect. The oldest data sheet identified is dated 1981 and includes the warning:
'Women of childbearing age
Valproic acid or sodium valproate, like certain other anti-convulsants have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings.'

Clinical Services Letter 216 (1983), states:
'Sodium valproate is removed from the list as it is considered that a sufficient cohort of users is now on computer to enable a rapid survey should further problems arise. Attention is drawn to recent reports of spina bifida occurring in 1 percent of fetuses exposed to sodium valproate during pregnancy'.

A document that appears to be either the data sheet or a proposed data sheet dated 1989 has a strengthened warning that includes the following:
'There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester'.

Therefore it is my conclusion that there has always been a suspicion that sodium valproate could be teratogenic and this was fully confirmed in the early 1980s, certainly by 1983.

I have identified and provided the documents within the scope of your request as shown in Table 1 (see also MARC meeting minutes itemised below in Table 7). Please note that some of the original documents were of poor quality due to their age. At the time they were produced there were no personal computers or photocopiers.

Table 1: DAAC minutes	
1	Minutes from the Meeting March 1973
2	Minutes from the Meeting March 1975
3	Minutes from the Meeting November 1975
4	Minutes from the Meeting November 1976
5	Minutes from the Meeting March 1977
6	Minutes from the Meeting February 1978
7	Minutes from the Meeting October 1980
8	Minutes from the Meeting March 1981
9	Minutes from the Meeting October 1982

Advice provided to prescribers and consumers

Advice is provided to prescribers through data sheets. Data sheets were not required until the Medicines Act 1981 came into effect. At that time data sheets were produced as a paper booklet by the sponsor and given to prescribers. Later, data sheets were published on the Medsafe website. Interested parties can sign up to receive emails from Medsafe informing them when data sheets are updated. I have identified and provided the different versions of Epilim data sheets since 1981 as shown in Table 2. I have also identified and provided copies of mail outs to subscribers indicating that the Epilim data sheet had been updated (Table 3).

Additional information is provided to prescribers in Ministry publications. I have identified and provided copies of the publications within the scope of your request as shown in Table 4.

Consumers are expected to be informed about the benefits and risks of harm of any medicines they may need, by the healthcare professionals involved in their care. To support these conversations, sponsors may volunteer to provide Consumer Medicine Information (CMI) for publication on the Medsafe website. This scheme has been in place since the late 1990s. I have identified and provided the different versions of the Epilim CMI as shown in Table 5.

Table 2: Epilim data sheets	
1	Undated
2	1981
3	1989
4	1993 – IV formulation
5	1993 – oral formulation
6	1994 – oral
7	1995 – oral
8	1997 – oral
9	1999 – IV

10	2001 – IV
11	2003 – IV
12	2003 – oral
13	2004 – IV
14	2004 – oral
15	2005 – IV
16	2005 – oral
17	2006 – IV
18	2006 – oral
19	2007 – oral
20	2008 – IV June
21	2008 – IV December
22	2009 – oral
23	2010 – IV
24	2011 – IV
25	2011 – IV
26	2011 – controlled release
27	2012 – oral
28	2014 – oral
29	2014 – controlled release
30	2015 – oral February
31	2015 – controlled release February
32	2015 – oral October
33	2016 – oral July
34	2016 – controlled release
35	2016 – oral October

Table 3: Medsafe mailouts alerting subscribers to updates	
1	Emails to website subscribers from September 2007
2	Emails to Prescriber Update subscribers

Table 4: Other healthcare professional communications	
Clinical Services Letters	
1	Clinical Services Letter 165 – Intensified Adverse Drug Reaction Reporting Scheme: Sodium valproate (Epilim). 18 March 1977
2	Clinical Services Letter 203 – Sodium valproate (Epilim). 17 June 1981
3	Clinical Services Letter 216 – Intensified adverse drug reaction reporting scheme January 1983
Prescriber Update articles	
1	Anticonvulsants and congenital malformations 30(1): 1 February 2009
2	Medicines and Use in Pregnancy 34(2):18-19. June 2013
3	Use of Sodium Valproate in Pregnancy 35(4): 46-48. December 2014
Safety Information	
1	Trans-Tasman Early Warning System – Alert Communication – Use of sodium valproate (Epilim) in pregnancy. 28 September 2015

Table 5: Epilim CMI	
1	2000 – oral
2	2001 – injection

3	2003 – oral March
4	2003 – oral November
5	2006 – injection
6	2006 – oral
7	2007 – injection
8	2009 – oral and IV
9	2012 – oral and IV
10	2014 – oral and IV
11	2015 – oral and IV
12	2016 – oral and IV

Communication between the UK and NZ

I have identified and provided one set of documents within the scope of your request. I have decided under 9(2)(a) of the Act to withhold details to protect the privacy of natural persons.

Other communications

Other communications within the Ministry of Health and with external groups or people (other than the UK) relating to the teratogenic effects of sodium valproate were identified. Table 6 lists the released documents. I have decided under 9(2)(a) of the Act to withhold details to protect the privacy of natural persons.

Table 6 Medsafe communications about teratogenic effects of Epilim	
Internal Correspondence	
1	2009 – memo
2	2009 – review of MARC minute
3	2010 – update to group manager
4	2012 – review of prescriber update text
5	2013 – discussion of FDA alert
6	2013 – discussion of complaint
7	2014 – data request
8	2015 – discussion re alert
9	2015 – query about data sheet
10	2016 – discussion re educational materials
11	2016 – discussion re labelling
12	2016 – media alert
Media Correspondence	
1	2014
2	2015
3	2017
External Correspondence	
1	ACC
2	CARM
3	HDC
4	Letter 1983
5	MARC
6	PHARMAC

7	TGA
Company correspondence	
1	Reckitt & Colman 1979-1994
2	Sanofi Aventis 2010
3	Sanofi 2014-2017

Number of females dispensed sodium valproate from 2014 to present

This information is displayed in the table below which was also included in the document: communication with the UK

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

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

How many children have been affected since 1975

Number of live births where mother was dispensed Valproate during estimated duration of pregnancy by year of delivery
Source: Ministry of Health Pharmaceutical Collection, extracted June 2017, ref: 2016-2644

Year of birth	Live Births
2007	124
2008	116
2009	103
2010	58
2011	86
2012	73
2013	56
2014	47
2015	51
2016	36

Please note that reporting on valproate dispensing during pregnancy requires an NHI number to be recorded on the pharmaceutical dispensing. Before 2007 NHI reporting was infrequent, therefore data before this time has not been provided.

Data is only provided for dispensings of PHARMAC subsidised community pharmaceuticals. Birth data for 2016 is provisional and subject to change. Still births and births with pregnancy outcome not stated have been excluded.

Copy of MARC meeting minutes

I have identified and provided documents within the scope of your request as shown in Table 7. I have decided under 9(2)(a) of the Act to withhold details to protect the privacy of natural persons.

Please note that some of the original documents were of poor quality due to their age. At the time they were produced there were no personal computers or photocopiers.

Table 7: Copies of MARC minutes from meetings when sodium valproate was discussed	
1	Minutes from the Meeting March 1966
2	Minutes from the Meeting September 1966
3	Minutes from the Meeting February 1967
4	Minutes from the Meeting February 1968
5	Minutes from the Meeting September 1968
6	Minutes from the Meeting April 1969
7	Minutes from the Meeting August 1969
8	Minutes from the Meeting February 1970
9	Minutes from the Meeting August 1970
10	Minutes from the Meeting February 1971
11	Minutes from the Meeting August 1971
12	Minutes from the Meeting August 1972
13	Minutes from the Meeting March 1973
14	Minutes from the Meeting August 1973
15	Minutes from the Meeting November 1974
16	Minutes from the Meeting July 1976
17	Minutes from the Meeting March 1978
18	Minutes from the Meeting July 1978
19	Minutes from the Meeting July 1979
20	Minutes from the Meeting December 1979
21	Minutes from the Meeting March 1980
22	Minutes from the Meeting March 1981
23	Minutes from the Meeting July 1981
24	Minutes from the Meeting July 1983
25	Minutes from the Meeting November 1983
26	Minutes from the Meeting March 1984
27	Minutes from the Meeting December 1984
28	Minutes from the Meeting March 1985
29	Minutes from the Meeting March 1995
30	Minutes from the Meeting December 1996
31	Minutes from the Meeting March 1997
32	Minutes from the Meeting March 1998
33	Minutes from the Meeting November 1998
34	Minutes from the Meeting June 2000
35	Minutes from the Meeting September 2001
36	Minutes from the Meeting December 2001
37	Minutes from the Meeting March 2002

38	Minutes from the Meeting June 2002
39	Minutes from the Meeting September 2002
40	Minutes from the Meeting September 2003
41	Minutes from the Meeting March 2004
42	Minutes from the Meeting June 2005
43	Minutes from the Meeting September 2005
44	Minutes from the Meeting December 2005
45	Minutes from the Meeting December 2006
46	Minutes from the Meeting March 2007
47	Minutes from the Meeting June 2007
48	Minutes from the Meeting March 2008
49	Minutes from the Meeting May 2008
50	Minutes from the Meeting September 2008
51	Minutes from the Meeting March 2009
52	Minutes from the Meeting June 2009
53	Minutes from the Meeting September 2009
54	Minutes from the Meeting December 2009
55	Minutes from the Meeting December 2010
56	Minutes from the Meeting March 2015
57	Minutes from the Meeting December 2015

I trust this information fulfils your request. You have the right, under section 28 of the Act, to ask the Ombudsman to review my decision to withhold information under this request.

Yours sincerely [redacted]

[redacted]

Group Manager
Medsafe