ETOP
HEALTHHO NZ3571
RECPITT NZ21190

26.2.79

ATTN PROFESSOR E G MC QUEEN AND/OR DR J MACINTOSH

RE VALPROATE IN FOETAL MALFORMATION

THE FOLLOWING TELEX RECEIVED FROM OUR MEDICAL DEPARTMENT IN HULL, DATED 23 FEBRUARY 1979 IS TEXT OF THEIR LETTER 19 FEB RECEIVED TODAY COPY UPCOMING

QUOTE

RE YR TLX 23 FEBRUARY TEXT OF EPILIM ADVERSE REACTION REPORT FOLLOWS BELOW. REPORT SENT BY LETTER 20 FEBRUARY BUT MAY NOT REACH YOU IN TIME.

THE MEDICAL DEPT HAS BEEN INVOLVED IN THE COLLECTION OF DATA ON THE USE OF EPILIM IN PREGNANCY FOR APPROXIMATELY FOUR YEARS. WHEN WE LEARN OF A PATIENT TAKING EPILIM DURING HER PREGNANCY WE ASK THE CLINICIAN IN CHARGE OF HER CASE TO COMPLETE A REPORT FORM. THIS IS THE ONLY WAY IN WHICH WE CAN GATHER DATA, IT IS A SLOW PROCESS AS IN GENERAL CONTACTS ARE NOT MADE UNLESS THE PATIENTS CLINICIAN ASKS THE PHARMACY TO SEEK ADVICE FROM US ABOUT THE POSSIBLE TERATOGENIC EFFECTS OF EPILIM.

AS AT FE 19 FEBRUARY 1979 OUR RESULTS ARE AS FOLLOWS

COMPLETED FORMS RETURNED	34
UNSOLICITED REPORTS	3
APPARENTLY NORMAL BABIES	26
(ONE TRANSIENT JAUNDICE, ANOTHER TRANSIENT ASPHYSIA AT BIRTH)	
ABNORMAL BABIES	6
SPONTANEOUS ABORTIONS	3
(FIRST TRIMESTER)	2
(SECOND TRIMESTER)	1
THERAPEUTIC ABORTIONS	2
(EXTERNAL EXAMINATION OF FOETAL MATERIAL IN ONE CASE ONLY. NO GROSS ABNORMALITIES SEEN)	

THE RATE OF SPONTANEOUS ABORTION IN THIS SERIES IS NOT CCONSIDERED SIGNIFICANT AS THE OCCURRENCE IN THE FEMALE POPULATION 'AT RISK' IS HIGH, AND IT IS NOT CONSIDERED THAT EPILIM CAUSED THESE ABORTIONS

BRIEF DETAILS OF THE ABNORMAL BABIES ARE AS FOLLOWS:

1 CONVULSIONS MENTAL RETARDATION. MOTHER RECEIVED EPILIM AND PHENOBARBITONE DURING FIRST TRIMESTER.

STRONG GENETIC ELEMENT PROBABLE IN ABNORMALITY

2 'FAILURE TO THRIVE'? COWS MILK SENSITIVITY. MOTHER RECEIVED EPILIM MYSOLINE AND EPANUTIN THROUGHOUT PREGNANCY.

3 CLEFT LIP AND PALATE. MOTHER ON MULTIPLE ANTICONVULSANTS. SHE RECEIVED EPILIM FOR SIX DAYS AT 20+ WEEKS.

4 OBSTRUCTED INTESTINAL HERNIA REQUIRING SURGERY BUT NOT RESECTION. MOTHER ALSO RECEIVED PHENYTOIL PRIMIDONE AND NITRAZEPAM DURING PREGNANCY.

5 SPINA BIFIDA. FEMALE CHILD BORN 19/8/77 LMP NOT STATED. EPILIM 600 MG/DAY. DECEMBER 1976 - FEBRUARY 1977. MOTHER 21 YEARS OLD BANGLADESHI. PAST OBSTETRIC HISTORY

1973 STILL BIRTH
1976 NORMAL BABY

6 LOW SET EARS SHORT NECK, SACRAL AGENESIS. DIED WITHIN 24 HOURS OF APNOEIC ATTACK. MOTHER 18 YEARS OLD. CHILD BORN 15/12/77.
DRUG HISTORY -
PHENYTOIN 200 MG BD JUNE 1976 - OCTOBER 1977
EPILIM 1200 MG/DAY OCTOBER 1977 - PRESENT

ONLY IN CASE 5 WAS EPILIM THE SOLE DRUG IN USE. IN CASES 3 AND 6 EPILIM WAS USED LATE IN THE PREGNANCY AND PROBABLY CANNOT BE IMPLICATED.
TERATOGENIC STUDIES IN ANIMALS HAVE SHOWN NO EFFECT WITH SMALL DOSES (30MG/KG-90MG/KG) FOETAL ABNORMALITIES WERE PRODUCED WHEN THE DOSES WERE INCREASED TO BETWEEN 100MG/KG AND 600 MG/KG. COMMONLY UNILATERAL RENAL AGENESIS AND ABNORMALITIES OF VERTEBRAL FUSION WERE CAUSED.

INFORMATION IS LIMITED AND IN THE UK WE ALWAYS POINT OUT THAT ULTIMATELY THE DECISION WHETHER TO USE OR CONTINUE EPILIM IS A CLINICAL ONE, BALANCING THE RISKS OF POSSIBLY UNCONTROLLED EPILEPSY AGAINST POSSIBLE EMBRYOPATHIC EFFECTS OF THE ANTICONVULSANTS.

UNQUOTE

REGARDS [redacted]

RECKITT NZ21190F
HEALTHHO NZ3571T

(a-)70/

Reckitt & Colman New Zealand Ltd.

6th October, 1982.

Director-General of Health,
Department of Health,
P.O. Box 5013,
WELLINGTON.

Attn: R. C. Griffith

Dear Mr. Griffith,

Re: I.A.D.R.R.S. - Epilim Review - October Meeting

Further to our recent telephone conversation regarding a delay in receiving Epilim data, I now attach in septuplicate the following information:-

1. Hepatic Lesions in Patients treated with Sodium Valproate
   Report No. 005.001 1982

2. Epilim in Pregnancy

Yours faithfully,
RECKITT & COLMAN (NEW ZEALAND) LIMITED

[redacted]

SIC:SAW

EPILIM IN PREGNANCY

Epilim has been shown to be teratogenic in rats and mice in doses ranging from 150-600 mg/kg/day and in rabbits in doses greater than 252 mg/kg/day (1-3). It is difficult to extrapolate these findings to the clinical setting because of species differences in teratogenic response and because the teratogenic doses are much higher than those used therapeutically.

Evidence to date indicates that valproic acid crosses the placenta freely. Values between 1.0 and 3.39 have been recorded for cord serum: maternal serum concentration ratios (see table 1). Reasons for serum levels being higher in the neonate than in the mother are not known, but could include the involvement of an active transport mechanism in the placenta and differences in protein binding between the maternal and foetal compartments. (Valproic acid is 90% protein bound.)

Table 1

Source	No of cases	Cord serum: Maternal serum concentration ratio
Bardy et al (4)	Not stated	Around 1
Alexander (5)	1	Around 1
Dickinson et al (6)	1	1.5
Froescher et al (7)	4	Between 1.3 and 3.39
Nau et al (8)	6	Between 1.2 and 3.0
Ishizaki et al (9)	4	Between 1.48 and 2.41

Published data on the clinical use of Epilim in pregnancy is limited. Alexander (5) describes a single case in which Epilim 1600 mg/day was given as sole therapy throughout pregnancy. Serum levels of valproic acid in the neonate were of the same order as that of in the mother's serum. There was no evidence of any abnormality in the infant. Dalens et al (10), describe a patient who received 1000 mg/day of valproate as sole therapy throughout pregnancy. The patient had a short gereralised seizure in the second week of pregnancy. A grossly dysmorphic female was produced which died at 19 days.

Brown et al (11), describe a series of 13 pregnancies in which valproic acid was administered, only one of which gave rise to abnormal offspring. Hillesmaa et al (12), report on 12 patients who took valproic acid throughout pregnancy, usually in combination with phenytoin or carbamazepine. Only 1 patient took valproic acid alone. No malformations or other abnormalities were encountered in the 12 infants, either at birth or during follow-up, which ranged from 2 months to 4 years. Simila et al (13), describe 2 patients who took sodium valproate together with other anticonvulsants throughout pregnancy. Both these patients produced healthy offspring, however, both these cases showed a transient secondary hyperglycinaemia in the neonatal period, which the author attributes to the use of sodium valproate in the last trimester of pregnancy. This could cause a false positive finding in metabolic screening for aminoacidaemias in newborn babies.

Gomez (14) reports on the case of a patient treated with valproic acid together with clonazepam and phenobarbitone throughout pregnancy. Valproic acid was given in a dose of 1500 mg daily during the first 2 months of pregnancy and reduced gradually to 500 mg at 3½ months. The patient gave birth to a male infant with lumbosacral meningocele which had ruptured, and sensory motor deficit in the distribution L_4 to S_2. Thomas and Buchanan (15) report teratogenic effects in an infant whose mother took carbamazepine, ptimidone and valproate throughout pregnancy. Seizure control had never been adequate and during pregnancy several grand mal fits had occurred each week. Dysmorphic features in the infant included hypoplastic nails, depressed nasal bridge, a small cleft in the centre of the upper alveolar margin, high-arched palate, splayed sutures, wide anterior fontanelle, abnormal palmar creases and tetralogy of Fallot.
Clay et al (16), describe a 28 year old woman with known neurofibromatosis who received 750 mg valproic acid throughout pregnancy which was seizure free. The woman produced a 3295 gm dysmorphic male infant. At 22 months the child had coarsened facies, a prominent forehead and a flat nasal bridge with a small nose. A grade 3/6 ventriculoseptal defect murmer was present. The neck was short, he had widely spaced nipples, a hypo-plastic right thumb and shortened fingers and toes. Additionally he had cutaneous stigmata of neurofibromatosis, including axillary freckling and numerous café-au-lait spots.

Cairney et al (17), report the case of a 27 year old woman taking sodium valproate 600 mg daily, whose pregnancy was terminated at 17 weeks gestation because of her anxiety with regard to the possible teratogenic effects of her medication. The foetus was examined carefully. There were no abnormalities and the size was consistent with the period of gestation.

A leading article in the British Medical Journal (18) on the teratogenic risks of anti-epileptic drugs concludes that, on balance, carbamazepine or sodium valproate seems preferable to phenytoin or phenobarbitone as the first choice for the treatment of appropriate types of epilepsy in young girls and women in their reproductive years.

The company has collected data on the outcome of 101 pregnancies in which Epilim was taken during pregnancy. Only 40 of the mothers were taking Epilim as the sole anticonvulsant; of those there were 4 spontaneous abortions and 6 abnormal births. The latter included 2 cases of spina bifida, 1 with meningocele, 1 case of syndactyly of 2 fingers of the left hand, 1 case of ventricular septal defect not requiring surgery (this patient has also taken chloroquine for a falciparum malaria infection), 1 case of abnormal facies, long fingers and toes, and 1 case of syndactyly of 2 toes of the left foot with an absent third toe and bilateral finger-like thumbs.

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In Legg N J ed. Clinical and pharmacological aspects of sodium valproate (Epilim) in the treatment of epilepsy
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4) Bardy A H, Hiilesmaa V K, Teramo K
Anti-epileptic drugs in amniotic fluid
Abstracts from Epilepsy International Congress (Kyoto, Japan) 1981

5) Alexander F W
Archives of Disease in Childhood, 1979, 54, 240-245

6) Dickinson, et al
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7) Froescher W, et al
Anti-epileptic therapy with carbamazepine and valproic acid during pregnancy and lactation period
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Valproic acid and its metabolites: Placental transfer, neonatal pharmacokinetics, transfer via mothers' milk and clinical status in neonates of epileptic mothers
J Pharmacol and Experimental Therapeutics 219, 768-777

9) Ishizaki T, et al
Placental transfer of anticonvulsants (phenobarbital, phenytoin, valproic acid) and the elimination from neonates
Paediatric Pharmacology, 1981, 1, 291-303

10) Dalens B, et al
J Paediatrics, 1980, 97, 332-333

11) Brown N A, et al
Lancet, 1980, 1, 660

12) Hiilesmaa V K, et al
Lancet, 1980, 1, 883

13) Simila S L, et al
Archives of Disease in Childhood, 1979, 54, 986-987

14) Gomez M R
J Paediatrics, 1981, 98, 509

15) Thomas D, Buchanan N
J Paediatrics, 1981, 91, 163

16) Clay S A, et al
J Paediatrics, 1981, 99, 828

17) Cairney P, et al
New Zealand Med J, 1981, 94, 233

18) BMJ, 22 August 1981, 515

SUMMARY OF UNPUBLISHED DATA ON EPILIM IN PREGNANCY

TOTAL CASES

Epilim alone or in combination with other anticonvulsants

Number of reports	101
Number of apparently normal babies	70
Number of abnormal babies	23
Number of spontaneous abortions	5
Number of therapeutic abortions	3

Epilim as sole anticonvulsant therapy during period of teratogenic risk

Number of reports	40
Number of apparently normal babies	30
Number of abnormal babies	6
Number of spontaneous abortions	4
Number of therapeutic abortions	0

Epilim in combination with other anticonvulsants

Number of reports	61
Number of apparently normal babies	40
Number of abnormal babies	17
Number of spontaneous abortions	1
Number of therapeutic abortions	3

abnormal births (in the attached summary)

The case numbers of abnormal births and abortions are listed below:-

Case numbers of all abnormal births relating to patients receiving Epilim alone or in combination with other anticonvulsants:-

1, 2, 11, 29, 30, 40, 45, 51, 56, 61, 65, 69, 74, 77, 80, 83, 84, 87, 95, 97

Case numbers of all spontaneous abortions relating to patients receiving Epilim alone or in combination with other anticonvulsants:-

7, 20, 25, 35, 78

Case numbers of therapeutic abortions relating to patients receiving Epilim alone or in combination with other anticonvulsants:-

34, 91, 96

Case numbers of all abnormal births relating to patients receiving Epilim as sole anticonvulsant therapy:-

30, 69, 84, 87, 95, 97

Case numbers of all spontaneous abortions relating to patients receiving Epilim as sole anticonvulsant therapy:-

7, 20, 25, 78

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...ts on Epilim

o	Epilim	Other drugs and relevant history	Outcome of pregnancy
	[redacted]	Soluble insulin Phenobarbitone Sulthiame Ethosuximide Ampicillin 4 previous spontaneous abortions	Male child with cleft lip and palate Intra uterine growth retardation
	[redacted] throughout pregnancy	Phenobarbitone throughout Flu-like illness at 12/52 with threatened abortion	Male - mental retardation Convulsions
	[redacted] throughout pregnancy	Nil	Normal baby transient neonatal jaundice
	[redacted] from about 10/52	Nitrazepam and acetazolamide throughout. Phenytoin during 1st trimester. Phenobarbitone and ethosuximide from about 8 weeks	Normal
	[redacted] throughout pregnancy	Nil	Normal baby
	[redacted] throughout pregnancy	Phenobarbitone throughout pregnancy	Normal baby
	[redacted] from conception	Nil	Spontaneous abortion 1st trimester
	[redacted] first 8-10 weeks only	Phenobarbitone Phenytoin throughout	Normal

		Other drugs and relevant history	Outcome of pregnancy
9	[redacted] throughout pregnancy	Phenytoin Primidone throughout pregnancy	Normal baby 'failure to thrive ? cows milk sensitivity
)	[redacted] from about 12 weeks	Primidone throughout pregnancy. Tetracycline [redacted] about 12 weeks.	Normal baby
	[redacted] during 1st 16 weeks perhaps longer [redacted]	Phenytoin at least 1st 16 weeks. Primidone at least 1st 10 weeks. Nitrazepam	Obstructive hernia and vomiting laparotomy. Release of obstruction without resection. Full details not available.
2	[redacted] throughout pregnancy	Phenobarbitone throughout pregnancy	Normal baby
3	[redacted] throughout pregnancy	Nil	Normal baby
4	[redacted] throughout pregnancy	Phenytoin Primidone reduced during pregnancy & stopped.	Normal: previous medical termination
5	[redacted] pregnancy to 36/52	Nil	Normal baby
;	[redacted] during last trimester	Phenytoin throughout	Normal baby
	[redacted] throughout pregnancy	Carbamazepine Primidone throughout.	Normal baby
	[redacted] throughout pregnancy	Phenytoin throughout	Normal baby

	Epilim	Other drugs and relevant history	Outcome of pregnancy
19	[redacted] throughout pregnancy	Nil	Foetal distress Normal baby
20	[redacted] throughout pregnancy	Nil	Spontaneous abortion in 1st trimester
21	[redacted] throughout pregnancy	Primidone Phenytoin throughout	Transient neonatal asphyxia. Normal baby
22	[redacted] throughout pregnancy	Phenytoin Carbamazepine throughout	Normal baby
23	[redacted] but Epilim taken throughout pregnancy	Other unspecified anticonvulsants also taken throughout pregnancy.	Normal baby
24	[redacted] throughout pregnancy	Iron	Normal baby
25	[redacted] throughout pregnancy	Nil	Spontaneous abortion 1st trimester
26	[redacted] for about 1/12 in first trimester	Phenobarbitone Phenytoin for about 12 weeks	Normal baby
27	[redacted] throughout pregnancy	Phenytoin throughout	Normal baby
28	[redacted] throughout pregnancy	Nil	Normal baby
29	[redacted] for last 2 months	Phenytoin until last trimester	Low set ears, short neck sacral agenesis. Died [redacted]

		Other drugs and relevant history	Outcome of pregnancy
30	[redacted] during 1st trimester	Nil Past obstetric history (pre-Epilim): 1 normal child 1 still-birth	Spina bifida
31	[redacted] throughout pregnancy	Phenytoin iron	Normal baby
32	[redacted] throughout pregnancy	Phenytoin throughout	Normal baby
33	[redacted] throughout pregnancy	Phenobarbitone Phenytoin throughout	Normal baby
34	[redacted] throughout pregnancy	Primidone Phenytoin	Termination of pregnancy on medical grounds
35	[redacted] throughout pregnancy	Carbamazepine throughout	Spontaneous abortion 1st trimester
36	[redacted] throughout pregnancy	Carbamazepine Temazepam Chlorpheniramine Iron	Normal baby
37	[redacted] during last trimester	Primidone Phenytoin throughout	Normal baby
38	[redacted] throughout	Ethosuximide Iron	Normal baby
39	[redacted] throughout	Nil	Normal baby

	Other drugs and relevant history	Outcome of pregnancy
[redacted] Given during 1st 8 weeks gestation	Phenytoin [redacted] Primidone [redacted] probably both given throughout pregnancy It is not made clear whether these drugs were also withdrawn at 8 weeks.	Premature birth at [redacted] Died a[redacted]. Gross congenital abnormalities Cleft lip/palate. Imperforate anus. Renal agenesis. Absent ureter and bladder. 1 lobe R lung
[redacted] throughout pregnancy	Phenobarbitone [redacted] throughout pregnancy	Normal baby (F)
[redacted] throughout pregnancy	Two tablets clonidine daily iron & folate	Normal baby (F)
[redacted] before and during pregnancy	Folic acid	Skeletally normal baby (F). Induced delivery at 42/52 by dates but foetal maturity only 35/52 Respiratory problems in first week
[redacted] throughout pregnancy	Phenobarbitone throughout	Normal baby
Dosage not stated but Epilim taken prior to and throughout pregnancy	Pentobarbitone Promazine Flurazepam	Male baby Visual problems, squint & organic retrogeniculate defect (barbiturate related attentional defect & developmental delay)
[redacted] throughout pregnancy	Iron	Normal baby (F)
[redacted] throughout pregnancy	Carbamazepine	Normal female baby

		Other drugs and relevant history	Outcome of pregnancy
8	[redacted] in first trimester. Stopped when she found she was pregnant	Nil	Normal male baby
9	[redacted] throughout pregnancy	Iron and folic acid	Normal female baby
0	[redacted] 8 days before delivery [redacted]	Phenytoin and Phenobarbitone three weeks before delivery but stopped 5 days before delivery	Normal female baby Slightly slow to establish feeding but only a mild problem.
	[redacted] throughout pregnancy	Phenobarbitone throughout	Female baby with spina bifida and hydrocephalus by forceps delivery
	[redacted] throughout	Nil	Normal female baby [redacted]
	[redacted] for first three months only	Nil	Normal male baby
	[redacted] throughout	Nil	Normal female baby
	[redacted] for first seven months [redacted]	Carbamazepine throughout	Normal male baby born by caesarian section

[redacted] first 12 weeks	Phenytoin and phenobarbitone continued throughout pregnancy [redacted]	Male baby by SVB, congenital absence of left radius and severe radial flexion deformity. Cardiac abnormalit catheterised in first week of life and found to have ASD, VSD; possible co-arctation of th aorta.
[redacted]	Nil	Normal female baby
[redacted]	Nil	Normal male baby
[redacted] increased to [redacted] mid 2nd trimester	Nil	[redacted] Normal male [redacted] (Forceps for cord prolapse)
[redacted] throughout	Phenytoin 200mg throughout	[redacted] Normal male [redacted]
[redacted] throughout	Not stated	[redacted] Male. Pyloric stenosis [redacted]
[redacted] 1st trimester 2nd trimester	Ampicillin/ Flucloxacillin and Diazepam [redacted] in mid 2nd trimester. Not anti-convulsants. Folic acid	[redacted] Normal male [redacted]
[redacted] throughout	Carbamazepine [redacted] throughout	[redacted] Normal female [redacted]

	Epilim	Other drugs and relevant history	Outcome of pregnancy
4	[redacted] 2nd and 3rd trimesters	Folic acid 5mg x 2	[redacted] Normal male [redacted]
5	[redacted] throughout	Carbamazepine [redacted] Phenytoin [redacted] throughout	[redacted] Male. Slightly low set ears, only one umbilical artery [redacted]
6	[redacted] until pregnancy known, [redacted]	Phenytoin [redacted] as Epilim	[redacted] Normal male [redacted]
7	[redacted] throughout	Nil	[redacted] Normal Male [redacted]
8	Discontinued mid-1st trimester	Not known	[redacted] Normal male [redacted]
9	[redacted] throughout	Iron Folic acid	[redacted] Male, [redacted] Syndactally [redacted]
0	[redacted] decreased to mid-2nd trimester	Iron Folic acid 'Debendox'	[redacted] Normal female, [redacted]
1	[redacted] 1st trimester	Phenobarbitone	[redacted] Normal male [redacted]

		Other drugs and relevant history	Outcome of pregnancy
	[redacted] throughout	Phenytoin [redacted] throughout	[redacted] Normal female [redacted]
	[redacted] throughout	Carbamazepine [redacted] throughout	[redacted] Normal male [redacted]
	[redacted] throughout	Phenobarbitone [redacted]	[redacted] Male. Major hypospadias with chordee, 2 cord vessels, low set ears, rocker bottom feet Ventricular septa defect. Flexion contractures fingers. ? Pulmona stenosis, ? Fits
;t)	[redacted] 3rd trimester	Not stated	Normal baby
;t)	[redacted] 1st trimester	Nil	Normal female
;t)	[redacted] throughout	Phenytoin Ethosuximide	Normal female with minor toe webbing, both fee
	[redacted] daily throughout pregnancy	None	Spontaneous abortion
	[redacted] daily throughout pregnancy	Phenytoin throughout	Normal baby
t)	[redacted] daily throughout pregnancy	Carbamazepine [redacted] Primidone [redacted] Published: J. Paediatrics 1981, 99, 163 Thomas & Buchanan	Dysmorphic child Hypoplastic nails depressed nasal bridge, cleft alveolus, high arched palate, splayed sutures, wide anterior fontanelle,

		Other drugs and relevant history	Outcome of pregnancy
1	[redacted] daily throughout pregnancy	None	Normal
2	[redacted] daily throughout pregnancy	Carbamazepine [redacted] Diazepam [redacted] throughout pregnancy	Hypotonic baby. [redacted]
3	[redacted] daily throughout	Phenytoin [redacted] Sulthiame [redacted] throughout pregnancy. Oral contraceptives at time of conception	Meningocele
4	[redacted] throughout pregnancy	None	Spina bifida with meningocele
5	[redacted] daily throughout pregnancy	Carbamazepine and phenytoin throughout	Normal baby
6 1st)	[redacted] day throughout pregnancy	Acetazolamide in last trimester	Normal female bab
7 1st)	[redacted] throughout pregnancy	Chloroquine, iron, vitamins Falciparum Malaria infection	Caesarian section [redacted] Ventricular septal defect not requiring surgery. Blocked tear ducts
	[redacted] from 16th week of pregnancy	Salbutamol inhaler Aminophylline [redacted]	Normal infant
	[redacted] throughout pregnancy	Carbamazepine [redacted] throughout pregnancy	Normal male infant

	Epilim	Other drugs and relevant history	Outcome of pregnancy
90	[redacted] throughout pregnancy	Iron & folic acid throughout pregnancy	Male infant with severe respiratory distress syndrome associated with pre-term delivery. Baby now feeding & thriving satisfactorily
91	Dose not stated	Carbamazepine dose not stated	Routine AFP raised confirmed on amniocentesis. Foetus aborted & confirmed to have spina bifida
92	[redacted] throughout pregnancy	Nil	Male infant failed to breathe at birth, but no foetal abnormality. Now normal
93	[redacted]/daily throughout pregnancy	Nil	Normal infant
94	[redacted]/daily throughout pregnancy	Nil	Normal female infant
95	[redacted]/daily throughout pregnancy [redacted]	Phenobarbitone taken in 9th month of pregnancy Intra-uterine infection including Rubella and Toxoplasmosis excluded. Appears patient may have fitted during pregnancy	Abnormal female infant delivered at term with abnormal facies, abnormal head shape, prominent frontal region, low set malformed ears with abnormal helices, long fingers, a flexion contracture of the left ring finger, tapering, slightly narrow nails, long toes, hypoplastic thenar eminencies with the thumb in flexion & a ligamentous click of the right

		Other drugs and relevant history	Outcome of pregnancy
96	[redacted]/daily throughout pregnancy	Phenobarbitone [redacted] throughout pregnancy	Male foetus terminated [redacted] with lumbar spina bifida and myelocele
97	4[redacted]/daily	Paracetamol and dextropropoxyphene after road traffic accident [redacted]	Male infant with bilateral finger-like thumbs. Left sided thumb triphalangeal and small rudimentary extra digit arising from the base of the right thumb. Left foot syndactyly of 1st & 2nd toes and 3rd toe absent. Failure to thrive. [redacted] suspected may have cyanotic congenital heart disease
98 Aust)	[redacted] prior to and throughout pregnancy	Carbamazepine Thyroxine	Male baby. Low lumbar myelomeningoccele treated surgically
99 Aust)	[redacted] 2nd & 3rd trimester	Phenytoin 1st trimester	[redacted] Hydrocephalic child
00 Aust)	[redacted]/daily prior to and throughout pregnancy	Carbamazepine Clonazepam	[redacted] Normal child
01 Aust)	[redacted]/daily prior to and throughout pregnancy	Carbamazepine Clonazepam	[redacted] intrauterine death [redacted] Hydrocephalic intracranial haemorrhage

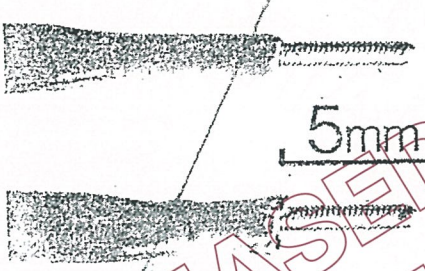
One Patient

v. 2 no 8304

SIR,—During the past decade silicone elastomer ('Silastic') catheters have largely replaced the more rigid 'Teflon' and polypropylene catheters for long-term parenteral nutrition. Given a safe and effective means of placement,[1] our experience now is of very few mechanical or thrombotic problems.

The recent correspondence regarding thrombosis of the superior cava related to the tip of central venous catheters has highlighted the association of this complication with rigid catheters, especially those used for haemodialysis. Since 1980 we have been using 'Vas-cath' (Gambro) catheters for short-term haemodialysis. Seventy catheters have been placed de novo in 65 patients. Poor flow has been infrequent and usually corrected by catheter change over a guidewire. Since none of our patients has been investigated by venography we cannot exclude the possibility of superior vena caval thrombosis around the catheter tip.

An assumption that intimal damage to the superior vena cava is important in the genesis of this complication explains the association with rigid catheters. However, I believe that the tips of these catheters can become seriously damaged during insertion over the guidewire. Such a damaged tip (figure) can have sharp everted



Damaged tip of vas-cath following insertion over guidewire without dilator (above), an unused catheter for comparison).

edges which will, I suggest, lead to intimal damage of the cava.

In view of this I have now changed our technique of insertion.[2] Whereas we used to dilate the track and the tunnel separately with the catheter itself, we now do this with a disposable dilator; passage of the vas-cath itself is now not attended by any snagging or the need for excessive pushing and twisting.

Until softer more pliable catheters are available I would strongly recommend the use of a dilator to avoid catheter tip damage.

Renal Transplant Unit,
St Mary's Hospital,
London W2 1NY

BRIAN W. ELLIS

MATERNAL VALPROIC ACID AND CONGENITAL NEURAL TUBE DEFECTS

SIR,—Our birth defects monitoring system for the Rhône-Alpes region of France, where there are about 72 000 births a year, operates with the collaboration of all paediatricians and obstetricians. We participate in the international clearing house for birth defects monitoring.[3] We collected, between Aug. 11, 1979, and Aug. 10, 1982, 72 case-records of infants born with lumbosacral neural tube defects (NTD) alone or associated with other malformations. 9 were infants born to epileptic mothers who had taken valproate during pregnancy. Gomez' letter[4] prompted us to describe these cases (see table).

We have no case of association of valproic acid with anencephaly (among the 17 cases of anencephaly collected during the same period), but our monitoring system is imperfect for stillbirths and for therapeutic abortions.

DETAILS OF NINE CASES OF NTD IN INFANTS BORN TO MOTHERS WHO HAD TAKEN VALPROATE DURING PREGNANCY

Case (and date of birth)	Valproate* (mg/day)	Defect(s)	Family history
1 (Nov. 8, 1979)	1500	LMS	Father's brother: SBA, died at 6 mo First cousin: mucoviscidosis
2 (June 28, 1980)	1500	Sacral meningocele	None
3 (March 6, 1981)	400	LSM + hydrocephaly and microcephaly	None
4 (April 5, 1981)	2000	Lumbar SBA	Grandmother's sister: trisomy 21 Second cousin: DMD Maternal grandmother and maternal second cousin: epilepsy
5 (Aug. 12, 1981)	1200	Epidermised lumbar SBA* + hydrocephaly	Second cousin: SBA First cousin: late enuresis
6 (Nov. 19, 1981)	1000	LSM + complex congenital cardiopathy + hypospadias (karyotype normal)	Mother's sister: SBO + late enuresis
7 (March 2, 1982)	1000	Sacral meningocele	None
8 (March 18, 1982)	750	Lumbar SBA	None
9 (Aug. 10, 1982)	1500	Sacral open meningocele	None

SBO = spina bifida occulta; SBA = spina bifida aperta; DMD = Duchenne muscular dystrophy; LSM = lumbar myelomeningocele.
*Throughout pregnancy except in case 2 (first trimester), other anticonvulsants (and daily doses in mg) were: phenobarbitone 50 (case 1), phenobarbitone 200 (case 2), phenobarbitone 200 + primidone 250 (case 3), and clonazepam 2 (case 9).

2 of the 9 cases had another case of severe NTD in their family, a larger than expected proportion.

All 9 cases required surgery, and 1 died (no. 6). Only one mother (no. 2) had non-stabilised epilepsy: she had had four epileptic seizures during the first trimester of pregnancy.

Valproic acid was given alone (5 cases) or with phenobarbitone (3 cases), or clonazepam (1 case). The doses of valproic acid were high, over 1 g daily in 7 cases. Blood concentrations of valproate in these women will be measured while they are on the same treatment.

We suspect that valproate may be teratogenic and have started a case-control study in collaboration with some other members of the International Clearinghouse.

Institut Européen des Génomutations,
69005 Lyon, France

ELISABETH ROBERT
PIERRE GUIBAUD

**In France and in West Germany, where the equivalents of data sheet compendia are readily available to the public, warnings about the possible teratogenicity of sodium valproate are low key, but in the U.K., U.S.A. and elsewhere the product information warnings are specific and refer to animal evidence. Besides Gomez' report there are other human data that warrant caution.—ED. L.

POLYCYSTIC OVARIES DISEASE: ONE OVARY TOO MANY?

SIR,—The Stein-Leventhal syndrome—consisting of hirsutism, oligomenorrhoea or amenorrhoea, and obesity combined with polycystic ovaries, and nowadays called the "polycystic ovaries syndrome" (PCO)—still has an uncertain aetiology. The primary lesion can (but generally does not) originate in the adrenal glands. In most cases it remains unclear whether one or both ovaries or hypothalamic-hypophyseal dysfunction is predominantly involved in the disease. However, it is well established that androgen production from ovaries and/or adrenal glands is increased and that continuous oestrogen release contributes to the syndrome.

There is a tendency to the view that PCO should not be left untreated. The androgen excess, it is argued, can cause hirsutism (or even virilism) and overweight because of the anabolic effects of androgens and the increased appetite while the continuous release of unopposed oestrogen could increase the risk of endometrial and mammary cancer.

1. Ellis BW, Fielding LP. Advanced techniques in intravenous therapy. In Rob G, Smith R, eds. Operative surgery: General principles, 3rd ed. London: Butterworths, 1977.
2. Ellis BW, Nicholls JP, Crombie AK, Thom SAMcG. A new technique in haemodialysis. *Nursing Times* 1982; 40: (suppl): 8–9.
3. Flynt JW, Hay S. International Clearinghouse for Birth Defects Monitoring system. *Centr Epidemiol Biostat* 1979; 1: 44–52.
4. Gomez M. Possible teratogenicity of valproic acid. *J Pediatr* 1981; 99: 508.

Contra-Indications, Warnings, etc.

Liver dysfunction, including hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. The incidents generally occured during the first six months of therapy, the period of maximum risk being 2-12 weeks.

Biochemical tests may not always become abnormal early in the evolution of hepatic failure; non specific findings such as loss of seizure control, malaise, anorexia and vomiting, developing after a period of satisfactory Epilim treatment may alert the clinician to the possibility of hepatic damage. Epilim should not be administered to patients with pre-existing hepatic dysfunction. All patients for whom treatment with Epilim is contemplated should have base line liver function assessed (including serum fibrinogen and albumin levels) prior to commencement of therapy. Liver function should be carefully monitored, particularly during the first six months of therapy, and when dosage is being titrated upwards. Patients with a prior history of liver disease or with severe or unusual seizure disorders, e.g. those accompanied by mental retardation and/or organic brain disease, should be followed particularly carefully. Transient elevations of liver enzymes are not uncommon during early treatment with Epilim. However, if liver enzyme elevations are accompanied by other evidence of hepatic dysfunction, especially raised serum bilirubin or lowered serum fibrinogen, then the drug should be immediately withdrawn.

Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. It has been suggested that this may be related to interference with propionic acid metabolism. This may manifest clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur, Epilim should be discontinued.

Valproic acid inhibits second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but have usually been associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving Epilim be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been reported with sodium valproate. The blood picture returned to normal when the drug was discontinued.
There have been reports of pancreatitis occurring in patients receiving valproic acid of sodium valproate. Patients experiencing acute abdominal pain should have the serum amylase estimated.

No cardiac effects attributed to Epilim have been reported. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Epilim tablets or syrup with or after food.

Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Tremor has occasionally been observed at high dosage; this may be controlled by reduction of dosage. Oedema has been reported. Increase in alertness, appetite and weight may occur.

Combined medication: Epilim is generally well tolerated in combination with other anti-epileptic agents; however owing to the interaction known to occur between these compounds, it may sometimes be necessary to reduce the dosage of other drugs when adding Epilim to existing anti-convulsant therapy. Epilim may block the metabolism of barbiturates giving rise to raised plasma barbiturate level. Like many other drugs, Epilim may also potentiate the effect of monoamine oxidase inhibitors and other anti-depressants, and dosage of such compounds should, therefore, also be reduced. Epilim does not induce liver enzymes, and there have been no reports of loss of efficacy of oral contraceptive agents.

Diabetic patients: Epilim is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with Epilim Syrup, as this contains 3.6g sucrose per 5ml.

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.

Overdosage

Nine cases of accidental and fourteen cases of suicidal overdosage have been reported. Full recovery occurred in 22 following treatment which included induced vomiting, gastric lavage, assisted ventilation, forced diuresis and other supportive measures; naloxone was used successfully in one patient.
The only known fatality followed a massive suicidal overdose resulting in a plasma level of 1970mg/litre.

Pharmaceutical Precautions

Epilim tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a cool, dry place. Epilim Syrup should be kept cool and away from direct sunlight.
Dilutions: If it is necessary to dilute Epilim Syrup, the recommended diluent is Syrup BP, but syrup containing SO_2 as a preservative should not be used. The diluted product will have a 14-day shelf-life.

Data Sheet Epilim 1/4(R) 2

FDA to strengthen valproate warning

Based on its receipt of French data associating sodium valproate (Abbott's Depakene) with human birth defects, the US FDA is preparing to strengthen the existing label warning for the drug, which now refers only to animal teratogenicity, although it cites an increased incidence of birth defects from anti-epileptic agents generally. In addition, Abbott is preparing to mail "Dear Doctor" letters to prescribers, alerting them to the French reports. The US Centres for Disease Control's October 29th weekly morbidity and mortality report contains a note on the human teratogenicity of Depakene issue.

The drug was approved by the US FDA in February 1978 amid a welter of publicity from consumer interests and some physicians who complained that the agency had delayed its review. In response to the pressure, the FDA took the unusual step of asking Abbott to submit an NDA for the drug, and it became the fastest NDA approval on record – 160 days.

. . . Lancet letter on valproate

French data on the possible teratogenicity of valproate are reported in a letter in the October 23rd issue of *The Lancet* (p 937). Drs Elizabeth Robert and Pierre Guibaud, of the Institut Européen des Génomutations in Lyon, write that examination of the case records of 72 infants born with neural tube defects in the Rhône-Alpes region between August 1979 and August 1982 showed that the mothers of nine of them had been treated with valproate for epilepsy during pregnancy. Four of the mothers also took other anticonvulsant medication, and two had another case of severe neural tube defect in their families, "a larger than expected proportion", note the French doctors.

In view of these findings, the French doctors suspect that valproate may be teratogenic, they write, and have begun a case-control study in collaboration with some other members of the International Clearinghouse.

. . . Sanofi's statement

Sanofi, the original developer of sodium valproate, has issued the following statement on the French report through its UK office: "This serious report is unusual and requires thorough investigation. It is not consistent with the information gathered from active monitoring by this company in the UK for over 8 years. With regard to this report, it should be noted that a number of cases are in families with hereditary abnormality problems and the data provided has a number of inconsistencies. It has not been derived from or set against an epidemiological epileptic base, but has been accumulated at a centre specialising in treating these neural tube defects.

"The incidence of adverse foetal effects is higher than normal in mothers with epilepsy and the risk to both mother and foetus can be very significant if left untreated. However, there are also clearly documented risks and warnings associated with therapy which are detailed in the literature given to all doctors who have the unenviable task at times of deciding and advising on this matter. However, the great majority of mothers do produce normal babies whilst receiving therapy.

"This matter will obviously be promptly investigated in conjunction with the medical profession and the regulatory authorities".

US FDA NEW DRUG APPROVALS

☆ 1982 ☆

When the FDA approves a new drug, the data on which the approval is based is consolidated into a Summary Basis of Approval (SBA). Including detailed information on pre-clinical and clinical studies as well as indications, dosage, pharmacology, side-effects and packaging/labelling, a product's SBA is an invaluable reference document for anyone with an interest in that drug.

Scrip can now offer SBAs for the following new drugs approved so far this year (1982) by the FDA:

SBA 50 Mead Johnson's Desyrel (trazodone)	£25.00	$53.00
SBA 53 W-Lambert's Lopid (gemfibrozil)	£25.00	$53.00
SBA 55 B Wellcome's Zovirax (aciclovir)	£10.00	$21.00
SBA 56 N-Eaton's Sarenin (saralasin)	£25.00	$53.00
SBA 57 MSD's Indocin SR (indometacin sustained release)	£20.00	$42.00
SBA 58 Pfizer's Feldene (piroxicam)	£20.00	$42.00
SBA 59 Gist-Brocades' Locoid (hydrocortisone butyrate)	£15.00	$32.00
SBA 64 Plantex' clomiphene citrate	£15.00	$32.00
SBA 65 Hoechst's Topicort (desoximetasone)	£15.00	$32.00
SBA 66 Miles' Niclocide (niclosamide)	£15.00	$32.00

A full list of SBAs is available on request from Scrip's Reader Service.

Orders should be accompanied by cheques, made payable to Scrip and drawn in sterling on a UK bank or US dollars on a US bank, and sent to: Scrip's Reader Servcice, 18-20 Hill Rise, Richmond, Surrey. TW10 6UA, UK: or to Mrs J Gann, c/o Barnum Communications, 500 Fifth Avenue, New York, NY 10110, US (tel: 212-398-0540).

New approach to duodenal ulcers

Dopaminergic agonists may offer a new approach to the therapy of duodenal ulcers, according to Dr Sandor Szabo of Harvard Medical School and Dr John L Neumeyer of Northeastern University. The two US scientists have found that several dopamine agonists, including bromocriptine, lergotrile, L-dopa and apomorphine and its derivatives, can both reduce the formation and accelerate the healing of experimentally-induced duodenal ulcers in rats. Some of the compounds studied were up to 200 times as potent as cimetidine. In contrast, dopamine antagonists such as haloperidol and pimozide were found to exacerbate ulcer formation. Several of the dopamine agonists studied are close to clinical investigation, according to Dr Szabo, who points out, however, that more selective agonists must be found for this approach to therapy to be really effective.

Product news in brief

■ *Merrell UK introduces 2-ingredient Debendox:* Merrell Pharmaceuticals has now introduced a revised formulation of the anti-emetic product, Debendox, in the UK (see *Scrip* No 657, p 15). Each sustained-release tablet now contains 10mg of doxylamine succinate and 10mg of pyridoxine hydrochloride. All current epidemiological studies relating to Debendox are based on this two-ingredient formula, says the company, which has been evaluated in the US for a number of years. The change in the ingredients of Debendox in the UK is part of a worldwide move to rationalise the formulation of the product.

Dr Phillips JW
Dr Boyd
Dr Feeney
Dr Sri Ananda Ch
File
To CADR

142-70-250

DETAILS OF NINE CASES OF NTD IN INFANTS BORN TO MOTHERS WHO HAD TAKEN VALPROATE DURING PREGNANCY

Case (and date of birth)	Valproate* (mg/day)	Defect(s)	Family history
1 (Nov. 8, 1979)	1500	LMS	Father's brother: SBA, died at 6 mo
2 (June 28, 1980)	1500	Sacral meningocele	First cousin: mucoviscidosis
3 (March 6, 1981)	400	LSM + hydrocephaly and microcephaly	None
4 (April 5, 1981)	2000	Lumbar SBA	None Grandmother's sister: trisomy 21
5 (Aug. 12, 1931)	1200	Epidermised lumbar SBA + hydrocephaly	Second cousin: DMD Maternal grandmother and maternal second cousin: epilepsy
6 (Nov. 19, 1981)	1000	LSM + complex congenital cardiopathy + hypospadias (karyotype normal)	Second cousin: SBA First cousin: late enuresis Mother's sister: SBO + late enuresis
7 (March 2, 1982)	1000	Sacral meningocele	None
8 (March 18, 1982)	750	Lumbar SBA	None
9 (Aug. 10, 1982)	1500	Sacral open meningocele	None

SBO = spina bifida occulta; SBA = spina bifida aperta; DMD = Duchenne muscular dystrophy; LSM = lumbar myelomeningocele.
*Throughout pregnancy except in case 2 (first trimester), other anticonvulsants (and daily doses in mg) were: phenobarbitone 50 (case 1), phenobarbitone 200 (case 2), phenobarbitone 200 + primidone 250 (case 3), and clonazepam 2 (case 9).

2 of the 9 cases had another case of severe NTD in their family, a larger than expected proportion.

All 9 cases required surgery, and 1 died (no. 6). Only one mother (no. 2) had non-stabilised epilepsy: she had had four epileptic seizures during the first trimester of pregnancy.

Valproic acid was given alone (5 cases) or with phenobarbitone (3 cases), or clonazepam (1 case). The doses of valproic acid were high, over 1 g daily in 7 cases. Blood concentrations of valproate in these women will be measured while they are on the same treatment.

We suspect that valproate may be teratogenic and have started a case-control study in collaboration with some other members of the International Clearinghouse.

Institut Européen des Génomutations,
69003 Lyon, France

ELISABETH ROBERT
PIERRE GUIBAUD

**In France and in West Germany, where the equivalents of data sheet compendia are readily available to the public, warnings about the possible teratogenicity of sodium valproate are low key, but in the U.K., U.S.A. and elsewhere the product information warnings are specific and refer to animal evidence. Besides Gomez' report there are other human data that warrant caution.—ED. L.

POLYCYSTIC OVARIES DISEASE: ONE OVARY TOO MANY?

SIR,—The Stein-Leventhal syndrome—consisting of hirsutism, oligomenorrhoea or amenorrhoea, and obesity combined with polycystic ovaries, and nowadays called the "polycystic ovaries syndrome" (PCO)—still has an uncertain aetiology. The primary lesion can (but generally does not) originate in the adrenal glands. In most cases it remains unclear whether one or both ovaries or hypothalamic-hypophyseal dysfunction is predominantly involved in the disease. However, it is well established that androgen production from ovaries and/or adrenal glands is increased and that continuous oestrogen release contributes to the syndrome.

There is a tendency to the view that PCO should not be left untreated. The androgen excess, it is argued, can cause hirsutism (or even virilism) and overweight because of the anabolic effects of androgens and the increased appetite while the continuous release of unopposed oestrogen could increase the risk of endometrial and mammary cancer.

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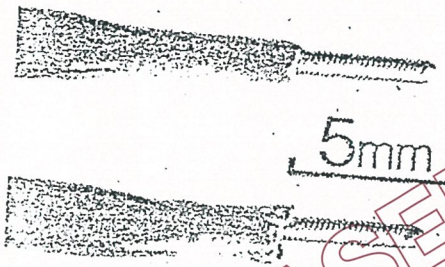

Damaged tip of vas-cath following insertion over guidewire without dilator (above, an unused catheter for comparison).

edges which will, I suggest, lead to intimal damage of the cava.

In view of this I have now changed our technique of insertion.[2] Whereas we used to dilate the track and the tunnel separately with the catheter itself, we now do this with a disposable dilator; passage of the vas-cath itself is now not attended by any snagging or the need for excessive pushing and twisting.

Until softer more pliable catheters are available I would strongly recommend the use of a dilator to avoid catheter tip damage.

Renal Transplant Unit,
St Mary's Hospital,
London W2 1NY

BRIAN W. ELLIS

MATERNAL VALPROIC ACID AND CONGENITAL NEURAL TUBE DEFECTS

SIR,—Our birth defects monitoring system for the Rhône-Alpes region of France, where there are about 72 000 births a year, operates with the collaboration of all paediatricians and obstetricians. We participate in the international clearing house for birth defects monitoring.[3] We collected, between Aug. 11, 1979, and Aug. 10, 1982, 72 case-records of infants born with lumbosacral neural tube defects (NTD) alone or associated with other malformations. 9 were infants born to epileptic mothers who had taken valproate during pregnancy. Gomez' letter[4] prompted us to describe these cases (see table).

We have no case of association of valproic acid with anencephaly (among the 17 cases of anencephaly collected during the same period), but our monitoring system is imperfect for stillbirths and for therapeutic abortions.

1. Ellis BW, Fielding LP. Advanced techniques in intravenous therapy. In Rob G, Smith R, eds. Operative surgery: General principles, 3rd ed. London: Butterworths, 1977.
2. Ellis BW, Nicholls JP, Crombie AK, Thom SAMcG. A new technique in haemodialysis. *Nursing Times* 1982; 40: (suppl): 8–9.
3. Flynt JW, Hay S. International Clearinghouse for Birth Defects Monitoring system. *Centr Epidemiol Biostat* 1979; 1: 44–52.
4. Gomez M. Possible teratogenicity of valproic acid. *J Pediatr* 1931; 99: 508.

Reckitt & Colman New Zealand Ltd.

27th October, 1982.

The Director-General of Health,
Department of Health,
Head Office,
P.O. Box 5013,
WELLINGTON.

Attn: Mr. R. Griffith

Dear Mr. Griffith,

Re: Valproic Acid - Adverse Reaction

I attach an extract supplied by our parent company, entitled "Valproic Acid and Neural Tube Defects (French Origin).

We have been advised of its publication in an October issue of the Lancet and will forward same on receipt.

Yours faithfully,
RECKITT & COLMAN (NEW ZEALAND) LIMITED

[redacted]

SIC:SAW

29/10

Reckitt & Colman (New Zealand) Limited. 550 Rosebank Road, Avondale.
Reckitt Telex N.Z. 21190. P.O. Box 19046. Avondale, Auckland 7, New Zealand. Telephone: 884-129 (10 lines).

RECKITT NZ21190
52166 RECCOL G

TLX H 53 21/10/82 HW 22 OCT 1982

TO MR R W BECK
FROM [redacted]

YOU SHOULD BE AWARE THAT THIS WEEK'S LANCET WILL CARRY AN ARTICLE DETAILING AN ALLEGED CONNECTION BETWEEN EPILIM TAKEN BY EXPECTANT MOTHERS AND SPINA BIFIDA BIRTHS. THE ARTICLE IS BASED ON FRENCH EVIDENCE. FURTHER ELABORATION WILL FOLLOW IN DUE COURSE.

L G STRONG

++
52166 RECCOL G
RECKITT NZ21190

VALPROIC ACID AND NEURAL TUBE DEFECTS

Sir,

Our birth defects monitoring system, which works in Rhona-Alpes region (about 72,000 births/year) with the collaboration of all paediatricians and obstetrician, and as a member of the International Clearinghouse for birth defects monitoring system(1), has collected, between August 11, 1979 and August 10, 1982, 72 files of infants born with lumbo-sacral neural tube defects (N.T.D.) isolated or associated with other malformations. Among these cases, 9 was infants born to epileptic mothers treated during pregnancy by Valproic acid. The letter to editor in the March 81 issue of the Journal of Paediatrics by Manuel Gomez M.D. (2) has prompted me to describe these cases. It is done in the following table:

(Please put here the table enclosed)

Comments

We have no case of association of Valproic acid with anencephaly among the 17 cases of anencephaly collected during the same period. But, our monitoring system is unperfect for still-births and therapeutical abortions.

2 of these new-borns have another case of severe N.T.D. in their family. 2/9 is a very large proportion compared with the expected number.

All these cases required surgery, and one died (No. 6).

Only one of the concerned mothers (no. 2) had a non stabilized epilepsy : she have presented 4 epileptic seizures during the first trimester of her pregnancy.

Among the 9 cases, 4 times Valproic acid was used in association with some other anticonvulsants (3 times with phenobarbital, 1 time with Clonazepam) and 5 times was used as monotherapy.

Doses of Valproic acid used are in 8 cases for 9 more than 1 Gr. which is rather a high dose.

Dosage of blood concentrations of Valproic acid for these women will be performed with the same treatment continued.

ese facts make us increasily suspect teratogenicity of
oic acid. We have begun a collaborative case-control study
t it, with some other members of the International
earinghouse for birth defects monitoring system.

Elisabeth Robert M.D.
Pierre GUIBAUD Prof.

Institut European des
Genomutations
80 rue Edmond Locard
69005 LYON - France

(Head: Pr. J.M. ROBERT)

1 - J.W. FLYNT and S. HAY - International Clearinghouse for birth defects monitoring system. Contr. Epidem. Biostatist. vol 1 pp 45-52 (Kargel, Basel 1979)

2 - Manuel GOMEZ M.D. Possible teratogenicity of Valproic acid, J. Pediatr. 98 - 508, 1981.

n°	birth	(daily doses)	anticonvul-sants daily	Timing during pregnancy	Description of the defects	Fa.
1	08.II.1979	I 500 mg	Phenobarbital 50 mg	all over	Lombo-sacral myelomeningocele	Father's broth. died at 6 months First cousin : mucov
2	06.28.1980	I 500 mg	Phenobarbital 200 mg	First trimester	Sacral meningocele	no family history
3	03.06.1981	400 mg	Phenobarbital 200 mg + Primidone 250 mg	all over	-Lumbo-sacral myelomeningocele -neo-natal hydrocephaly -microcephaly	no family history
4	04.05.1981	2 030 mg	—	all over	Lumbar S B A *	Grand mother's sister : T 21 Second cousin : D M D Mat. Grd moth.and mat. second cousin : epilepsy
5	08.12.1981	I 200 mg	—	all over	Epidermized lumbar S B A * néo natal hydrocephaly	Second cousin : S B A First cousin : late enuresis
6	II.19.1981	I 000 mg	—	all over	Lumbo-sacral myelomeningocele complex congenital cardiopathy hypospadias - caryotype normal	Mother's sister : S B O + late enuresis
7	03.02.1982	I 000 mg	—	all over	sacral-meningocele	no family history
8	03.18.1982	750 mg	—	all over	lumbar S B A *	no family history
9	08.10.1982	I 500 mg	Clonazepam 2 mg	all over	sacral opened meningocele	no family history

S B O : spina bifida occulta S B A : spina bifida aperta

D M D : Duchenne Muscular Dystrophy T 21 : trisomy 21

Reckitt & Colman New Zealand Ltd.

8th July, 1983.

Director General of Health,
Division of Clinical Services,
P.O. Box 5013,
WELLINGTON.

Dear Sir,

REF. EPILIM 142/70/2501.

I attach an updated review of "EPILIM IN PREGNANCY" dated March, 1983.

A copy has also been forwarded to Professor R. Edwards, Pharmacology Department, Otago University.

Yours faithfully,
RECKITT & COLMAN (NEW ZEALAND) LTD.,

[redacted]

Copy to Professor R. Edwards.

F

Drugs

Reckitt & Colman (New Zealand) Limited. 550 Rosebank Road, Avondale.
Reckitt Telex N.Z. 21190. P.O. Box 19046. Avondale, Auckland 7, New Zealand. Telephone: 884-129 (10 lines).

MARCH 1983

EPILIM IN PREGNANCY

Epilim has been shown to be teratogenic in rats and mice in doses ranging from 150-600 mg/kg/day and in rabbits in doses greater than 252 mg/kg/day (1-3). It is difficult to extrapolate these findings to the clinical setting because of species differences in teratogenic response and because the teratogenic doses are much higher than those used therapeutically.

Evidence to date indicates that valproic acid crosses the human placenta freely in late pregnancy. Values between 1.0 and 3.39 have been recorded for cord serum: maternal serum concentration ratios, (see table 1). Reasons for serum levels being higher in the neonate than in the mother are not known. The foetus may act as a deep compartment, active transport mechanisms across the placenta may be functional or there may be protein binding differences between the maternal and foetal compartments (valproic acid is 90% protein bound).

Table 1

Source		No of cases	Cord serum: Maternal serum concentration ratio
Bardy et-al	(4)	Not stated	Around 1
Alexander	(5)	1	Around 1
Dickinson et-al	(6)	1	1.5
Froescher et-al	(7)	4	Between 1.3 and 3.39
Nau et-al	(8)	6	Between 1.2 and 3.0
Ishizaki et-al	(9)	4	Between 1.48 and 2.41

It is estimated that since the U.K. introduction of Epilim in 1974 there have been approximately one hundred million days of patient exposure to the drug in the U.K. During this time certain data have been accumulated on the use of Epilim in Pregnancy.

Data has been collected as a result of positive encouragement and active surveillance by the Company in association with clinicians. In addition information has also appeared in the published literature.

To March 1983 the Company holds data on the clinical use of Epilim in 123 pregnancies. Of these, 84 resulted in normal births, 29 in abnormal births, 6 in spontaneous abortions and 4 in therapeutic abortions. In only 52 of these pregnanices was Epilim the sole anticonvulsant. A summary of these birth records is attached.

It should be noted that any compilation of data resulting from this type of reporting is likely to introduce a bias in the result in favour of the adverse events, the doctor being more likely to recollect and/or report an abnormal outcome of pregnancy than a normal one. Therefore, the number of abnormal outcomes reported in this document will be artificially high.

This is particularly true of published data where individual case reports of abnormal births tend to predominate. To March 1983 there are references in the literature to the clinical use of sodium valproate or valproic acid in 69 pregnancies of which 35 resulted in normal births, 33 in abnormal births and 1 in therapeutic abortion. In only 21 of these pregnancies was sodium valproate or valproic acid the sole anticonvulsant.

A tabulated summary of the published pregnancy reports and full bibliography is included at the end of this document.

A recent report originating from the French programme of the International Clearing House for monitoring birth defects has drawn attention to a possible association between the use of sodium valproate or valproic acid during pregnancy and the birth of infants with neural tube defects (10). This was based on data collected in the Rhone-Alps region.

Macrae (11) has subsequently advised close scrutiny of the basic data and study design of the Rhone-Alps monitoring programme because of the possibility of bias, suspected or unsuspected. He concluded that corroboration of the apparent association be sought elsewhere, preferably with a different study design.

The Committee on Safety of Medicines has discussed sodium valproate and cogenital abnormalities in "Current Problems" (12). They conclude "The malformations reported to occur with Valproate are similar to those with other anticonvulsants, namely neural tube defects, congenital heart lesions, digital abnormalities and oral defects" and state "there is no clear evidence that any one anticonvulsant drug is safer or more dangerous than any other." They recommend review of anticonvulsant therapy in any epileptic woman who is pregnant or comtemplating pregnancy, so that the simplest effective regimen can be implemented and indicate that maternal serum alphafetoprotein, high resolution ultrasound scanning and even diagnostic amniocentesis are available to assist with counselling.

A copy of "Current Problems" is attached.

SUMMARY OF UNPUBLISHED DATA ON EPILIM IN PREGNANCY

TOTAL CASES

Epilim alone or in combination with other anticonvulsants

Number of reports	123
Number of apparently normal babies	84
Number of abnormal babies	29
Number of spontaneous abortions	6
Number of therapeutic abortions	4

Epilim as sole anticonvulsant therapy during period of teratogenic risk

Number of reports	52
Number of apparently normal babies	38
Number of abnormal babies	8
Number of spontaneous abortions	5
Number of therapeutic abortions	1

Epilim in combination with other anticonvulsants

Number of reports	71
Number of apparently normal babies	46
Number of abnormal babies	21
Number of spontaneous abortions	1
Number of therapeutic abortions	3

Case numbers of abnormal births (in the attached summary)

The case numbers of abnormal births and abortions are listed below:-

Case numbers of all abnormal births relating to patients receiving Epilim alone or in combination with other anticonvulsants:-

1, 2, 11, 29, 30, 40, 45, 51, 56, 61, 65, 69, 74, 77, 80, 83, 84, 87, 95, 97, 98, 99, 101, 104, 109, 110, 113, 116, 120.

Case numbers of all spontaneous abortions relating to patients receiving Epilim alone or in combination with other anticonvulsants:-

7, 20, 25, 35, 78, 115.

Case numbers of therapeutic abortions relating to patients receiving Epilim alone or in combination with other anticonvulsants:-

34, 91, 96, 105.

Case numbers of all abnormal births relating to patients receiving Epilim as sole anticonvulsant therapy:-

30, 69, 84, 87, 95, 97, 110, 120.

Case numbers of all spontaneous abortions relating to patients receiving Epilim as sole anticonvulsant therapy:-

7, 20, 25, 78, 115.

Summary of Birth Records of Pregnant Patients on Epilim

o	Epilim	Other drugs and relevant history	Outcome of pregnancy
	[redacted] at approx 27 weeks gestation.	Soluble insulin Phenobarbitone Sulthiame Ethosuximide Ampicillin [redacted]	Male child with cleft lip and palate Intra uterine growth retardation
	[redacted] throughout pregnancy	Phenobarbitone throughout Flu-like illness at [redacted] with threatened abortion	Male - mental retardation. Convulsions
	[redacted] throughout pregnancy	Nil	Normal baby transient neonatal jaundice
	[redacted] day from about 10/52	Nitrazepam and acetazolamide throughout. Phenytoin during 1st trimester. Phenobarbitone and ethosuximide from about 8 weeks	Normal
5	[redacted] throughout pregnancy	Nil	Normal baby
6	[redacted] throughout pregnancy	Phenobarbitone throughout pregnancy	Normal baby
7	[redacted] from conception	Nil	Spontaneous abortion 1st trimester
8	[redacted] first 8-10 weeks only	Phenobarbitone Phenytoin throughout	Normal

Epilim	Other drugs and relevant history	Outcome of pregnancy
[redacted] throughout pregnancy	Phenytoin Primidone throughout pregnancy	Normal baby 'failure to thrive' ? cows milk sensitivity
[redacted] from about 12 weeks	Primidone throughout pregnancy. Tetracycline [redacted] about 12 weeks.	Normal baby
[redacted] during 1st 16 weeks perhaps longer [redacted]	Phenytoin at least 1st 16 weeks. Primidone at least 1st 10 weeks. Nitrazepam	Obstructive hernia and vomiting laparotomy. Release of obstruction without resection. Full details not available.
[redacted] throughout pregnancy	Phenobarbitone throughout pregnancy	Normal baby
[redacted] throughout pregnancy	Nil	Normal baby
[redacted] throughout pregnancy	Phenytoin Primidone reduced during pregnancy & stopped.	Normal: [redacted]
[redacted] throughout pregnancy [redacted]	Nil	Normal baby
[redacted] during last trimester	Phenytoin throughout	Normal baby
[redacted] throughout pregnancy	Carbamazepine Primidone throughout.	Normal baby
[redacted] throughout pregnancy	Phenytoin throughout	Normal baby

No	Epilim	Other drugs and relevant history	Outcome of pregnancy
19	[redacted] throughout pregnancy	Nil	Foetal distress Normal baby
20	[redacted] throughout pregnancy	Nil	Spontaneous abortion in 1st trimester
21	[redacted] throughout pregnancy	Primidone Phenytoin throughout	Transient neonatal asphyxia. Normal baby
22	[redacted] throughout pregnancy	Phenytoin Carbamazepine throughout	Normal baby
23	Dosage not stated but Epilim taken throughout pregnancy	Other unspecified anticonvulsants also taken throughout pregnancy.	Normal baby
24	[redacted] throughout pregnancy	Iron	Normal baby
25	[redacted] throughout pregnancy	Nil	Spontaneous abortion 1st trimester
26	[redacted] in first trimester	Phenobarbitone Phenytoin [redacted]	Normal baby
27	[redacted] throughout pregnancy	Phenytoin throughout	Normal baby
28	[redacted] throughout pregnancy	Nil	Normal baby
29	[redacted] for last 2 months	Phenytoin until last trimester	Low set ears, short neck sacral agenesis. Died on day 1

o	Epilim	Other drugs and relevant history	Outcome of pregnancy
30	[redacted] during 1st trimester	Nil [redacted]	Spina bifida
31	[redacted] throughout pregnancy	Phenytoin iron	Normal baby
32	[redacted] throughout pregnancy	Phenytoin throughout	Normal baby
33	[redacted] throughout pregnancy	Phenobarbitone Phenytoin throughout	Normal baby
34	[redacted] throughout pregnancy	Primidone Phenytoin	Termination of pregnancy on medical grounds
35	[redacted] throughout pregnancy	Carbamazepine throughout	Spontaneous abortion 1st trimester
36	[redacted] throughout pregnancy	Carbamazepine Temazepam Chlorpheniramine Iron	Normal baby
37	[redacted] during last trimester	Primidone Phenytoin throughout	Normal baby
38	[redacted] throughout	Ethosuximide Iron	Normal baby
39	[redacted] throughout	Nil	Normal baby

	Epilim	Other drugs and relevant history	Outcome of pregnancy
and	Dosage not stated Given during 1st 8 weeks gestation	Phenytoin [redacted] Primidone probably both given throughout pregnancy It is not made clear whether these drugs were also withdrawn at 8 weeks.	Premature birth [redacted] Died [redacted] Gross congenital abnormalities Cleft lip/palate. Imperforate anus. Renal agenesis. Absent ureter and bladder. 1 lobe R lung
	[redacted] throughout pregnancy	Phenobarbitone [redacted] throughout pregnancy	Normal baby (F)
	[redacted] throughout pregnancy	Two tablets clonidine daily iron & folate	Normal baby (F)
	[redacted] during pregnancy	Folic acid	Skeletally normal baby (F). [redacted] Respiratory problems in first week
	[redacted] throughout pregnancy	Phenobarbitone throughout	Normal baby
	Dosage not stated but Epilim taken prior to and throughout pregnancy	Pentobarbitone Promazine Flurazepam	Male baby Visual problems, squint & organic retrogeniculate defect (barbiturate related attentional defect & developmental delay)
6	[redacted] throughout pregnancy	Iron	Normal baby (F)
7	[redacted] throughout pregnancy	Carbamazepine	Normal female baby

No	Epilim	Other drugs and relevant history	Outcome of pregnancy
48	[redacted] in first trimester. Stopped when she found she was pregnant	Nil	Normal male baby
49	[redacted] throughout pregnancy	Iron and folic acid	Normal female baby
50	[redacted] 8 days before delivery [redacted]	Phenytoin and Phenobarbitone three weeks before delivery but stopped 5 days before delivery	Normal female baby Slightly slow to establish feeding but only a mild problem.
51	[redacted] throughout pregnancy	Phenobarbitone throughout	Female baby with spina bifida and hydrocephalus by forceps delivery.
52	[redacted] throughout	Nil	Normal female baby. [redacted]
53	[redacted] for first three months only	Nil	Normal male baby
54	[redacted] throughout	Nil	Normal female baby
55	[redacted] for first seven months then [redacted]	Carbamazepine throughout	Normal male baby born by caesarian section

o	Epilim	Other drugs and relevant history	Outcome of pregnancy
6	[redacted] for first 12 weeks	Phenytoin and phenobarbitone continued throughout pregnancy. [redacted]	Male baby [redacted] congenital absence of left radius and severe radial flexion deformity. Cardiac abnormality catheterised in first week of life and found to have ASD, VSD; possible co-arctation of the aorta.
7	[redacted]	Nil	Normal female baby
8	[redacted]	Nil	Normal male baby
	[redacted] increased to [redacted] mid 2nd trimester	Nil	Normal male [redacted] (Forceps for cord prolapse)
0	[redacted] throughout	Phenytoin [redacted] throughout	Normal male [redacted]
1	[redacted] throughout	Not stated	Male. Pyloric stenosis First child
	[redacted] 1st trimester 2nd trimester	Ampicillin/ Flucloxacillin and Diazepam [redacted] Not anti-convulsants. Folic acid	Normal male First child
	[redacted] throughout	Carbamazepine [redacted] throughout	Normal female First child

	Epilim	Other drugs and relevant history	Outcome of pregnancy
	[redacted] 2nd and 3rd trimesters	Folic acid 5 mg x 2	Normal male [redacted]
	[redacted] throughout	Carbamazepine [redacted] increased to 1 [redacted] Phenytoin [redacted] throughout	Male. Slightly Low set ears, only one umbilical artery [redacted]
6	[redacted] until pregnancy known, [redacted]	Phenytoin [redacted] as Epilim	Normal male [redacted]
7	[redacted] throughout	Nil	Normal Male [redacted]
8	Discontinued mid-1st trimester	Not known	Normal male, [redacted]
69	[redacted] throughout	Iron Folic acid	Male, [redacted] Syndactally of 2 fingers of left hand. [redacted]
70	[redacted] decreased to mid-2nd trimester	Iron Folic acid 'Debendox'	Normal female, caesarean delivery [redacted]
71	[redacted] mg 1st trimester	Phenobarbitone	Normal male [redacted]

	Epilim	Other drugs and relevant history	Outcome of pregnancy
	[redacted] throughout	Phenytoin [redacted] throughout	Normal female First child
	[redacted] throughout	Carbamazepine [redacted] throghout	Normal male First child
	[redacted] increasing gradually [redacted] throughout pregnancy	Phenobarbitone immediately prior conception	Male infant 2 vessels in cord; upslanting palpebral fissures, thin upper lip, narrow forehead, abnormal rotated ears, finger contractures, penoscrotal hypo-spadias, calcaneo-valgus feet, persistent ductus arteriosus. Twitching episodes
75 [redacted]	[redacted] 3rd trimester	Not stated	Normal baby
76 [redacted]	[redacted] 1st trimester	Nil	Normal female
77 [redacted]	[redacted] throughout	Phenytoin Ethosuximide	Normal female with minor toe webbing, both feet
78	[redacted] throughout pregnancy	None	Spontaneous abortion
79	[redacted] throughout pregnancy	Phenytoin throughout	Normal baby
80 [redacted]	[redacted] throughout pregnancy	Carbamazepine [redacted] Primidone [redacted] Published: J Paediatrics 1981, 99, 163 Thomas & Buchanan	Dysmorphic child Hypoplastic nails, depressed nasal bridge, cleft alveolus, high arched palate, splayed sutures, wide anterior fontanelle, abnormal palmar creases, Fallot's tetralogy

o	Epilim	Other drugs and relevant history	Outcome of pregnancy
1	[redacted] daily throughout pregnancy	None	Normal
2	[redacted] through-out pregnancy	Carbamazepine [redacted] Diazepam [redacted] throughout pregnancy	Hypotonic baby. [redacted]
83	[redacted] throughout	Phenytoin [redacted] Sulthiame throughout pregnancy Oral contraceptives at time of conception	Meningocele
84	[redacted] throughout pregnancy	None	Spina bifida with meningocele
85	[redacted] throughout pregnancy	Carbamazepine and phenytoin throughout	Normal baby
86 [redacted]	[redacted] throughout pregnancy	Acetazolamide in last trimester	Normal female baby
87 [redacted]	[redacted] throughout pregnancy	Chloroquine, iron, vitamins Falciparum Malaria infection	Caesarian section [redacted] Ventricular septal defect not requireing surgery. Blocked tear ducts
88	[redacted] from 16th week of pregnancy	Salbutamol inhaler Aminophylline [redacted] o.d	Normal infant
89	[redacted] throughout pregnancy	Carbamazepine [redacted] o.d throughout pregnancy	Normal male infant

No	Epilim	Other drugs and relevant history	Outcome of pregnancy
90	[redacted] throughout pregnancy	Iron & folic acid throughout pregnancy	Male infant with severe respiratory distress syndrome associated with pre-term delivery. Baby now feeding & thriving satisfactorily
91	Dose not stated	Carbamazepine dose not stated	Routine AFP raised confirmed on amniocentesis. Foetus aborted & confirmed to have spina bifida
92	[redacted] throughout pregnancy	Nil	Male infant failed to breathe at birth, but no foetal abnormality. Now normal
93	[redacted] throughout pregnancy	Nil	Normal infant
94	[redacted] throughout pregnancy	Nil	Normal female infant
95	[redacted] throughout pregnancy [redacted]	Phenobarbitone taken in 9th month of pregnancy Intra-uterine infection including Rubella and Toxoplasmosis excluded. Appears patient may have fitted during pregnancy	Abnormal female infant delivered at term with abnormal facies, abnormal head shape, prominent frontal region, low set malformed ears with abnormal helices, long fingers, a flexion contracture of the left ring finger, tapering, slightly narrow nails, long toes, hypoplastic thenar eminencies with the thumb in flexion & a ligamentous click of the right hip

No	Epilim	Other drugs and relevant histroy	Outcome of pregnancy
96	[redacted] throughout pregnancy	Phenobarbitone [redacted] throughout pregnancy	Male foetus terminated a[redacted] with lumbar spina bifida and myelocele
97	[redacted]/daily	Paracetamol and dextroproxyphene after road traffic accident [redacted] Published: BMJ 1983, 286, (6360), 190, Baily, Pool, Poskitt & Harris	Male infant with bilateral finger-like thumbs. Left sided thumb triphalangeal and small rudimentary extra digit arising from the base of the right thumb. Left foot syndactyly of 1st & 2nd toes and 3rd toe absent. Failure to thrive. At 6 weeks suspected may have cyanotic congenital heart disease
98 [redacted]	[redacted] prior to and throughout pregnancy	Carbamazepine Thyroxine	Male baby. Low lumbar myelomeningocele treated surgically
99 [redacted]	[redacted] 2nd & 3rd trimester	Phenytoin 1st trimester	C[redacted]n a[redacted] Hydrocephalic child
00 [redacted]	[redacted] prior to and throughout pregnancy	Carbamazepine Clonazepam	[redacted] Normal child
01 [redacted]	[redacted] prior to and throughout pregnancy	Carbamazepine Clonazepam	[redacted] Intrauterine death [redacted] Hydrocephalic intracranial haemorrhage

One Patient

No	Epilim	Other drugs and relevant history	Outcome of pregnancy
102	[redacted] throughout pregnancy	Phenobarbitone	Normal female hypotonic at birth
103	[redacted] throughout pregnancy	Nil	Normal male
104	[redacted] for the first 5 months of pregnancy	Not stated	Infant with imperforate anus, deformed right leg, crossed ectopic Kidneys, systolic murmur and unusual facies
105	[redacted]	Nil	Terminated on grounds of mother's health. No data on condition of foetus
106	[redacted] throughout pregnancy [redacted]	Primidone Vitamin K Potassium Chlorthalidone	Normal female
107 (Australia)	[redacted] during 1st trimester	Primidone - 1st trimester Methsuximide - throughout pregnancy	Normal female
108	[redacted] throughout	None	Normal female
109	[redacted] throughout	Diazepam throughout	Small female with micrognathia, small palpebral fissures and Bifid thumb (left hand)

No	Epilim	Other drugs and relevant history	Outcome of pregnancy
110	[redacted] throughout	None stated	Male infant with radial hemimelia with an absent digit, rudimentary thumb and radial deviation at wrist, left radial aplasia, right talipes equino-varus, left calcaneo-valgus and limited hip abduction.
111	[redacted]	None stated	Normal female
112	[redacted]	Carbamazepine	Normal female
113	[redacted]	Phenytoin	Female infant with Down's syndrome - probably trisomy 21. [redacted] Family histor of Down's syndrome
114	[redacted]	Iron and folic acid	Normal female. [redacted]
115	[redacted] throughout	None stated	Missed abortion. [redacted]
116 [redacted]	[redacted] throughout	Carbamazepine [redacted]	Spina Bifida L2-L3. Died [redacted]
117 [redacted]	[redacted] throughout	Carbamazepine	Normal male. [redacted]

o	Epilim	Other drugs and relevant history	Outcome of pregnancy
18 [redacted]	[redacted] daily	None	Normal Infant
19	[redacted] throughout	Carbamazepine	Normal Infant
20	[redacted] throughout	None Published: Lancet 1982, II, 1282, Stanley OH, Chambers TL	Lumbo-sacral meningocele. [redacted]
21	[redacted] throughout	None	Normal Infant
22	[redacted] throughout	None	Normal infant found to have bilateral inguinal hernia which was repaired. Previous normal birth on phenytoin and phenobarbitone
123	[redacted] throughout	Lorazepam [redacted] and mianserin [redacted] daily throughout	Normal male

SUMMARY OF PUBLISHED DATA ON THE

CLINICAL USE OF SODIUM VALPROATE OR VALPROIC ACID

IN PREGNANCY

ource	No Of Cases	Medication	Outcome of Pregnancy	Additional Information
lexander 5)	1	Sodium Valproate 1600 mg daily throughout pregnancy	Normal Infant	Monotherapy
alens et-al 13)	1	Valproic Acid 100 mg daily throughout pregnancy	Grossly dysmorphic female Died at 19 days	Monotherapy Patient had a short, generalised seizure at the onset of pregnancy
hakir et-al 14)	1	Sodium Valproate 1200 mg daily for 3 months reduced of patients own accord to 400 mg daily	Normal Infant	Monotherapy
akane et-al 15)	8	Sodium Valproate. Dose and concommitant therapy not stated	One abnormal birth (congenital dislocation of the hip)	Multi-institutional collaborative study in Japan on the teratogenicity and foetal toxicity of anti-epileptic drugs
rown et-al 16)	13	Valproic acid. Dose and concommitant therapy not stated	One abnormal offspring	
illesmaa t-al 17)	12	Valproic acid. Dose not stated	No malformations encountered at birth or during follow up which ranged from 2 months to 4 years	One patient on monotherapy. Others also taking phenytoin or carbamazepine (usually)

Source	No Of Cases	Medication	Outcome Of Pregnancy	Additional Information
Similä et-al (18)	1	Sodium Valproate 1350 mg daily and phenytoin 450 mg daily throughout pregnancy	Healthy infants with transient neonatal secondary hyperglycinaemia which did not affect CNS development. Authors concluded this was due to the use of sodium valproate in the last trimester and warned that this may cause a false positive finding in metabolic screening for aminoacidaemias in new born babies	Patient had several major convulsions during early pregnancy
	1	Sodium Valproate 1200 mg daily, phenytoin 400 mg daily, clonazepam 1 mg daily and carbamazepine 600 mg daily throughout pregnancy		
Nau et-al (8)	7	Sodium Valproate monotherapy	One case of ductus arteriosus persistens.	In addition to the heart defects there were a number of minor anomalies including hernias, diastasis of musculus rectus abdominis and weak abdominal walls
	3	Sodium Valproate and primidone	One ventricular septal defect	
	1	Sodium Valproate and phenytoin		
Gomez (19)	1	Valproic Acid 1500 mg daily reducing to 500 mg daily throughout pregnancy. Phenobarbitone 120 mg daily and clonazepam 6 mg reducing to 2 mg daily throughout pregnancy	Male infant with lumbosacral meningocele which had ruptured and sensorymotor deficit in the distribution L_4 to S_2. Head radiograph showed excessive separation of the sutures and head CT showed dilatation of both lateral and third ventricles. A minor deformity of the feet appeared flexible and correctible	The meningocele was repaired. Head growth diminished and the CT scan showed no further enlargement of the cerebral ventricles

Source	No Of Cases	Medication	Outcome of Pregnancy	Additional Information
Thomas & Buchanan (20)	1	Sodium Valproate 1200 mg daily Carbamazepine 800 mg daily and primidone 800 mg daily throughout pregnancy	Dysmorphic female with hypoplastic nails, depressed nasal bridge, a small cleft in the centre of the upper alveolar margin high-arched palate, splayed sutures, wide anterior fontanelle, abnormal palmar creases and tetralogy of Fallot	Several grand mal fits occured each week during pregnancy. There had been 2 previous pregnancies (drug therapy not stated) one was terminated and the other resulted in a normal child. Premature labour was complicated by a grand mal seizure. Subsequent delivery was by cesarean section
Clay et-al (21)	1	Valproic Acid 750 mg daily throughout pregnancy	Dysmorphic male who, at 22 months had coarsened facies, a prominent fore-head, a flat nasal bridge with a small nose, a short neck, wide spaced nipples, a hypoplastic right thumb, shortened fingers and toes, a grade 3/6 ventric-uloseptal defect murmur and a patent anterior fontanelle. Additionally he had minor cutaneous stigmata of neuro-fibromatosis.	Monotherapy patient had known neuro-fibromatosis

Source	No of Cases	Medication	Outcome of Pregnancy	Additional Information
Cairney et-al (22)	1	Sodium Valproate 600 mg daily	Terminated at 17 weeks because of patients anxiety. No abnormalities of the foetus and the size was consistent with the period of gestation	Monotherapy
Robert and Guibaud (10) Retrospective data from the French programme of the International clearing house for monitoring birth defects	1	Sodium Valproate 1500 mg daily throughout pregnancy Phenobarbitone 50 mg daily	Lumbar myelo-meningocele requiring surgery	Family history of spina bifida
	1	Sodium Valproate 1500 mg daily in first trimester Phenobarbitone 200 mg daily	Sacral meningocele requiring surgery	Patient had four seizures during 1st trimester
	1	Sodium Valproate 400 mg daily throughout pregnancy Phenobarbitone 200 mg daily and primidone 250 mg daily	Lumbar myelo-meningocele, hydrocephaly and micro-cephaly requiring surgery	
	1	Sodium Valproate 2000 mg daily throughout pregnancy	Lumbar spina bifida aperta requiring surgery	Monotherapy Family history of trisomy 21 and Duchenne muscular dystrophy
	1	Sodium Valproate 1200 mg daily throughout pregnancy	Epidermised lumbar spina bifida aperta and hydrocephaly requiring surgery	Monotherapy Family history of spina bifida

Source	No Of Cases	Medication	Outcome Of Pregnancy	Additional Information
Robert and Guibaud (10) Retrospective data from the French programme of the International clearing house for monitoring birth defects	1	Sodium Valproate 1000 mg daily throughout pregnancy	Lumbar myelo-meningocele and complex cardiopathy and hypospadias. Died	Monotherapy Family of Spina bifida
	1	Sodium Valproate 1000 mg daily throughout pregnancy	Sacral meningocele requiring surgery	Monotherapy
	1	Sodium Valproate 750 mg daily throughout pregnancy	Lumbar spina bifida aperta requiring surgery	Monotherapy
	1	Sodium Valproate 1800 mg daily throughout pregnancy clonazepam .2 mg daily	Sacral open meningocele requiring surgery	
Bjerkedal et-al (23)	3	Valproic Acid. Dose duration and con-commitant therapy not stated	2 cases of spina bifida one of omphalocele and limb deformities.	Information collected retrospectively by the Italian programme of the International clearing house for monitoring birth defects
Stanley and Chambers (24)	1	Sodium Valproate throughout pregnancy	Female with a small lumbosacral meningocele	Monotherapy. No family history of neural tube defects. Pregnancy complicated by four short grand mal seizures between 9 and 23 weeks gestation. Two previous normal births on no drugs. 2nd pregnancy complicated by undiagnosed epilepsy

ɔurce	No Of Cases	Medication	Outcome of Pregnancy	Additional Information
ailey t-al 25)	1	Valproic Acid 800 mg daily throughout pregnancy. Six tablets of dextro-propoxyphene and paracetamol four weeks after last menstrual period	Male infant with bilateral finger-like thumbs, one of which was triphalangeal. A rudimentary extra digit arose from the base of the right thumb. A median cleft of the left foot was present with syndactyly of the 1st and 2nd toes	No family history of congenital malformations Subsequent investigation of failure to thrive showed bilateral renal hypoplasia
	1	Valproic Acid 1800 mg daily throughout pregnancy	Male infant with micrognathia, bilateral undescended testes, glandular hypospadias, flexion deformity of the left wrist with shortening of the forearm, elongated and proximally inserted left fifth digit, finger-like thumb, and moderately severe valvular aortic stenosis.	Monotherapy. Previous pregnancy on the same medication resulted in a spontaneous abortion at 8 weeks. Pregnancy was complicated by 4 grand mal seizures during the last trimester. No family history of congenital malformations. Intravenous pyelography and chromosome analysis yielded normal results.
Blaw and Woody (26)	1	Valproic Acid 1000 mg daily until 3rd month of gestation and sporadically therafter when headaches occurred	Male infant with a large mening-omyelocele in the mid-lumbosacral region. An Arnold-Chiari malformation was diagnosed clinically and radiographically	Monotherapy. One seizure occurred during pregnancy. An ultrasonographic examination at 4 months was reported to be normal. Patient was a previous drug abuser and had taken 1500 mg amitriptylline 1 month prior to conception

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COMMITTEE ON SAFETY OF MEDICINES

NUMBER

CURRENT PROBLEMS

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JANUARY
1983

CONTENTS

INTRODUCTION

The Current Problems series is intended to draw attention to matters of particular concern or interest which have been considered by the CSM. It also indicates some of the topics about which reports will be especially valuable.

It is hoped that Current Problems will facilitate the flow of information to and from the Committee. The CSM always welcomes reports where adverse effects are suspected, particularly when they are clinically serious, unexpected, or when new medicinal products are involved.

SODIUM VALPROATE (EPILIM) AND CONGENITAL ABNORMALITIES

Over the past fifteen years there have been a number of epidemiological surveys in various parts of the world reporting an increase in the incidence of congenital malformations in the children born to women with epilepsy.[1,2,3,4] Although it is difficult to determine whether it is the disease itself or the medication used in its treatment which is responsible for the increased malformation rate. In most of the surveys, the incidence of malformations has been higher in epileptics receiving drug treatment during pregnancy than in those untreated.[5,6] Although the major structural abnormalities are induced in early pregnancy there is some evidence that treatment in later pregnancy also affects development.[5,7,8] Folic acid deficiency may be important since many anticonvulsant drugs lower serum folate levels, and altered folate metabolism could be responsible for some of the malformations observed.

Almost all surveys show a two- to three-fold increase in the incidence of congenital anomalies among babies born to epileptic women. The most frequently occurring defects, in 2285 children exposed to anticonvulsant therapy in utero[5] were cleft lip with or without cleft palate (3.0%), skeletal anomalies (1.9%), congenital heart disease (1.4%), CNS defects (1.2%), anomalies of the gastro-intestinal tract (1.1%), facial and ear abnormalities (1.0%), mental retardation (0.7%), genito-urinary anomalies (0.6%). Other isolated anomalies occurred. The risk to a woman with epilepsy, who is receiving an anticonvulsant, of delivering a malformed child is thus about one in ten.[9] Nevertheless, withdrawal of anticonvulsants is not generally advisable because fetal hypoxia due to maternal fits is likely to be at least as damaging as the drugs themselves.[10]

Recent reports have drawn attention to valproate and its apparent association with neural tube defects in babies born to women with epilepsy treated with it during pregnancy. Valproate, like other anticonvulsants, is known to be teratogenic in animals and one report suggests that it may also be teratogenic in humans.[11] The malformations reported to occur with valproate are similar to those with other anticonvulsants, namely neural tube defects, congenital heart lesions, digital anomalies and oral clefts. The recent recommendations[12,13] that "newer" drugs such as valproate may be the drugs of choice for treating epileptic women cannot be accepted uncritically. A new drug may only appear less hazardous because evidence of hazard has not accumulated.

There is no clear evidence that any one anticonvulsant drug is safer or more dangerous than any other. Anticonvulsant therapy should be reviewed in any epileptic woman who is pregnant, or contemplating pregnancy, so that the simplest effective regimen can be implemented. There may be a case for withdrawing treatment during pregnancy in suitable patients with minor epilepsy where consciousness is not lost during attacks. In general, it is preferable to use single drug therapy in women of reproductive potential. Established folate deficiency should certainly be remedied, though the precise role of altered folate metabolism is in doubt. Maternal serum alphafetoprotein, high resolution ultrasound scanning and even diagnostic amniocentesis are available, if indicated, to assist with counselling.

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Issued by: Committee on Safety of Medicines, Market Towers, 1 Nine Elms Lane, London, SW8 5NQ

142-70-2501

Dr Boyd
File IC

13 November 1984

The General Manager
Reckitt & Colman (NZ) Ltd
P O Box 19-046
AUCKLAND

Dear Sir

VALPROATE

Recently Meyer et al. expressed concern regarding the combined usage of valpromide and carbamazepine which was apparently associated with potentially serious adverse reactions (Lancet 1-802, 7 April 1984).

Would you please comment on this report, since valproate is the active metabolite of valpromide.

Yours faithfully

K H Goh
for Director
Division of Clinical Services

142/70/2501

Plasmodium falciparum — Continued

recommended. Weekly doses of Fansidar and chloroquine may be taken together on the same day. It should be noted, however, that this combination may not be completely effective in preventing episodes of symptomatic malaria, as prophylaxis failures with sulfonamide-antifolate combination drugs have occurred (*7,8*). Travelers should be advised that any acute febrile illness may be malaria and that medical attention should be sought, regardless of whether chemoprophylaxis is being taken.

Further updates of this rapidly evolving situation will be published as accurate information becomes available. An expanded discussion of the recommendations for the prophylaxis of malaria is available in *Prevention of Malaria in Travelers, 1982* (*9*).

Reported by Malaria Br, Div of Parasitic Diseases, Center for Infectious Diseases, CDC.

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Epidemiologic Notes and Reports

Valproate: A New Cause of Birth Defects — Report from Italy and Follow-Up from France

Studies by the Indagine Policentrica Italiana sulle Malformazioni Congenite (IPIMC) in 1980-1982 found a significant association between valproic-acid exposure during the first trimester of pregnancy and spina bifida (Table 2). Among 118 infants with spina bifida, two (1.7%) were exposed to valproic acid; in the group with other malformations, three (0.1%) of 4,489 were exposed.

Further data from France on the association between spina bifida aperta among infants with birth defects and valproic-acid use during the first trimester update the preliminary report from Lyon (Tables 3 and 4) (*1*). An infant with spina bifida, who had intrauterine exposure to valproic acid, has been added, and an infant with spina bifida, whose mother had not

TABLE 2. Association between spina bifida (SB) and maternal treatment with valproic acid (VA) among malformed neonates registered with the Indagine Policentrica Italiana sulle Malformazioni Congenite — Italy

	SB	Other malformations	Total
VA treatment	2	3	5
No VA treatment	116	4,486	4,602
Total	118	4,489	4,607

Odds ratio = 25.8; 95% confidence limits, 3.0-191.0; $p < 0.001$

File #

Valproate — Continued

been recognized as having epilepsy, has been properly classified. These data represent the cumulative experience during 1976 and from 1978 to December 1982.

Reported by Bolletino Epidemiologica Nazionale (November 25, 1982); E Robert, MD, Institut Europeen des Genomutations, Lyon, France; Birth Defects Br, Chronic Diseases Div, Center for Environmental Health, CDC.

Editorial Note: In addition to these new data from Italy and France, a United Kingdom researcher has reported that, of infants born to 196 pregnant women treated with valproic acid, 157 (80%) were normal and nine (5%) had spina bifida (*2*). The remaining 30 infants had other structural defects, including cardiovascular defects, orofacial clefts, and digital abnormalities. Since most of the pregnancies were reported either to the U.K. researcher or to a drug company and since normal pregnancies would tend not to be reported, there is probably some bias in the direction of reporting abnormal pregnancies. Given that these data were collected before the report from France and that spina bifida accounted for 23% (9/39) of the reported abnormalities, the 10-fold excess reported from the United Kingdom is probably not due entirely to reporting bias.

With these new data, valproic acid and sodium valproate should be considered human teratogens. CDC has estimated that a pregnant woman in the United States treated with these drugs would have a 1%-2% risk of having a child with spina bifida.* Since this risk is similar to the risk of spina bifida recurrence in subsequent pregnancies, women exposed in the first trimester should consult their physicians about further prenatal counseling. A pregnant woman undergoing treatment for epilepsy should not change her drug therapy without first consulting her physician.

Little is known about the relationship between valproic acid and other birth defects. To better define the risk of such therapy, CDC is assembling a registry of women taking valproic acid during pregnancy. Physicians caring for such women are urged to report these pregnancies to the CDC registry as soon as possible by calling (404) 452-4035 on weekdays between 8 a.m. and 4:30 p.m., Eastern time, or by writing the Birth Defects Branch, Chronic Diseases Division, Center for Environmental Health, Centers for Disease Control, Atlanta, Georgia 30333.

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*Estimate based on the Bayse theorem.

TABLE 3. Association between spina bifida aperta (SBA) and treatment with valproic acid (VA) of mothers who delivered infants with birth defects — Lyon, France

	SBA	Other birth defects	Total
VA treatment	10	21	31
No VA treatment	140	7,566	7,706
Total	150	7,587	7,737

Odds ratio = 25.7; 95% confidence limits, 10.9-58.6; $p < 0.001$

TABLE 4. Association between spina bifida aperta (SBA) and treatment with valproic acid (VA) of mothers who have seizure disorders and who delivered infants with birth defects — Lyon, France

	SBA	Other birth defects	Total
VA treatment	10	21	31
No VA treatment	2	41*	43
Total	12	62	74

Odds ratio = 9.8; 95% confidence limits, 1.7-70.0; $p = < 0.002$

*Five with unknown treatment; three with no treatment.

Department of Health
TE TARI ORA

133 Molesworth St
Wellington
New Zealand
P.O. Box 5013, Wellington
Phone (04) 496 2000
Fax (04) 496 2340

142/70/2501
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18 October, 1991

[redacted]
Group Produ
Reckitt & Colman (NZ) Ltd
Private Bag
Avondale
AUCKLAND 7

Dear Ms Moser

Data Sheet for Epilim (sodium valproate) products

I have been asked to assess the data sheet for your Epilim medicines. The draft we have on our files are dated January 1989.

In June 1989 Dr Ronaldson wrote to Reckitt & Colman (NZ) requesting inclusion of the risk of spina bifida during pregnancy in the data sheet. This was shortly after your CMN submission to update the data sheet. There is no indication that your updates had been examined at that time.

In order to not repeat the assessment, I would greatly appreciate it if you could send me your latest data sheets on the medicines.

Yours sincerely

Khay Ooi

Khay Ooi
Scientist
Therapeutics Section

[illegible] Fax (09) 884-648

RECKITT & COLMAN
NEW ZEALAND

7 December 1993

The Director General
Ministry of Health
PO Box 5013
WELLINGTON

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Attention: Kathlyn J Ronaldson, Scientist
Therapeutic Section

Dear Madam

Data Sheet for Epilim

Thank you for your letter dated 28 October 1993. Please find attached the reformatted data sheet with additional statements under "Women of Childbearing Age" regarding the use of folic acid to reduce the risk of neural tube defects.

Also attached is a separate updated data sheet for Epilim Intravenous, which was omitted in the original submission.

We hope that this fulfils the Ministry's requirements and look forward to your response.

Yours faithfully
RECKITT & COLMAN (NZ) LTD

[redacted]

Reckitt & Colman (New Zealand) Limited. Private Bag 19990, Avondale.
550 Rosebank Road, Avondale, Auckland 7. New Zealand ☎ (09) 828-4129 Fax (09) 828-4648.

RECKITT & COLMAN
NEW ZEALAND

31 March 1994

Director General
Ministry of Health
PO Box 5013
WELLINGTON

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2501-5
re hypoglycaemia

Attention: Kathlyn Ronaldson,
Scientist
Therapeutics Section

Dear Sir

Epilim Data Sheets

Further to my telephone message of this morning, please find attached the latest revision of the Epilim Data Sheets. The changes made are very minor and have been highlighted for your convenience.

Revised data sheets incorporating a warning with regard to the incidence of neural tube defects and a statement that the incidence of these defects can be reduced if the patient receives folate supplementation, were submitted some months ago. We consider that this information is important to both the clinician and the patient. It should be available before Epilim is prescirbed to women of child-bearing age.

We would greatly appreciate it if you could please assess these revised data sheets at your earliest possible convenience.

Thank you for your assistance in this matter. Please contact me [redacted] if you have any questions.

Yours faithfully
RECKITT & COLMAN (NZ) LTD

[redacted]

Reckitt & Colman (New Zealand) Limited. Private Bag 19990, Avondale.
550 Rosebank Road, Avondale, Auckland 7. New Zealand ☎ (09) 828-4129 Fax (09) 828-4648.

SIR,—During the past decade silicone elastomer ('Silastic') catheters have largely replaced the more rigid 'Teflon' and polypropylene catheters for long-term parenteral nutrition. Given a safe and effective means of placement,[1] our experience now is of very few mechanical or thrombotic problems.

The recent correspondence regarding thrombosis of the superior cava related to the tip of central venous catheters has highlighted the association of this complication with rigid catheters, especially those used for haemodialysis. Since 1980 we have been using 'Vas-cath' (Gambro) catheters for short-term haemodialysis. Seventy catheters have been placed de novo in 65 patients. Poor flow has been infrequent and usually corrected by catheter change over a guidewire. Since none of our patients has been investigated by venography we cannot exclude the possibility of superior vena caval thrombosis around the catheter tip.

An assumption that intimal damage to the superior vena cava is important in the genesis of this complication explains the association with rigid catheters. However, I believe that the tips of these catheters can become seriously damaged during insertion over the guidewire. Such a damaged tip (figure) can have sharp everted

Damaged tip of vas-cath following insertion over guidewire without dilator (above, an unused catheter for comparison).

edges which will, I suggest, lead to intimal damage of the cava.

In view of this I have now changed our technique of insertion.[2] Whereas we used to dilate the track and the tunnel separately with the catheter itself, we now do this with a disposable dilator; passage of the vas-cath itself is now not attended by any snagging or the need for excessive pushing and twisting.

Until softer more pliable catheters are available I would strongly recommend the use of a dilator to avoid catheter tip damage.

Renal Transplant Unit,
St Mary's Hospital,
London W2 1NY

BRIAN W. ELLIS

MATERNAL VALPROIC ACID AND CONGENITAL NEURAL TUBE DEFECTS

SIR,—Our birth defects monitoring system for the Rhône-Alpes region of France, where there are about 72 000 births a year, operates with the collaboration of all paediatricians and obstetricians. We participate in the international clearing house for birth defects monitoring.[3] We collected, between Aug. 11, 1979, and Aug. 10, 1982, 72 case-records of infants born with lumbosacral neural tube defects (NTD) alone or associated with other malformations. 9 were infants born to epileptic mothers who had taken valproate during pregnancy. Gomez' letter[4] prompted us to describe these cases (see table).

We have no case of association of valproic acid with anencephaly (among the 17 cases of anencephaly collected during the same period), but our monitoring system is imperfect for stillbirths and for therapeutic abortions.

DETAILS OF NINE CASES OF NTD IN INFANTS BORN TO MOTHERS WHO HAD TAKEN VALPROATE DURING PREGNANCY

Case (and date of birth)	Valproate* (mg/day)	Defect(s)	Family history
1 (Nov. 8, 1979)	1500	LMS	Father's brother: SBA, died at 6 mo
2 (June 28, 1980)	1500	Sacral meningocele	First cousin: mucoviscidosis
3 (March 6, 1981)	400	LSM + hydrocephaly and microcephaly	None
4 (April 5, 1981)	2000	Lumbar SBA	None Grandmother's sister: trisomy 21 Second cousin: DMD Maternal grandmother and maternal second cousin: epilepsy
5 (Aug. 12, 1981)	1200	Epidermised lumbar SBA* + hydrocephaly	Second cousin: SBA First cousin: late enuresis
6 (Nov. 19, 1981)	1000	LSM + complex congenital cardiopathy + hypospadias (karyotype normal)	Mother's sister: SBO + late enuresis
7 (March 2, 1982)	1000	Sacral meningocele	None
8 (March 18, 1982)	750	Lumbar SBA	None
9 (Aug. 10, 1982)	1500	Sacral open meningocele	None

SBO = spina bifida occulta; SBA = spina bifida aperta; DMD = Duchenne muscular dystrophy; LSM = lumbar myelomeningocele.
*Throughout pregnancy except in case 2 (first trimester), other anticonvulsants (and daily doses in mg) were: phenobarbitone 50 (case 1), phenobarbitone 200 (case 2), phenobarbitone 200 + primidone 250 (case 3), and clonazepam 2 (case 9).

2 of the 9 cases had another case of severe NTD in their family, a larger than expected proportion.

All 9 cases required surgery, and 1 died (no. 6). Only one mother (no. 2) had non-stabilised epilepsy: she had had four epileptic seizures during the first trimester of pregnancy.

Valproic acid was given alone (5 cases) or with phenobarbitone (3 cases), or clonazepam (1 case). The doses of valproic acid were high, over 1 g daily in 7 cases. Blood concentrations of valproate in these women will be measured while they are on the same treatment.

We suspect that valproate may be teratogenic and have started a case-control study in collaboration with some other members of the International Clearinghouse.

Institut Européen des Génomutations,
69005 Lyon, France

ELISABETH ROBERT
PIERRE GUIBAUD

**In France and in West Germany, where the equivalents of data sheet compendia are readily available to the public, warnings about the possible teratogenicity of sodium valproate are low key, but in the U.K., U.S.A. and elsewhere the product information warnings are specific and refer to animal evidence. Besides Gomez' report there are other human data that warrant caution.—ED. L.

POLYCYSTIC OVARIES DISEASE: ONE OVARY TOO MANY?

SIR,—The Stein-Leventhal syndrome—consisting of hirsutism, oligomenorrhoea or amenorrhoea, and obesity combined with polycystic ovaries, and nowadays called the "polycystic ovaries syndrome" (PCO)—still has an uncertain aetiology. The primary lesion can (but generally does not) originate in the adrenal glands. In most cases it remains unclear whether one or both ovaries or hypothalamic-hypophyseal dysfunction is predominantly involved in the disease. However, it is well established that androgen production from ovaries and/or adrenal glands is increased and that continuous oestrogen release contributes to the syndrome.

There is a tendency to the view that PCO should not be left untreated. The androgen excess, it is argued, can cause hirsutism (or even virilism) and overweight because of the anabolic effects of androgens and the increased appetite while the continuous release of unopposed oestrogen could increase the risk of endometrial and mammary cancer.

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3. Flynt JW, Hay S. International Clearinghouse for Birth Defects Monitoring system. *Constr Epidemiol Biostat* 1979; **1**: 44–52.
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Letters to the Editor

VALPROIC ACID AND SPINA BIFIDA

SIR,—At the annual meeting in September of the International Clearinghouse for Birth Defects Monitoring Systems,[1] Dr Elisabeth Robert of the Rhône-Alpes programme gave a preliminary report of her data linking valproic acid with spina bifida aperta (SBA), data now published in *The Lancet*'s correspondence columns (Oct. 23 p. 937). The directors of the monitoring programmes were asked to investigate this matter and report their findings in Strasbourg during the week of Oct. 10–15. We have the outcome of these investigations. Although the results are preliminary, we believe the association of valproic acid with SBA to be a matter of urgent concern and are reporting our findings.

A further analysis of data is available from Rhône-Alpes for 1976/1978–82, showing that 9 of 146 mothers who had SBA infants were exposed to valproic acid in the first trimester of pregnancy. Of the mothers of 6616 infants with other malformations, 21 were exposed, giving an odds ratio of 20·6 ($p<0·000001$). Among the malformed group of infants without SBA, 61 of the mothers had a history of epilepsy; 21 (34·4%) of these women were exposed to valproic acid (odds ratio 17·1, $p=0·00068$). Besides suggesting a strong relation between valproic acid and SBA, these data indicate that about 35% of epileptic women in the Rhône-Alpes region are treated with valproic acid.

Data from other programmes help in the evaluation of the Rhône-Alpes data (table). If we exclude the data from Italy (see below) we find that 12 (0·7%) of 1669 mothers of infants with neural tube defects from six programmes had epilepsy. These data show that the 10 (6·8%) of 146 epileptic women observed among women who gave birth to infants with neural tube defects in Rhône-Alpes is unusual. The director of the Italian programme found that, in 1980–82, 3 epileptic women had given birth to a child with spina bifida; 2 of these women had taken valproic acid. There were 5 mothers with epilepsy among the mothers of 827 malformed infants reported from the Italian programme in 1982; none of these 5 babies had spina bifida. 1 of the women, the mother of a baby with omphalocele and limb reduction deformities, had taken valproic acid.

No cases of spina bifida associated with valproic acid use were reported from other programmes. The data from these programmes suggest that this drug is not widely used in other regions. In Hungary, there were no exposures to valproic acid in 5580 normal control infants; 11 of those mothers were treated for epilepsy. The drug is not produced in Hungary and is rarely imported. In Sweden, none of 108 pregnant epileptic women were found to have been treated with valproic acid. In Paris-Yvelines, only 2 of 28 women with epilepsy whose malformed infants (none with SBA) were reported to the registry had been exposed to valproic acid. In Atlanta, there were no exposures among 21 women with epilepsy whose malformed babies were reported to the registry. In a review of all births to epileptic women in two hospitals in the Paris-Yvelines programme, 24 women were identified, 4 of whom were treated with valproic acid. Exposure data are unknown for epileptic women who produced children with neural tube defects in Norway. Data available from national statistics indicate that only 15 (<10%) of pregnant epileptic women could be expected to have been treated with valproic acid in each of the last two years. Although many women worldwide have been treated with valproic acid, published cohort data are limited. Hillesmaan, from Finland,[2] reported 12 exposed pregnant women who had normal babies. Since it appears that SBA occurs in about 1% of births with first trimester valproic-acid exposure, this small cohort study is an inadequate test of the hypothesis. We will continue to study this problem and encourage others to do so and to report their findings.

On the basis of present data, we believe that it is highly likely that valproic acid causes spina bifida among about 1% of fetuses exposed to it in early pregnancy. This risk is similar to the risk (1–3%) of having a baby with spina bifida after previously having had a baby with neural tube defects. We believe that women who have been exposed to valproic acid in the first trimester should be informed of the risk and offered prenatal counselling.

NUMBER AND TREATMENT OF EPILEPTIC WOMEN AMONG THE MOTHERS OF BABIES WITH NEURAL TUBE DEFECTS REPORTED TO EIGHT BIRTH DEFECTS SURVEILLANCE SYSTEMS

Country: region	Number of NTD (SBA) (*and years*)	Epileptic mothers	Type of NTD and anticonvulsant
France: Rhône-Alpes	(146) (*1976–82*)	10	5 SBA: valproic acid alone 3 SBA: valproic and barbitone 1 SBA: valproic acid and clonazepam 1 SBA: barbitone
France: Paris-Yvelines	113 (41) (*1980–82 July*)	0	..
Hungary	583 (319) (*1980–82*)	4 (0·7%)	SBA: phenytoin SBA: trimethadione SBA: phenytoin and barbitone AN: phenytoin and diazepam
Italy	214 (95) (*1980–82*)	3 (1·4%)	SBA: valproic acid alone SBA: valproic acid alone AN: phenytoin
Northern Ireland	324 (*1979–81*)	3 (0·9%)	SBA AN phenytoin and barbitone
Norway	(457) (*1967–81*)	3	.. ..
Sweden	114 (*1975–76*)	1	SBA: phenytoin
U.S.A.: Atlanta	78 (*1980–82*)	1	AN: none

BA = spina bifida aperta; AN = anencephaly.

Contributed by the following participants in the International Clearinghouse for Birth Defects Monitoring Systems:

Institute of Preventive Medicine, University of Oslo, Oslo, Norway — TOR BJERKEDAL

National Institute of Hygiene, Budapest, Hungary — ANDREW CZEIZEL

INSERM Statistical Research Unit and Maternity/paediatrics Section, Villejuif, France — JANINE GOUJARD

Department of Embryology, University of Lund, Lund, Sweden — BENGT KALLEN

Paediatrics Clinic, Catholic University of Rome, Rome, Italy — PIERPAOLO MASTROIACOVA

Department of Medical Genetics, Queen's University, Belfast — NORMAN NEVIN

Center for Environmental Health, Centers for Disease Control, Atlanta, Georgia 30333, U.S.A. — GODFREY OAKLEY, JR

Institut Européen des Génomutations, Lyons, France — ELISABETH ROBERT

EARLY RESUSCITATION AFTER MARATHON COLLAPSE

SIR,—We wish to report the resuscitation of a 47-year-old man who collapsed within 30 m of the finishing line during the Glasgow marathon.

The race took place on Oct. 17 in cold (12°C), mainly dry, but windy (16–40 km/h) conditions, and the runner was competing in his second marathon. Within seconds of his collapse he was put on a trolley and taken to a medical treatment tent about 100 m away. On

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2. Hillesmaa VK. Valproic acid during pregnancy. *Lancet* 1980; i: 883.

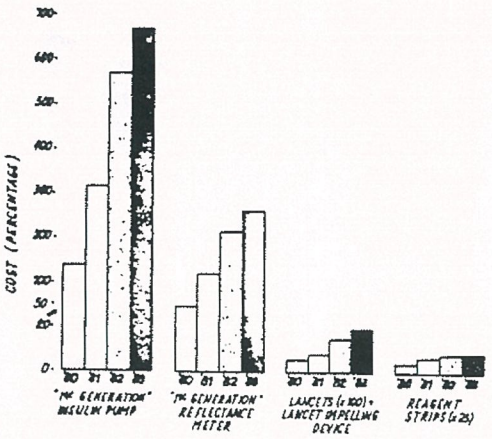

Fig 2—Inflation of monthly costs of different elements required to implement home blood glucose monitoring associated with SCII, expressed as percentage of monthly salary of senior hospital administrative clerk. Medical fees not included.

important factor in determining the feasibility of a home blood glucose monitoring programme. Where the national economy is erratic imported technology can be affordable at one time yet prohibitively expensive at another (fig 2), and patients have abandoned home monitoring even though they have been told that the benefits of normoglycaemia may be reaped only after several years of strict compliance.

Over the past few years clinical research in diabetes has been heavily biased towards evaluating increasingly complex and expensive equipment such as insulin pumps, reflectance meters, and closed loop infusion devices. If home blood glucose monitoring proves to be a critical element in maintaining near-normal blood glucose levels, irrespective of the way in which an intensive insulin regimen is delivered, more research effort should be dedicated to the development of cheap, reliable reagent strips that can be read with the naked eye. Colleagues in socioeconomic settings similar to Argentina's should discuss the wisdom of motivating patients onto home blood glucose monitoring without first carefully assessing the likelihood of an intensive insulin treatment programme being complied with long term.

Endocrinology and Nuclear Medicine Unit,
Hospital Italiano,
1181 Buenos Aires, Argentina

JAMES A. FAGIN
LEON LITWAK
RAUL A. GUTMAN

VALPROIC ACID AND SPINA BIFIDA

SIR,—ECLAMC (Latin American Collaborative Study of Congenital Malformations), a member of the International Clearinghouse for Birth Defects Monitoring Systems, was unable to meet the deadline for inclusion of its data in the November, 1982, letter by Bjerkedal et al[1] on the relation between valproic acid and spina bifida, an association proposed by Robert and Guibaud[2] and discussed editorially.[3] We present our data here, which are negative for a valproic-acid/spina-bifida association.

ECLAMC is a hospital based, case-control study of birth defects in which fifty genetic and environmental risk factors are considered. Since valproic acid has been used in South America since about 1978, our 1979–82 records were searched for maternal epilepsy and anticonvulsant therapy during the first trimester of pregnancy. In these four years, ECLAMC covered 230 700 births (live and still) in twenty-nine hospitals from eight South American countries. 6418 malformed and 6254 matched non-malformed control babies were registered in this period. Data on maternal epilepsy, anticonvulsant drugs, and neural tube defects are as follows:

	Epileptic mothers		
Newborn babies	*Taking valproic acid*	*Total*	*Total number of mothers*
Anencephaly	0	0	134
Spina bifida	0	0	150
Other malformations	1	26	6134
Non-malformed	0	16	6254

The only registered exposure to valproic acid was that of a sacral dimple (or fistula) in an otherwise normal baby, born in 1980 in Cordoba (Argentina) from an epileptic mother treated with 'Logical' (magnesium valproate) throughout the entire pregnancy. Even though a sacral dimple is a common minor anomaly, without proven relationship with open spina bifida, it seems odd that the only instance of prenatal use of valproic acid registered here was associated with an axial caudal defect.

The ECLAMC programme has registered neural tube defect cases at the usual incidence rates for this part of the world—5·8 per 10 000 for anencephaly and 6·5 per 10 000 for spina bifida. ECLAMC also detected maternal epilepsy at the expected prevalence rate of approximately 1 per 300 for females of reproductive age[4,5]—namely, 26/6418 or 1 in 247 among the malformed and 16/6254 or 1 in 391 among the non-malformed group, resulting in a 1·58 odds ratio for maternal epilepsy among the malformed.

ECLAMC recognised the use of an anticonvulsant as rare as valproic acid at least once among 42 epileptic mothers, so the lack of evidence for an association between prenatal exposure to valproic acid and neural tube defects, found in the ECLAMC series, cannot be ascribed to a lack of sensitivity in the ECLAMC epidemiological system.

IMMICE,
Casilla 403,
1900 La Plata, Argentina

EDUARDO CASTILLA

MEASLES VACCINE ASSOCIATED ENCEPHALITIS IN CANADA

SIR,—Dr Berlin (June 18, p 1380) notes that the true frequency of convulsions after measles vaccine has not yet been determined, and asks for studies of the temporal association between vaccination and convulsions to offset a possible negative impact on this aspect of childhood immunisation programmes. The underlying concern appears to be that convulsions may indicate encephalitis, which could result in brain damage.

In 1977 I reviewed Canadian experience with measles vaccines, based on cases reported to the Drug Adverse Reaction Program, Health and Welfare, Canada. Suspected neurological reactions to measles vaccines, reported during 1965–76 are listed in the table. Denominators used for the calculations of rates were based on doses "distributed" but not necessarily administered.

Encephalitis was reported at an overall rate of 1·79 cases per million doses distributed, and convulsions at an overall rate of 8·46 per million. No significant difference was observed between earlier and current preparations with regard to suspected neurological reactions, although more recently developed vaccines exhibited lower rates of febrile reactions.

This type of assessment is limited. There is no standard case definition. In the vast majority, the incident is not "proven" but is simply viewed as consistent with respect to clinical features and temporal relationship. Some reactions may go unrecognised and some that are suspected may go unreported. Considerable regional variation in adverse reaction reporting has been noted in Canada.[1] Denominators based on doses distributed will be overestimates of doses administered and will bias rates in a downward direction.

A reported "reaction" associated temporally with vaccine

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successful in a previous study,[3] was tried as an initial step before the sample was passed down the sephadex column, but no real improvement was observed. No conclusions could be drawn about the presence or otherwise of the abnormal ganglioside species in plasma samples.

However, with samples of tumour reasonable results were obtained with the modified procedure (ie, ultracentrifugation followed by gel filtration). The abnormal species (GD_2) was observed; but it was in samples from all three histological regions so there was no correlation between the degree of differentiation and the presence or absence of specific ganglioside species. This would tend to support the findings of others.[3]

Preparative thin-layer chromatography followed by neuraminidase digestion of the ganglioside confirmed the findings of Ladisch and Wu.[1] Additional studies,[4] using gas-liquid chromatography of the monopolysaccharides present in a hydrolysate, further supported their view that the ganglioside was GD_2. However, our failure to find it in plasma and the fact that a large tumour sample is required for analysis means that considerable refinement of the analytical technique will be necessary for it to be a useful diagnostic test for neuroblastoma.

Our work was supported by the Cancer and Leukaemia in Childhood Trust.

Pathology Department,
Bristol Maternity Hospital,
Bristol BS2 8EG

J. D. PEAK
P. J. BERRY
C. A. PENNOCK

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IN-UTERO EXPOSURE TO VALPROATE AND NEURAL TUBE DEFECTS

SIR,—Previous studies have revealed an association between prenatal exposure to valproate (VPA) and spina bifida (SB).[1–3] However, the evidence is still indirect since it is based on a higher prevalence of maternal VPA exposure among SB cases than among other birth defect cases or the general population, and these studies have not provided well-defined exposure denominators. Although rostrally localised defects such as exencephaly have been observed with VPA administered to pregnant rodents,[4] no significant association with anencephaly has yet been reported in man. This might indicate interspecies differences in site-specific sensitivity for VPA teratogenicity. However, the lack of reports on a VPA/anencephaly association may also be due to attention being focused on SB by the early publications and to the fact that anencephaly is much more likely to escape registration than SB because it is easier to detect on routine obstetric ultrasound studies (and is followed by therapeutic abortion in early pregnancy).

Cohort studies of pregnant women with epilepsy where anticonvulsant drug exposure is prospectively recorded and all subsequent outcomes are evaluated will define exposure denominators, achieve equal ascertainment of SB and anencephaly, and measure the true risk of neural tube defects (NTD) for the various exposures. However, the prospective studies in progress and known to us do have too few cases of VPA exposure for statistics to be meaningful.[1] For this reason we sent a questionnaire to eighteen groups doing such prospective studies, asking about the prevalence of SB and/or anencephaly among infants with first trimester exposure to VPA, in comparison with infants exposed to other anticonvulsant drugs, infants of epileptic mothers not taking drugs, infants with epileptic fathers, and healthy controls.

Thirteen groups shared their data with us (table I). Prenatally diagnosed cases with termination of pregnancy were included but spontaneous abortions were excluded. Of a total of 2111 infants exposed to any anticonvulsant drug, 12 had an NTD (11 SB and anencephaly). The frequency of NTD among infants exposed to

TABLE I—FIRST TRIMESTER EXPOSURE TO VALPROATE OR OTHER ANTICONVULSANTS AND NUMBER OF NEURAL TUBE DEFECTS

Anticonvulsant exposure	Exposed infants (no)	Infants with NTD (no)	Infants with NTD (%)
Maternal epilepsy			
Valproate only	120	3* *(a)*	2·5
Valproate plus other	273	3	1·1
Valproate (any)	393	6* *(b)*	1·5
Other	1718	6 *(a,b)*	0·35
Any	2111	12	0·57
None	221	1	0·5
Paternal epilepsy	95	0	
Non-epileptic controls	599	0	

χ^2 tests: *(a)* $p < 0{\cdot}01$ (all NTDs) and $p > 0{\cdot}05$ (SB only); *(b)* $p < 0{\cdot}05$ (all NTDs) and $p > 0{\cdot}05$ (SB only).
*1 case of anencephaly with VPA only, prenatally diagnosed at 4 months of gestation and therapeutically aborted.

VPA with or without other anticonvulsants (6/393 or 1·5%) or to VPA alone (3/120 or 2·5%) is significantly higher than that among infants exposed to other anticonvulsant drugs (6/1718 or 0·35%). 0·35% is similar to the frequency found before the general introduction of VPA,[5] which suggests that maternal VPA treatment itself carries a considerable additional risk of causing NTD, and that the prescription of VPA is not merely an indicator of, for example, a possible increased genetic risk of NTD related to maternal epilepsy itself. Although, in this study, the ascertainment of SB and anencephaly was the same, the SB/anencephaly ratio of 11:1 (for VPA 5:1, for other anticonvulsants 6:0) still deviates from the ratios observed in the general populations studied (eg, 1·25–2·25:1 in the Netherlands and close to 1:1 in other countries). This supports the view that, in man, VPA induces more specifically SB and not NTD in general. Assuming an average population incidence of anencephaly of 1–3 per 1000, the lack of anencephaly in the much larger group of other anticonvulsant exposures (1718) can still be explained by chance.

Two kinds of bias may have occurred. Some of the groups may have responded because they were already aware of NTD cases in their data. If so, this happened probably regardless of the type of exposure, and cannot explain the difference found between VPA exposures and other exposures. Secondly, the relative contribution of VPA exposures differed widely among the thirteen cohorts (table II). This might be a source of bias if the various cohorts are derived

TABLE II—CONTRIBUTIONS OF THIRTEEN STUDY GROUPS

Group*	% of exposures contributed to collaborative study		No of cases of NTD	
	Any	VPA	Any exposure	VPA exposure
Amsterdam/Heemstede-Rotterdam	15	40	2	1
Berlin	7	9	1	1
Charlottesville	10	2	0	0
Fukushima	1	1	0	0
Helsinki	15	8	3	1
Hirosaki	5	4	0	0
Magdeburg	5	5	1	0
Milan	10	8	1†	1†
Montreal	6	4	1	1
Nagasaki	14	4	2	0
Nancy	5	2	0	0
Plymouth	1	1	0	0
Shizuoka	6	13	1	1
Total	..	..	12	6

*Population incidences of NTD (SB + anencephaly were: 0·05–0·09% SB) and 0·04% (anencephaly) in the three Dutch series; 0·03–0·05% in Helsinki; and 0·2–0·3% in Montreal.
†Anencephaly.

from populations with different background incidences of NTDs. Such bias is unlikely to be the cause of the association found because the cohort contributing 40% of all VPA exposures is Dutch, a country which has a fairly low population incidence of NTD.[6,7] However, more extensive cohort studies are required to evaluate other possible risk factors such as genetic predisposition and the role of concurrent medication, and to estimate the risk of each of the other anticonvulsant drugs. Furthermore, each of the cooperative cohort studies should preferably be done on total population basis, to obtain results that can be better extrapolated to the general epileptic population.

The difference in NTD prevalence between VPA alone (2·5%) and VPA plus other drugs (1·1%) is not significant, but a similar difference was found in the birth defects registry in France.[8] If this discrepancy should prove to be consistent, the reason might be that epilepsy requiring treatment with VPA plus other drugs is associated with a genetic (predisposing) background for NTDs which is different from that in epilepsies which are treated with VPA only; or that the other drugs alter the metabolism of VPA, decreasing the teratogenic effect; or that co-medication is associated with lower serum levels of VPA.

This collaborative study provided sufficient numbers for statistical analysis. The results confirm that VPA exposure during the first trimester of pregnancy is causally associated with a considerably increased risk of NTD of 1·5% (95% confidence limits 0·42–3·00%). We conclude that the use of VPA during pregnancy should be avoided or that prenatal diagnosis (amniotic fluid analysis and ultrasound) should be offered.

We thank Prof H. Meinardi, Prof H. Helge, Prof D. Janz, Prof F. Dreifuss, Dr H. Kumashiro, Dr A. H. Bardy, Dr S. Kaneko, Dr H. Klepel, Prof R. Canger, Dr E. Andermann, Dr J. Nakane, Prof P. Vert, Dr E. M. Allen, Dr M. Seino, Dr M. Miyakoshi, and Dr T. Wada for providing their data.

Department of Clinical Genetics,
Erasmus University,
3000 DR Rotterdam, Netherlands,
and Instituut voor Epilepsiebestrijding
Meer en Bosch-De Cruquiushoeve, Heemstede — D. LINDHOUT

Department of Neurology,
Klinikum Grosshadern,
Munich, West Germany — D. SCHMIDT

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FAILURE OF THE KLEIHAUER TEST TO DETECT RED BLOOD CELLS IN AMNIOTIC FLUID

SIR,—We, like Dr Stockley and colleagues (April 26, p 973), used to check all bloodstained amniotic fluid for fetal blood cells by Kleihauer test (Boehringer). The procedure was replaced last year by electrophoresis of haemoglobin, after the failure of Kleihauer test to detect fetal blood in an amniotic fluid. Amniocentesis in a 26-year-old woman was done at 20 weeks of gestation after two raised serum α-fetoprotein (AFP) levels at 2·5 and 2·8 times the median for 16 and 19 weeks' gestation, respectively. The liquor was heavily bloodstained and the AFP level, at 2·5 times the median, was on the cut-off point. The Kleihauer test did not show any fetal blood cells. In view of a normal ultrasound scan and a borderline high liquor AFP level, the specimen was further investigated by electrophoresis (cellulose acetate) for fetal haemoglobin (HbF). HbF was the predominant haemoglobin present in this bloodstained specimen. Pregnancy was allowed to continue and a normal baby was delivered at term.

Normally in adults HbF is present in trace amounts below 1%,[1] increasing slightly in pregnancy, whereas it is the principal haemoglobin (90–95%)[2] in fetal blood.[2] Presence of a large proportion of HbF in a bloodstained liquor is therefore consistent with contamination of amniotic fluid with fetal blood. We think electrophoresis can be conveniently used to exclude/confirm fetal blood contamination and it is unlikely to give any false negative results in visibly bloodstained samples.

Department of Pathology,
Countess of Chester Hospital,
Chester CH2 1BQ — J. AHMED, C. BROWN

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SYSTEMIC EFFECTS AND INHALED BECLOMETHASONE DIPROPIONATE

SIR,—Dr Law and colleagues (April 26, p 942) demonstrate a significant dose-related systemic effect of inhaled beclomethasone dipropionate (BDP) in asthmatic children, within a therapeutically relevant dose-range.

Would cortisol secretion during the night have been normal (similar to that in untreated controls) in the twelve index asthmatic children if they had not inhaled BDP? The two groups of patients may have differed in the severity of their asthma: in children on inhaled steroids asthma may have been worse (eg, with a more severe nocturnal asthma) and a basic defect in endocrine secretion may have been one determinant of the severity of their asthma.[1] Barnes and colleagues showed in asthmatics that diurnal swings in peak expiratory flow rate, plasma adrenaline concentration, and plasma cyclic adenosine monophosphate concentration were in phase. A tempting hypothesis to explain nocturnal asthma would be that it is the consequence of a disturbance in the natural fall in cortisol production during the night.[3] Thus we cannot exclude the possibility that the observed reduction in nocturnal cortisol secretion was independent of the inhaled BDP.

It is necessary to demonstrate a different cortisol profile during the night in the same group of children, both before and after receiving inhaled steroids before convincing conclusions can be drawn.

University Paediatrics Clinic,
Istituto per l'Infanzia,
34100 Trieste, Italy — A. VENTURA, R. STRINATI, G. LONGO

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PERCUTANEOUS LIVER BIOPSY

SIR,—In my letter of April 26 (p 975), referring to the article by Dr Maharaj and co-workers (March 8, p 523), my phrase "length of the biopsies" (I meant length in mm) was changed to "duration of the procedure". In their reply (April 26, p 975) Dr Maharaj and colleagues ask whether the 7% complication prevalence is based on my own data. On the contrary, it is based on their data: they report a complication rate in 75 patients of 0%, which has an upper 99·5% confidence limit of 6·82%. I notice that they do not provide the inter-observer and intra-observer error.

Department of Gastroenterology C,
Herlev University Hospital,
DK-2730 Herlev, Denmark — CHRISTIAN GLUUD

these had a proboscis. Absence of olfactory structures, with or without a proboscis, is common in holoprosencephaly (Pauli et al., '83; Mieden, '82).

Data from this study are equivocal as they relate to Gropp's suggestion that defects found in Ts 1 are an early developmental stage of the holoprosencephaly-cyclopia complex. However, similarities in morphological development of the brain and the eyes in human Ts 13 and murine Ts 1 could not be satisfactorily defined from our results. No parallels were found between these syndromes in limb and heart defects, which are very characteristic of human Ts 13 (Bartalos and Baramki, '67; Colacino and Pettersen, '78; Pettersen et al., '79).

ACKNOWLEDGMENTS

This work was supported by an NIH General Research Support Sub-Grant from the University of Wisconsin Medical School Research Committee and by funds from the University of Wisconsin Graduate School. We wish to thank Dr. Edward T. Bersu for sharing his expertise on breeding, karyotyping, and analyzing trisomic mouse embryos and to Mr. James Olson for photographing the whole embryos.

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REF 5

TERATOLOGY 35:465–473 (1987)

Teratogen Update: Valproic Acid

EDWARD J. LAMMER, LOWELL E. SEVER, AND GODFREY P. OAKLEY, JR.
Division of Birth Defects and Developmental Disabilities, Center for Environmental Health, Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia 30333

ABSTRACT Valproic acid use during pregnancy results in an absolute risk for spina bifida of 1–2%. This increased risk is comparable to the recurrence risk for neural tube defects and warrants informed counselling and access to prenatal diagnosis. There is no substantial evidence that valproic acid use increases the risk for other specific major malformations above the increased risk due to maternal epilepsy. Valproic acid may cause a characteristic pattern of minor facial malformations. Further definition and confirmation are required, and the magnitude of the risk needs to be determined. There are inadequate data to assess the magnitude, if any, of the risks for postnatal growth abnormalities and developmental disabilities associated with the use of valproic acid during pregnancy. Birth-defect monitoring programs and international collaboration among the staffs of monitoring programs played a major role in determining that valproic acid is a human teratogen.

Valproic acid, also known as dipropylacetic acid, is a simple, eight-carbon, branched-chain fatty acid that is used for the treatment of patients with epilepsy. It is not structurally related to other anticonvulsants. Valproic acid's beneficial properties were serendipitously discovered. While it was being used as a vehicle to deliver other compounds that were being tested for their anticonvulsant activity, researchers noted that it had substantial ability to prevent seizures. Further experimentation revealed that the vehicle, valproic acid, did have anticonvulsant properties, and this led to its eventual testing in humans.

Valproic acid was released for human use in Europe in 1967 and became available in the United States in 1978. In the United States, valproic acid is approved by the Food and Drug Administration only for the treatment of absence seizures with or without other types of seizures. In European countries, it may be used for all types of seizures (Loiseau, '84). It appears to be most efficacious for the treatment of absence seizures, but it has been used for the treatment of various types of epilepsy and is often used as an adjunctive treatment for patients whose epilepsy is not controlled by a single anticonvulsant.

PHARMACOKINETICS

The mean serum half-life of valproic acid is 7–9 hours for adults on chronic therapy. It is rapidly eliminated, primarily by urinary excretion of the glucuronide conjugate. The usual chronic adult dosage is 1,000–1,600 mg per day, to a maximum of 2,600 mg/day (Pinder et al., '77). The therapeutic serum range is 50–150 μg/ml (Browne, '80). Dickinson et al. ('79) showed that valproic acid crossed the placenta and that the umbilical cord and newborn serum concentrations exceeded the concentration in the maternal serum. Nau et al. ('84) provided additional evidence that human fetuses at delivery are exposed to higher total valproic acid concentrations than their mothers. During embryogenesis, it is unclear whether the fetal serum concentration of valproic acid is higher than that of the mother.

HUMAN STUDIES

Case reports and case series

The first case report of a malformed infant whose mother had taken only valproic acid during her pregnancy was by Dalens et al. ('80). This was followed by a number of case reports describing malformed infants whose

Received July 27, 1986; accepted October 30, 1986.

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mothers used valproic acid during pregnancy (Thomas and Buchanan, '81; Clay et al., '81; Bailey et al., '83; Bantz, '84; Tein and MacGregor, '85). Except for the mother of the infant reported by Thomas and Buchanan ('81), all of the mothers used valproic acid monotherapy throughout the pregnancy. The following malformations were described among the seven infants in those reports: flat nasal bridge (4), fingerlike thumbs (3), prominent forehead (2), eyebrow depigmentation (2), low-set malformed ears (2), micrognathia (2), microcephaly, cleft lip, small nose, valvular aortic stenosis, ventricular septal defect, tetralogy of Fallot, levocardia, duodenal atresia, renal hypoplasia, hypospadias, vertebral anomalies, congenital hip dislocation, shortened forearm, hypoplastic thumb, preaxial polydactyly, syndactyly, and hypoplastic nails. In addition, three reports of valproic-acid-exposed infants with isolated spina bifida have been made (Gomez, '81; Stanley and Chalmers, '82; Blaw and Woody, '83).

DiLiberti et al. ('84) described seven dysmorphic infants whose mothers had used valproic acid during pregnancy. During five of these pregnancies, however, other anticonvulsants were also taken. Two of the seven infants were siblings born to a mother whose seizure disorder resulted from a head injury. It is unlikely that these infants' malformations resulted from a genetic etiology that also was related to maternal epilepsy. The authors reported a characteristic facial phenotype among all of the valproic-acid-exposed infants: epicanthal folds with an infraorbital crease, flat nasal bridge, small upturned nose, long upper lip with a relatively shallow philtrum, thin upper vermillion border, and downturned angles of the mouth. Three infants had posteriorly angulated ears and one of these infants had small, malformed ears. Two infants had hypospadias and strabismus, and two others had nystagmus.

At the Society for Pediatric Research meeting in May 1984, Hanson et al. ('84) presented a summary of 13 valproic-acid-exposed infants with malformations. Some of these infants were included in the case series of DiLiberti et al. ('84). Hanson et al. ('84) also described a characteristic facial phenotype: midfacial hypoplasia, telecanthus, and a broad, low nasal bridge with a short nose. Major malformations reported included spina bifida (2), cardiac malformations (3), and cleft lip (1). Several infants had postnatal growth retardation and developmental delay.

These case reports raised questions about possible adverse effects from prenatal exposure to valproic acid. The observations were not, however, so unusual that a causal relationship could be inferred.

Case-control studies

Case-control studies of valproic acid teratogenicity have compared the frequency of valproic acid use among mothers of infants with a given malformation with the frequency of valproic acid use among mothers of infants with other structural malformations. The results of these studies, and similar case-control studies involving other anticonvulsant medications, can be difficult to interpret because of the potential confounding effect of maternal epilepsy. Maternal epilepsy is a potential confounder because it is associated with the exposure (anticonvulsants) and the outcome (infants of epileptic mothers are at increased risk for having structural malformations). If a study finds an increased risk for a malformation after exposure to an anticonvulsant, all or part of that risk may be related to the maternal epilepsy. Determining what portion of the risk is attributable to the anticonvulsant and not to the maternal epilepsy is difficult.

1. Spina bifida.

In 1982, Robert and Guibaud reported a study of valproic acid use among mothers of infants with spina bifida who were registered in the Rhone-Alps birth defects surveillance system. During 1976 and 1978–1982, the research team of the Institut Européen des Génomutations in Lyon, France, interviewed 146 mothers of infants with spina bifida. They noticed that an unusual number of the mothers had epilepsy and had used valproic acid during their pregnancies. A case-control study found that nine (6.2%) of the 146 mothers had used valproic acid during pregnancy. Twenty-one (0.3%) of the mothers of 6,616 infants with other structural malformations had used valproic acid. The odds ratio was 20.6 (95% confidence limits [CL] 8.2, 47.9) for the association of spina bifida and valproic acid use during the first trimester of pregnancy.

When the analysis was restricted to the 71 malformed infants of epileptic mothers in the Rhone-Alps registry, the odds ratio was 17.1 (95% CL 2.1, 769). Thus, the high relative risk persisted after the increased risk for malformations associated with maternal epilepsy was controlled. Assuming a U.S. spina bifida rate of six per 10,000 births and a relative risk for spina bifida after valproic acid exposure of 20.6, then the absolute risk of a valproic-acid-exposed fetus having spina bifida is 1.2% (Robert, '82).

The data of Robert ('82) suggested that nearly half of the epileptic women in that region of France were taking valproic acid. An important question could not be answered with the Rhone-Alps data: was valproic acid exposure associated with spina bifida because maternal epilepsy significantly increased the risk for spina bifida? Maternal epilepsy and its treatment were known to be associated with an increased risk for several major malformations, but not for neural tube defects. It seemed unlikely that maternal epilepsy, rather than treatment with valproic acid, caused the excess of infants with spina bifida in the Lyon region. It was possible, however,, to quickly answer the above question by using data collected and reported by members of the International Clearinghouse for Birth Defects Monitoring Systems (Bjerkedal et al., '82). Excluding the data from Italy and France, the members reported that only 12 (0.7%) of 1,669 mothers of infants with spina bifida had epilepsy. Valproic-acid-exposed infants with spina bifida were reported only from France and Italy. The report suggested that valproic acid was not widely used during pregnancy in the other countries. Since the frequency of valproic acid use among mothers of infants with spina bifida in the Rhone-Alps region (6.2%) was much higher than the expected frequency of 0.7%, it was very unlikely that the increased risk for spina bifida was due to the maternal epilepsy. The authors concluded that a causal relationship was highly likely between valproic acid exposure and spina bifida, and that the absolute risk for spina bifida was about 1%.

The Indagine Policentrica Italiana sulle Malformazioni Congenite (IPIMC) reported several valproic-acid-exposed infants with spina bifida in the report from Bjerkedal et al. ('82). Using a case-control study design, they reported a significant association between valproic acid exposure and spina bifida (Mastroiacovo et al., '82; MMWR, '83). Among 118 infants with spina bifida, two were exposed to valproic acid, whereas three of 4,489 malformed control infants were exposed (odds ratio 25.8, 95% CL 3.0,191.0). Their findings confirmed the results of Robert ('82) from France.

In the Netherlands, Lindhout and Meinardi ('84) sought to identify all infants with spina bifida born between January 1972 and July 1983. The infants were ascertained from surveys of clinical centers. The authors identified 221 infants and determined how many of these infants were born to women with epilepsy and what anticonvulsants the mothers took. The mothers of six infants were epileptic. All six had taken valproic acid during early pregnancy. Although they did not interview a control population, the relative risk for spina bifida can be approximated. Prescription records showed that 25% of reproductive-age women who received an anticonvulsant prescription received valproic acid. If the frequency of epilepsy among mothers of infants with spina bifida is 0.7% and if 25% of pregnant epileptics took valproic acid, then 0.4 valproic-acid-exposed infants among the 221 infants with spina bifida would be expected. Because six cases were observed, this provides more evidence of a causal relationship between valproic acid exposure and spina bifida.

2. Other malformations.

Several case-control studies were conducted to see whether valproic acid exposure increased the risk for other specific major malformations. Robert and Rosa ('83) updated the Rhone-Alps experience with valproic acid and birth defects by assessing the risk for spina bifida, congenital heart defects, and orofacial clefts. They reported that 91 of 9,550 malformed infants had been exposed to maternal anticonvulsants; 38 of the mothers had used valproic acid. Of these 38 pregnancies, 25 resulted in an infant with spina bifida, orofacial cleft, or congenital heart defect, while 13 valproate-exposed infants were found among the 7,917 infants with other malformations. They reported an odds ratio of 4.3 (95% CL 1.8, 10.3) for the association of valproic acid exposure and congenital heart disease (11 exposed among 1,541 infants with congenital heart defects). They also found an odds ratio of 5.4 (95% CL 1.7, 16.3) for the association of valproate exposure and orofacial clefts (five exposed among 566 cleft cases). The interpretation of these data depends upon the contribution to the increased relative risks that is due to maternal epilepsy and not to valproic acid. To address this question, Mastroiacovo et al. ('83) analyzed the teratogenic risks of anticonvulsant drug use among 35 malformed anticonvulsant-exposed infants. They found that the frequency of congenital heart defects and orofacial clefts among valproic acid-exposed malformed infants was not different from that among malformed infants of mothers who used other anticonvulsants. They concluded that the association between valproic acid and congeni-

tal heart defects or clefts, reported by Robert and Rosa ('83), was attributable to confounding from the increased risk for those defects due to maternal epilepsy and/or other anticonvulsants. Only the association between spina bifida and valproic acid exposure persisted when the increased risk due to maternal epilepsy was controlled.

Cohort studies

Three prospective, longitudinal cohort studies of the reproductive outcomes of epileptic women included women who used valproic acid during pregnancy: the Helsinki study, the Berlin study, and the Tokyo study. Because each study contained small numbers of valproic-acid-exposed infants, none had adequate statistical power to accurately assess the risks for malformations, growth problems, or developmental disabilities. In addition, the outcomes of a fourth cohort of valproic-acid-exposed infants from the Netherlands have been reported. This was the largest cohort studied, but only information on the risk for major malformations was available.

The Helsinki study was conducted from 1976 to 1979 and included 170 births to epileptic women. Twelve of those pregnancies occurred among women taking valproic acid, although only one mother used valproic acid monotherapy (Hiilesmaa et al., '80). The 12 infants had no apparent major malformations at birth. In the next publication from the study (Hiilesmaa et al., '81), concerning head circumference at birth and 18 months, only nine valproic-acid-exposed infants were included. For the data analysis, valproic-acid-exposed infants were categorized into a heterogeneous exposure group, "combination therapy." Since the valproic-acid-exposed infants accounted for only nine of 51 infants in the combination group, it is impossible to know whether maternal valproic acid use had an effect on head growth. Similarly, data on longitudinal growth and development of the valproic-acid-exposed infants were not specifically discussed (Granstrom and Hiilesmaa, '82; Granstrom, '82). In the latter study, the authors inappropriately used the Denver Developmental Screening Test (DDST) as a measure of developmental outcome rather than as a screening test.

The collaborative Berlin study of the development of children of epileptic parents began in 1976. The study included nine infants born to mothers who used valproic acid monotherapy and five whose mothers used a combination of anticonvulsants, including valproic acid. Koch et al. ('82) reported on the risk for major malformations in this cohort and reported that one of 11 infants exposed to valproic acid had a patent ductus arteriosus; no other major malformations were reported. Rating et al. ('82) studied the risk for minor anomalies in the cohort, but only eight valproic-acid-exposed infants were examined (four exposed to monotherapy). Because of the small number of exposed subjects, no meaningful conclusions can be drawn about the risk for minor malformations. In the growth evaluation, Jager-Roman et al. ('82) reported that one of 11 valproic-acid-exposed infants had postnatal growth retardation.

In a later publication, Koch et al. ('83) reported the outcomes of a prospectively ascertained cohort of 14 infants born to women using valproic acid monotherapy. It was not clear whether any of these infants were also included in the reports of the collaborative Berlin study. One infant was retarded and microcephalic. Five other infants had arachnodactyly, overlapping digits, and a characteristic facial phenotype: brachycephaly, small nose, small mouth, thin lips, low-set rotated ears, and shallow orbits. Additionally, one of these five infants had spina bifida and two had metopic suture synostosis and aplasia of both first ribs.

The collaborative Japanese study was a prospective cohort study of the pregnancy outcomes of 657 epileptic women from 1974 to 1977 (Nakane et al., '80). Valproic acid was used during eight pregnancies. One infant was born with a congenital hip dislocation.

Lindout et al. ('82) reported the outcomes of a cohort of 65 valproic-acid-exposed pregnancies from the Netherlands. Of the 46 mothers taking valproic acid monotherapy, one delivered an infant with tetralogy of Fallot. Nine of 19 infants born to mothers taking a combination of anticonvulsants, including valproic acid, were malformed. Two of these infants had cleft lip. Outcomes other than major malformations were not reported. In a more recent publication, Lindhout and Meinardi ('84) reported on neural tube defects among valproate-exposed pregnancies from their prospectively followed cohort. One case of spina bifida was observed among 141 pregnancies. It is unclear whether this case was exposed to valproic acid monotherapy or combination therapy. Lindhout and Meinardi ('84) also derived relative risk estimates for spina bifida by assuming that they had ascertained nearly all infants with spina bifida in the Netherlands by their previously discussed survey. During the survey period, January 1972 to July 1983, there were 2,094,272 births in the Netherlands. Their prescription survey found that the frequency of valproic acid use among reproductive age women was 0.1%. Knowing that the prevalence of spina bifida in the Netherlands was about one per 1,000, they estimated that two or three babies with spina bifida would be expected to be born to women taking valproic acid, if there were no association between valproic acid exposure and spina bifida. But they identified ten such infants with their survey methods and believed that the case ascertainment was incomplete. This additional data provided further evidence of a causal association between valproic acid exposure and spina bifida.

EXPERIMENTAL ANIMAL STUDIES

Valproic acid, calcium valproate, and sodium valproate are developmentally toxic in several animal species. Whittle ('76) reported that valproic acid was teratogenic in rabbits, rats, and mice. Although earlier investigators found no significant teratogenic effects at "relatively modest doses," Whittle reported that the frequency of resorptions increased with increasing dosages of valproate given to pregnant rabbits. Fetal abnormalities (unilateral renal agenesis and vertebral fusions) were produced only at dosages near the maternal toxic dose. Dose-related teratogenesis was found in valproic-acid-treated rat embryos; spinal defects, mainly lumbar, and renal defects were reported. Whittle also noted that malformations in mice were inducible at lower dosages.

Brown et al. ('80) studied the teratogenicity of valproic acid in CD-1 mice. They reported that treating pregnant mice with valproic acid with 105–389 mg/kg produces dose-related malformations. Using a relative teratogenic index, they suggestd that valproic acid was equal in teratogenicity to trimethadione. A subsequent report from the same group (Kao et al., '81) more clearly established the dose-dependent teratogenicity of valproic acid in mice. Valproic acid caused growth retardation and exencephaly in their study. The concept of the relative teratogenic index was discussed further in a report from Fabro et al. ('82). The teratogenicity of eight substances was evaluated, and sodium valproate had the highest relative teratog[illegible] index.

Buckner et al. ('83) confirmed the dose-dependent teratogenic effects of valproic acid in the mouse. They found exencephaly, abnormalities of body curvature, craniofacial malformations, and yolk sac defects.

Nau et al. ('81) compared the fetal effects of single doses and a constant-rate dosing regimen of valproic acid. The latter was designed to produce more constant serum drug levels, similar to those of an epileptic mother. Using the single dose regimen, they found dose-dependent growth retardation, a high resorption rate, and a high frequency of exencephaly. This contrasted with a slight increase in growth retardation and resorptions, but no increase in exencephaly, following the constant-rate dosing regimen. In a subsequent report, Nau and Spielmann ('83) showed that comparable doses of valproic acid can produce very different fetal effects, depending on the administration schedule.

Loscher et al. ('84) studied the teratogenicity of several metabolites of valproic acid. They found no evidence that the major metabolite, 2-en-valproic acid, is teratogenic. Nau and Loscher ('84), however, did find that another metabolite, 4-en-valproic acid, produced exencephaly in frequencies comparable to those induced by valproic acid at the same dosages.

In summary, the animal studies reviewed clearly establish the teratogenicity of valproic acid for several animal species. The defects observed, involving failure of neural tube closure, are analogous to those observed in humans.

TERATOGENIC DISCUSSION

A number of structural malformations have been associated with valproic acid use during pregnancy. Since maternal epilepsy increases the risk for bearing a malformed infant, some of these associations may not be causally related to the valproic acid exposure. In addition, many malformed valproic-acid-exposed infants were simultaneously exposed to other anticonvulsants that may be teratogenic in isolated or combined therapy.

What are the strengths and weaknesses of the evidence that valproic acid causes birth defects? The most compelling evidence for a causal relationship is the magnitude of the relative risk for spina bifida found in the case-control studies. A relative risk of 20 is unlikely to be explained by confounding from

some unknown variable. When the most likely potential confounder (maternal epilepsy) was controlled, the relative risk remained significantly elevated. The reproducibility of the association provided further evidence of a causal relationship. Similar magnitudes of increased relative risk were found in two case-control studies (France and Italy), and this is supported by the survey data from the Netherlands. Lindhout and Meinardi ('84) found that among a prospectively identified cohort of 141 epileptic women treated with valproic acid, one women had an infant with spina bifida. This risk is consistent with the magnitude of the relative risk estimated from the case-control studies. Other smaller cohorts have not identified infants with spina bifida. Because the expected rate of spina bifida after valproic acid exposure is about 1%, a cohort study enrolling several hundred exposed pregnancies is necessary to find that level of risk.

Further evidence that valproic acid causes spina bifida comes from the experimental animal work. That valproic acid has been shown to cause spina bifida and exencephaly in several laboratory species makes a causal relationship in humans more biologically plausible.

The relative risks for congenital heart defects or orofacial clefts associated with valproic acid use are much lower than the relative risk for spina bifida (Robert and Rosa, '83). Mastroiacovo et al. ('83) presented evidence that these elevated risks for congenital heart defects and clefts are due to confounding from the increased risk for those malformations due to maternal epilepsy and its treatment. These associations have not been replicated in other studies. No laboratory studies have produced similar malformations with valproic acid exposure. Evidence does not provide adequate support for a causal relationship between valproic acid exposure and any major malformation except spina bifida.

Is there evidence for an increased risk for minor malformations? Koch et al. ('83) reported a high relative risk (5/14) for a pattern of minor facial malformations in a small cohort. All of these infants were exposed to valproic acid monotherapy. A similar facial phenotype was reported in the case series of DiLiberti et al. ('84) and Hanson et al. ('84). Two of the infants reported by DiLiberti et al. ('84) were born to mothers whose seizures resulted from trauma. These infants should only be at risk for malformations resulting from the anticonvulsant exposure. Since their dysmorphic facial appearance was identical to that of the affected infants of mothers with idiopathic epilepsy, valproic acid probably caused the abnormalities. In these reports, however, observer bias is a potential problem, since the examiners were apparently aware of the infants' exposure status at the time of the evaluations. If the relative risk for the facial phenotype is as high as Koch et al. ('83) reported, then a small prospective cohort study, with well-defined diagnostic criteria and blinded examinations, should be adequate to define the facial phenotype and quantitate the risk for its occcurrence.

An interesting feature of the teratogenicity of valproic acid in humans is that spina bifida, but not other neural tube defects, has occurred with in utero exposure. This contrasts with the experimental animal studies, in which valproic acid induces exencephaly much more frequently than spina bifida. Yet no valproic-acid-exposed infant with anencephaly has been reported. Differential ascertainment is unlikely to be the explanation for this finding, because approximately half of infants with anencephalus are live born (Sever, '82). If defects of neural tube closure caused by valproic acid are limited to spina bifida, then this supports the concept that anencephaly and spina bifida can be etiologically distinct malformations (Sever and Strassburg, '85). Although in some epidemiologic studies the two types of neural tube defects are often treated as a single group, evidence is accumulating that, in searches for etiologic relationships, the defects should also be considered individually. Recent experimental evidence suggests that neural tube closure is a complex, staged process (Golden and Chernoff, '83). Each stage of closure may be controlled by different mechanisms that differ in susceptibility to teratogenic agents. This may explain why some teratogens cause spina bifida, but not exencephaly, or vice versa.

LESSONS FROM THE VALPROIC ACID EXPERIENCE

Valproic acid was released for human use in Europe in 1967 and in the United States in 1978. Between September 1982, when Dr. Elisabeth Robert presented her preliminary findings to the annual meeting of the International Clearinghouse for Birth Defects Monitoring Systems, and the end of 1982,

valproic acid was firmly established as a human teratogen. This experience teaches us several valuable lessons.

New drugs/chemicals—unknown human teratogenic risk

It reminds us that a new drug or other chemical with significant teratogenic risks for human fetuses can be marketed for years before we learn that a potential risk is a real risk. Said another way, children and adults are living today with the morbidity of spina bifida caused by a prenatal exposure to valproic acid that was not known to cause birth defects in human beings at the time the drug was given. Thus, however good our defenses are against the introduction into our environment of a drug or chemical agent that can cause birth defects in human beings, they are still not perfect, and the imperfections are associated with human tragedy.

Better defenses

Our defenses are, nevertheless, better than they were in the late 1950s, when the thalidomide tragedy occurred. There is premarket animal screening. There is more suspicion that unknown, harmful effects can occur. In the United States, for example, the labeling material used with valproic acid stated that the drug was teratogenic in animals and that it might be a human teratogen. Furthermore, the proposed indications for drug use were rigorously scrutinized, and the drug was approved for use only for patients with absence seizure disorders—a small proportion of the patients with epilepsy. No doubt the decisions made by the Food and Drug Administration and the manufacturer to produce such labeling minimized the number of Americans who have spina bifida because of exposure to valproic acid.

Birth-defect surveillance

In addition to the new requirements for premarket drug testing, the thalidomide tragedy prompted some groups and countries to add new, or to improve old, birth-defect surveillance systems (Kallen et al., '84). These commitments for surveillance were made in the belief that such systems might reduce the number of children malformed from possible "thalidomides" of the future.

In 1974, the March of Dimes/Birth Defects Foundation sponsored a workshop in Helsinki for scientists performing birth-defect surveillance (Flynt and Hay, '79). The group assembled believed that regular meetings and regular written communications among program directors would improve the quality of the programs and would thereby increase the likelihood that the programs would help reduce mortality and morbidity due to birth defects. Because of these beliefs and because the March of Dimes/Birth Defects Foundation, on the advice of Mr. Gabriel Stickle, agreed to support the idea of a clearinghouse, the International Clearinghouse for Birth Defects Monitoring Systems was born. The investments in surveillance systems and in the clearinghouse paid a significant dividend because they provided the medical community with enough data to conclude that valproic acid was a human teratogen, thereby reducing the morbidity and mortality caused by the drug.

An unusual set of circumstances in France

Valproic acid was marketed in several countries. Why did the data providing the predominant, primary evidence for human teratogenicity come from France? One can never know with certainty, but one can make observations about the events in the Rhone-Alps region of France that gave Robert and her colleagues the opportunity to identify this new human teratogen. On the one hand, these observations show the benefit of programs that societies have established to prevent birth defects. On the other hand, they show that these defense mechanisms are imperfect and that the discovery of human teratogens rests on a fragile process that includes both art and science, serendipity, and objective observations.

1) J.M. Robert, professor of Genetics in Lyon, was concerned about chemicals in the environment causing mutations, and in the mid-1970s, he attracted sufficient funds to set up, in Lyon, the Institut Européen des Génomutations and to establish a birth-defect surveillance program for the Rhone-Alps region, an area with some 70,000 births a year. The routine data collection form included a question about maternal epilepsy and its treatment.

2) In 1981, Professor Robert hired his daughter-in-law, Elisabeth, a pediatrician who had just completed her genetics training, to join the surveillance project full-time.

3) Dr. Elisabeth Robert's thesis had concerned the genetics of spina bifida in the Rhone-Alps region. To collect data for her

thesis, she regularly interviewed mothers of infants with spina bifida ready for discharge from the neurosurgical hospital in Lyon. Even though her thesis was completed and she had a new full-time job, she continued to interview.

4) The questionnaire she used included a routine question about epilepsy and anticonvulsants because there was evidence that certain anticonvulsants caused birth defects, although at the time the interview form was designed, there was no evidence to link epilepsy or its treatment with neural tube defects.

5) Physicians in the region were treating almost half of the pregnant women who had epilepsy with valproic acid. The prescribing habit occurred, no doubt, in the attempt to avoid the known problems with other anticonvulsants: that turned out to be a move to an unknown problem.

Fortunately for infants conceived after 1982, these events occurred. Had any one of these factors been missing, valproic acid would have remained an unknown human teratogen for an undetermined period. Because of these factors, Dr. Elisabeth Robert and her interviewer had the opportunity, one day in 1982, to be suspicious that among recently interviewed mothers of infants with spina bifida, they had seen an unusually large number who had taken valproic acid during the pregnancy. Once the question of an association was raised, the large registry, Robert's willingness to promptly share these data with members of the clearinghouse, and the willingness of clearinghouse members and staff, particularly Professor Bengt Kallen of Lund, Sweden, to work to resolve the issue swiftly led to the chemical's being put on the list of human teratogens. As tragic as the birth of any child with an unnecessary birth defect is, we can be thankful that the various programs that societies have established to minimize that number of infants with unnecessary birth defects and the unique circumstances in Rhone-Alps region did come together in 1982 and did establish valproic acid as a human teratogen.

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SUMMARY OF 39 PREGNANCIES WITH ABNORMAL OUTCOME WHERE THE MOTHER HAD TAKEN SODIUM VALPROATE

Abnormality	Valproate therapy		
	Alone	With other drugs	Total
Neural tube defects	3	6	9
Cardiovascular	4	5	9
Dysmorphic	3	4	7
Cleft lip/palate	1	3	4
Abnormal digits	2	1	3
Other	—	7	7

and the unpublished cases. From the Labaz list, I excluded 8 cases because valproate was not given in the first trimester, 5 where information was inadequate, and 5 miscarriages where the state of the fetus is unknown. This left 196 pregnancies of known outcome from nine countries (excluding the 9 French cases reported by Robert and Guibaud). 157 babies were normal and 39 pregnancies were abnormal (including 2 therapeutic abortions). Of the 157 normal babies 49 had mothers who had received monotherapy with valproate and 108 had received valproate together with other antiepileptic drugs. For the 39 abnormal events, the mothers had received monotherapy with valproate in 13 cases and combined therapy in 26 cases (table).

The 9 neural tube defects included 2 spina bifidas, 1 spina bifida with hydrocephalus, 1 spina bifida with myelocele, 1 spina bifida with meningocele, 2 myelomeningoceles, and 2 meningoceles. Among the cases of spina bifida, 2 of the mothers had a history of stillbirth and 2 others had had a therapeutic abortion. 5 of the mothers had been on monotherapy with sodium valproate (1 spina bifida, 1 spina bifida with meningocele, and 3 myelomeningoceles). Combined medication was valproate with phenobarbitone (2), carbamazepine (2), phenobarbitone and clonazepam (1), and phenytoin and suithiame (1).

The teratogenicity of antiepileptic drugs is very difficult to evaluate[1-3]. Furthermore, to assess the risks one needs information on the outcome of all pregnancies where these drugs were taken during the first trimester.

It is generally accepted by doctors experienced in the treatment of epilepsy that antiepileptic drugs should not be withdrawn in pregnancy, and since in practice pregnancy may not be diagnosed for some weeks it may well be too late to avoid neural tube and other defects. To withdraw drugs before conception is not normally a practical solution. Our information on the teratogenicity of valproate is based on a biased sample, because abnormal babies are more likely to be reported than normal ones. May I repeat my plea that the outcome of all pregnancies be reported to the manufacturers.

Clinical Neuropathology Unit,
University of Aston in Birmingham,
Birmingham B4 7ET

P. M. JEAVONS

*A list of the reports referred to may be had from the author.

SIR,—I would like to add two points to the interesting letter from Dr Bjerkedal and his colleagues on the apparent association between use of valproic acid and spina bifida found in the data from the Rhône-Alpes region of France.

First, by the simple method based on the logarithm of the odds ratio, the 95% confidence intervals for the overall odds ratio of 20·6 are 9·1 to 46·6, and for the odds ratio of 17·1 for those with a history of epilepsy are 3 to 151. The fourfold tables from which these odds ratios were calculated both depend heavily on just 9 cases of spina bifida born to mothers using valproic acid, and the widths of the confidence intervals reflect this fact.

Second, case-control studies can be affected by many sorts of bias in sampling and measurement,[2] and, although the data published by Bjerkedal and colleagues are consistent with the hypothesis that valproic acid causes spina bifida, they could also represent, at least in part, the influence of bias. For example, knowledge of drug exposure, when that drug is under suspicion, may influence the nature of the diagnostic process, or knowledge of the type of birth defect may affect the manner in which drug exposure data are obtained. Because of the possibility of bias, suspected or unsuspected, it therefore seems most important that the basic data and study design of the Rhône-Alpes monitoring programme are scrutinised closely, and the corroboration of the apparent association be sought elsewhere, preferably with a different study design.

Charing Cross Hospital Medical School,
London W6 8RF

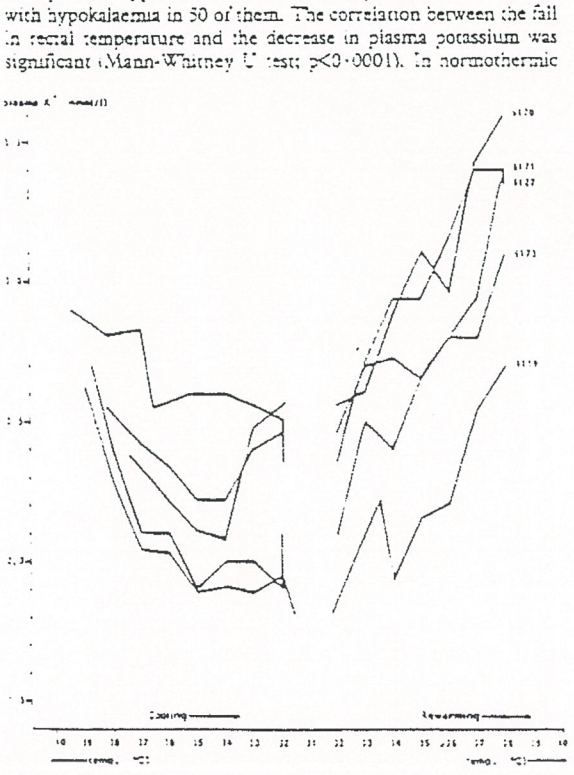
R. D. MACRAE

ACUTE TRANSIENT HYPOKALAEMIA AND BODY TEMPERATURE

SIR,—Professor Morgan and Dr Young (Oct. 2, p 751) describe hypokalaemia in up to 50% of acutely admitted patients. They speculate that this may have been due to an intracellular shift in potassium, possibly mediated by endogenous adrenaline. Hypothermia may also be a factor.

We noted hypokalaemia (2·75 mmol/l) in a 2½-year-old girl with an accidental hypothermia (31°C) and have also noted it on admission in hypothermic trauma victims, suggesting a correlation between hypothermia and hypokalaemia. This correlation was confirmed experimentally by cooling and rewarming rabbits (figure).

The correlation was also studied in patients sustaining hypothermia during gastrointestinal and vascular surgery. The direct postoperative plasma potassium concentration and rectal temperature were measured in 226 patients with a preoperative normothermia (36·5–37·5°C) and normokalaemia (3·50–5·50 mmol/l). Patients on medication that could influence plasma potassium (diuretics, steroids, insulin, bicarbonate) were excluded. Postoperative hypothermia was noted in 92 patients; this coincided with hypokalaemia in 50 of them. The correlation between the fall in rectal temperature and the decrease in plasma potassium was significant (Mann-Whitney U test; $p<0·0001$). In normothermic



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DEPARTMENT OF HEALTH

HEAD OFFICE
MACARTHY TRUST BUILDING
LAMBTON QUAY, WELLINGTON
NEW ZEALAND

P.O. Box 5013
TELEX NZ 3571
FAX (04) 711 717
TELEPHONE
(04) 727 627

REPLY REFERENCE

152/70/2501

20 June 1989

[redacted]
Reckitt & Colman Pharmaceuticals
Private Bag
Avondale
AUCKLAND

Dear [redacted]

A recent issue of Scrip contained an item on sodium valproate and spina bifida (26 May 1989, p31). The item mentions that the US prescribing information clearly states that a 1-2% risk of spina bifida is present if vaproate is taken during pregnancy. Please include this material in the product information for Epilim and submit an updated data sheet with this information included.

Yours sincerely

KR

Kathlyn J Ronaldson
for Manager
Medicines and Benefits

F

GP ignorance of valproate risks

Three cases of spina bifida in children born to women taking Sanofi's anti-epileptic, sodium valproate (Epilim), as monotherapy, who were unaware of the risk associated with the drug and were not offered prenatal diagnosis, highlight the low level of awareness amongst UK GPs of the drug's side-effects, according to a recent study.

The first epidemiological evidence that valproate might be associated with spina bifida came from French researchers in 1982 (*Scrip* No 763, p 13), and in 1983, the US Centers for Disease Control analysed data from Italy, France and the UK, and estimated the risk to a pregnant woman treated with valproate of having a child with spina bifida to be 1-2%, according to Dr Pippa Oakeshott and Gillian Hunt writing in the BMJ (May 13th, p 1,300). More recently, several groups of researchers have independently concluded that valproate is a strong teratogen.

By 1988, the UK CSM had received 97 reports through the yellow card system of foetal abnormalities possibly associated with mothers taking valproate during pregnancy, according to the researchers. Of these, 26 cases were spina bifida, and a further 20 were multiple malformations or hydrocephalus, which may have included some cases of spina bifida. The remaining 51 cases were of 25 other anomalies, most of which were less serious, they add.

Few GPs seem to be aware of the risk of spina bifida associated with valproate, Dr Oakeshott et al note. The UK data sheet fails to mention the risk of spina bifida and merely states that the drug is teratogenic in animals and that "pregnancies must be monitored", while the BNF only mentions it in the section on prescribing in pregnancy. This is in marked contrast to the situation in the US, where the prescribing information clearly states a 1-2% risk of spina bifida with valproate, and the drug is administered only for absence seizure disorders, it is pointed out. In France, counselling, amniocentesis and foetal ultrasound have been available since 1983 for women taking the anticonvulsant—when conducted at 16-18 weeks of gestation, this should detect 92-95% of all neural tube defects, the authors say.

The fact that three French cases of spina bifida diagnosed in utero and terminated as a result occurred at the same time as the three UK cases which continued to full term, "underlines the need for awareness of the teratogenicity of valproate and for counselling and the offer of prenatal diagnosis of spina bifida for pregnant women using the drug", the authors conclude. In addition, GPs should possibly "review their routine repeat prescriptions of sodium valproate to epileptic women of childbearing age", they add.

. . . product news in brief

■ ***Synergen's bFGF to begin trials in US:***
Synergen has announced that it plans to begin US clinical trials with its basic fibroblast growth factor (bFGF) for the treatment of topical ulcers. The product is also being evaluated for possible cardiovascular and CNS indications (see *Scrip* No 1411, p 16).

■ ***US FDA review period for Eulexin:***
The US FDA has determined that the regulatory review period for Schering-Plough's Eulexin (flutamide) was 6,359 days, 3,317 days during the testing phase and 3,042 during the approval phase. Schering-Plough is seeking 730 days of patent term extension under US Patent No 4,329,364 and 500 days of patent extension under US Patent No. 4,472,382. The NDA for Eulexin was submitted to the FDA on September 20th, 1980, and was approved on January 27th, 1989.

People

■ *Dr David Winter* has been appointed vice-president, external affairs, at **Sandoz Corporation** (US); he was previously vice-president, clinical R&D, at the Sandoz Research Institute.

■ *George Ohye*, who was previously vice-president, worldwide drug regulatory affairs, at Bristol-Myers, has been named senior vice-president, regulatory affairs worldwide, at the **R W Johnson Pharmaceutical Research Institute**, which is responsible for co-ordinating the R&D activities of four Johnson & Johnson units, Ortho, Ortho Biotech, Cilag International, and McNeil.

■ Four appointments to the **US NIAID Council** have been announced by DHHS Secretary Louis Sullivan: *Dr Glenn Cobbs*, professor of medicine at the University of Alabama; attorney *Richard Kingham* of Covington and Burling; *Dr Adel Mahmoud*, chairman of the department of medicine at Case Western Reserve University School of Medicine, Cleveland; and *Dr Edmund Pellegrino*, director of the Kennedy School of Ethics at Georgetown University in Washington, DC.

■ *William Mounce* has joined **Pharmaco (US)** as associate director of client services; he was formerly associate director of clinical research services at SK&F.

■ *George Kennedy*, chairman of Smiths Industries Medical Systems, has been elected the first chairman of the new **Association of British Healthcare Industries** (ABHI).

■ *Sylvain Roux* has been appointed head of the **Operant Behaviour Laboratory** the new laboratory of the French Institut Téchnique pour L'Etude du Médicament Laboratoire de Recherche (ITEM-labo). Mr Roux was previously with the Delalande Research Centre.

■ *Lisbet Coulton*, currently senior product manager at Merrell Dow Pharmaceuticals (UK), has been appointed marketing manager at the medical microbiological company, **GR Micro Ltd.**

■ The **Royal Society of Medicine** has announced that *Janet Locker* has been appointed conference and television executive within its medical services department.

■ *Dr Chris Bushe* has been appointed UK medical director for **Schwarz Pharma**; he was formerly medical adviser for TPA at Boehringer Ingelheim UK.

■ **Cygnus Corporation** (US) has announced the appointment of *Melinda Harris* as director of human resources.

■ *Zuhair Malhas* has been appointed **Minister of Health and Social Development** in the government of **Jordan.**

Meetings

The Royal Society of Medicine, in conjunction with the New York Academy of Sciences, is to hold an international meeting on October 1st-3rd, 1990, on ***Advances in the Understanding and Treatment of Asthma***, at the Royal College of Surgeons, Lincoln's Inn Fields, London. Speakers will include Dr Sonia Buist of the University of Oregon, Professor Frank Austin of Harvard Medical School, Professor Bengt Samuelsson of the Karolinska Institute and Professor Stephen Holgate of Southampton General Hospital, UK. For further details contact Janet Locker, Conference Executive, Medical Services Department, RSM, 1 Wimpole Street, London W1M 8AE, UK. Tel: 01 408 2119.

DATA SHEET

NAME OF MEDICINE

EPILIM®

Tablet, sodium valproate 200mg
Tablet, sodium valproate 200mg Enteric-Coated
Tablet, sodium valproate 500mg Enteric-Coated
Syrup, sodium valproate 200mg per 5ml.

PRESENTATION

EPILIM 200 Plain Tablet. A round flat white scored table 11mm in diameter containing 200mg sodium valproate.

EPILIM 200 Enteric-Coated Tablet. A round biconvex lilac-coloured enteric-coated tablet, approx. 9.4mm in diameter, containing 200mg sodium valproate.

EPILIM 500 Enteric-coated tablet. A round biconvex lilac-coated enteric-coated tablet, approx. 13.1mm in diameter, containing 500mg sodium valproate.

EPILIM Syrup. A red cherry-flavoured syrup containing 200mg sodium valproate per 5ml.

USES

PHARMACOLOGY

The mechanism of action of EPILIM is unknown. It is possible, however, that at least in part, and particularly at high doses, its anticonvulsant effect is mediated through effects on the function of brain gamma-amino-butyric acid (GABA).

Valproic acid is rapidly and almost completely absorbed in fasting patients following oral dosing with EPILIM plain tablets and syrup with peak blood levels occurring within 1-4 hours. Absorption of valproic acid from the enteric coated tablet given to fasting subjects is delayed with peak blood levels usually occurring within 3-7 hours. This variability is thought to reflect the delay in tablet dissolution probably associated with the rate of gastric emptying.

Plasma half life is variable but generally appears to be within the range 8-20 hours. It may be shorter in patients receiving other anticonvulsants or in children and patients receiving the drug for long periods.

Sodium valproate is almost completely metabolised prior to excretion. Only 1-3% of the ingested dose is found to be excreted unchanged in the urine. Its metabolism is complex; the major elimination pathway is via glucuronidation. The remainder is largely metabolised via oxidative pathways, particularly B-oxidation.

INDICATIONS

In the treatment of generalised, partial or other epilepsy. In women of

childbearing age EPILIM should be used only in severe cases or in those resistant to other treatment.

DOSAGE AND ADMINISTRATION

Daily dosage requirements vary according to age and body weight.

MONOTHERAPY

Usual requirements are as folows:-

Adults: Dosage should start at 600mg daily increasing by 200mg at three day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day ie 20-30 mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500mg/per/day.

Children over 20kg: Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day.
Children under 20kg: 20mg/kg of body weight per day; in severe cases this may be increased up to 40mg/kg/day but increases above this should be undertaken only in patients in whom plasma valproic acid levels, clinical chemistry and haematological parameters can be monitored.

Use in the Elderly: Although the pharmacokinetics of EPILIM are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Administration: EPILIM tablets, and Syrup may be given twice daily. Uncoated tablets may be crushed if necessary.,

COMBINED THERAPY

In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, eg phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of EPILIM. When barbiturates are being administered concomitantly the dosage of barbiturate should be reduced should sedation be observed.

GENERAL CONSIDERATIONS

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see Further Information.

er point 1. **CONTRA-INDICATIONS**

Active liver disease

WARNINGS

Monitoring of liver and platelet functions see under "Side Effects".

DIABETIC PATIENTS

EPILIM is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics. In addition, care should be taken when treating diabetic patients with EPILIM Syrup, as this contains 3.6g sucrose per 5ml.

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 and their pregnancies should be carefully monitored.

BREASTFEEDING

The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There are no known contra-indications to breast feeding by patients on EPILIM. The decision to allow the patient to breast feed should be taken with regard to all known facts.

Under WARNINGS as per letter

SIDE-EFFECTS

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children under the age of three years and those with congenital metabolic disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2-12 weeks and usually involved multiple anti-convulsant therapy.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. The onset of an acute illness, especially within the first six months, which may include symptoms of vomiting, lethargy or weakness, drowsiness, anorexia, jaundice or loss of seizure control, is an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician should they occur. Available evidence to date does not establish which, if any, investigation could predict this possible adverse effect. However, routine measurement of liver function should be undertaken in the first six months of therapy in those who seem most at risk and those with a prior history of liver disease: such patient shoud have close clinical supervision. Raised liver enzymes are not uncommon during treatment with EPILIM and are usually transient or respond to reduction in dosage of EPILIM.

corrected spelling point 5

Patients with such biochemical abnormalities should be re-assessed

clinically and tests of liver function should be monitored until they return to normal.

U/C Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur EPILIM should be discontinued.
Oedema has been rarely reported.

U/C Pancreatic: There has been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

U/C Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations; it is recommended that patients receiving EPILIM be monitored for platelet function before major surgery. Red cell hypoplasia and leucopenia have been rarely reported; the blood picture returned to normal when the drug was discontinued.

U/C Neurological: Ataxia and tremor have been occasionally reported and appear to be dose related effects.

Sedation has been reported occasionally, usually when used in combination with other anticonvulsants. In EPILIM monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations have been reported. Coma has very rarely been observed. These cases have usually been in association with other anticonvulsants, notably phenobarbitone and have been reversible on withdrawal of treatment.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.
Gastro-intestinal: increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Enteric Coated EPILIM or administering EPILIM with or after food.

U/C Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Endocrine: There have been isolated reports of amenorrhoea.

As per point 2

DRUG INTERACTIONS

Like many other drugs, EPILIM may potentiate the effect of monoamine oxidase inhibitors and other anti-depressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anti-convulsants and loss of efficacy of oral contraceptive agents does not appear to be a problem.

Dosage of EPILIM may require adjustment when used in combination with other anti-convulsants. See Dosage, Combined Therapy Section.

OVERDOSAGE

Cases of accidental and suicidal overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose ie. with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

PHARMACEUTICAL PRECAUTIONS

EPILIM tablets are hygroscopic and must be kept in their protective foil until taken; they should be stored in a dry place. EPILIM Syrup should be kept cool and away from direct sunlight.

corrected spelling Point 5

Dilutions: If it is necessary to dilute EPILIM Syrup, the recommended diluent is Syrup BP, but syrup containing S02 as a preservative should not be used. The diluted product will have a 14 day shelf life.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

EPILIM 200mg plain, EPILIM 200 Enteric-Coated, EPILIM 500 Enteric-Coated tablets are packed in foil, in cartons of 100 tablets. EPILIM Syrup is packed in 200ml bottles.

FURTHER INFORMATION

The beneficial effects of EPILIM may not be clearly correlated with the total plasma valproic acid levels. The reported effective range is usually between 40-100mg/litre (278-694 micro mol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

NAME AND ADDRESS

Reckitt & Colman Pharmaceuticals,
Private Bag,
Avondale, AUCKLAND.

DATE OF PRESENTATION

2nd August 1986.

DEPARTMENT OF HEALTH

NATIONAL HEALTH STATISTICS CENTRE
BALLANTYNE HOUSE
133 WILLIS STREET
WELLINGTON
NEW ZEALAND

PRIVATE BAG 2
HIGHER WILLIS ST
WELLINGTON
TELEX 3071
TELEPHONE (04) 384-1837
FACSIMILE (04) 384-1847

27 June 1989

142/70/2501

Dr H Goh
Medicines and Benefits
Head Office
Department of Health
P O Box 5013
WELLINGTON

RECEIVED
28/JUN/1989
KHG

Dear Dr Goh

Attached is a photocopy of Form H661 for [redacted]
who has hypospadias and query sodium valproate syndrome.

Yours sincerely

[redacted]

National Health Statistics Centre

Encl.

HEALTH FOR ALL

F

DR 75/4

ICAL NOTIFICATION OF RTH OR STILLBIRTH UNDER OBSTETRIC REGULATIONS 1975

Place of confinement MATERNITY UNIT Town [redacted]

If home birth was this planned? Yes [ ] No [ ]

To the Medical Officer of Health [redacted] Health District [redacted]

Serial No. [redacted]

The following particulars concerning a birth are hereby notified:

PLEASE CIRCLE THE APPROPRIATE BOX WHERE A CHOICE IS GIVEN

SECTION A. MAY BE COMPLETED BY THE MOTHER (with advice of staff if required)

NOTE: The information on this notification is confidential. It will assist in the provision of care for your child and in the planning of health services.

1. Surname [redacted]
2. Given name(s) [redacted]
3. Address [redacted]
4. Date of birth [redacted]
5. Age in Years [redacted]
6. First day of last menstrual period (best estimate if unknown) [redacted]
7. Number of previous pregnancies that ended: after 28 completed weeks [redacted] (if no previous pregnancies please put 0)
   before 28 completed weeks [redacted]
8. Race: [redacted]
9. Educational status: highest level of attendance [redacted]

Signature of mother: [redacted] Please tick box if you wish to see completed form [ ]

SECTION B. INFANT

0.	Sex	Male (1)	Female 2	
1.	Livebirth	Yes (1)	No 2	
2.	Date of birth	[redacted]		
3.	Duration of gestation (in completed weeks)	[redacted]		
4	(a) Multiple birth	Yes 1	No (2)	
	(b) If 'Yes' state birth order (a separate form is required for each baby)			
5.	Birthweight in grams	[redacted]		
6.	Alive on discharge/or transfer	Yes (1)	No 2	

SECTION C.

7.	(a) Was any congenital malformation noted? [redacted]	Yes (1)	No 2
	(b) Was any congenital malformation suspected?	Yes (1)	No 2

If 'Yes' please state fully: (use block letters) (see notes on reverse) (1) Hypospadius

(2) ? Sodium Valproate Syndrome M

SECTION D. RUBELLA STATUS OF MOTHER:

8. [redacted]

(Mother should be aware that the Department of Health might follow up any particular notification)

Name of family doctor [redacted]

The infant was discharged or transferred to: [redacted] 2

Signature of: Medical Practitioner responsible for confinement or [redacted]

She said that the GMC "successfully kept the whole question of self regulation off the agenda." Although the absolute number of lay members was increased their proportion had decreased. "It could be argued," she wrote, "that the act, rather than being a radical reform, was a revision, a revision which made it possible for a medical elite, as little changed as possible, to remain in power and for professional self-regulation to continue unchallenged." For Stacey the reforms of 1978 reunited the profession—which has so often threatened to split into factions of academics, royal colleges, and general practitioners—but did little for the public interest.

Stacey thinks—with others—that self regulation looks anachronistic at the end of the twentieth century. "A task," she said, "which now faces the profession, and commentators upon it, is to think through what might be viable alternatives, more appropriate for modern health care practice. . . ."[7]

Conclusion

Originally it was primarily doctors who wanted a General Medical Council—in order to keep out the quacks. The difficulties in forming the council resulted from conflicts among the factions of the profession, and because of these conflicts the first council had few effective powers. It had to fight the royal colleges to gain power over undergraduate education, which remained inadequate long after the council was formed. Now the council is struggling to exert its influence over postgraduate and continuing education; still it is being resisted. Since the beginning of the council general practitioners have had to struggle to be represented, and although elected members are now in the majority, many think that they are excluded from real power.

The public interest, meanwhile, does not seem to have been the first concern of the council, although most members will insist that such is the council's first concern. In the early days priority was given to bringing together the various factions and little attention was paid to education and still less to discipline. Until very recently the council seemed to be more concerned with doctors bringing the profession into disrepute than with them failing in their clinical performance. The emphasis is beginning to change, but the question is whether the council can change fast enough to fend off demands for a body dominated by lay people or directly answerable to government.

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Lesson of the Week

Valproate and spina bifida

Pippa Oakeshott, Gillian M Hunt

Pregnant women taking valproate should be counselled about the risk of spina bifida and offered ultrasonography and amniocentesis

In 1983 it was shown that when a pregnant woman takes the antiepileptic drug sodium valproate (Epilim) during the first trimester she has a 1-2% risk of having a child with spina bifida.[1] This risk becomes more evident with the decline in the overall prevalence of spina bifida.[2-4] It may be prevented by avoiding the drug during pregnancy or by informed counselling followed by antenatal screening for spina bifida with high resolution ultrasonography, amniocentesis, and abortion of affected fetuses.[5] In Britain few general practitioners seem to be aware of the risk of spina bifida and the special need for screening pregnant women taking valproate.

We report three cases of spina bifida in children born to women taking valproate as monotherapy who were unaware of the risk and were not offered prenatal diagnosis. All the children are currently receiving care.

Case reports

Case 1—A 27 year old woman had had her epilepsy well controlled with sodium valproate since the age of 22. In 1983 she had a miscarriage, but there were no details. In 1984, after a normal pregnancy, she gave birth at term to a 3020 g boy with open spina bifida at motor level L4. She had continued to take sodium valproate throughout her pregnancy. She had not been screened.

Case 2—In 1985 a 25 year old epileptic woman gave birth at term to a 3500 g girl with open spina bifida at motor level L5. (She had had a previous termination of pregnancy for social reasons.) She had taken sodium valproate 400 mg twice daily throughout her pregnancy. She was not screened until she was admitted with raised blood pressure at 34 weeks, when an ultrasound scan showed spina bifida.

Case 3—In 1986 a 25 year old epileptic woman gave birth at term to a 3200 g boy with closed spina bifida at motor level L3 and sacral agenesis. She had taken sodium valproate 200 mg three times a day throughout her pregnancy. She had previously had two normal children while taking this drug. She was not screened until she had vaginal bleeding at 30 weeks, when an ultrasound scan showed placenta praevia and spina bifida.

Discussion

The first important epidemiological evidence that valproate might cause spina bifida came in 1982 from Robert and Guibaud in the Rhône-Alpes region of France.[6] They found that of 72 children with neural tube defects, nine were born to epileptic mothers who had taken valproate during pregnancy. By including these data in a larger study the International Clearing House for Birth Defects Monitoring Systems decided "It is highly likely that valproate causes spina bifida in 1% of fetuses exposed to it in early pregnancy."[7]

Jeavons, in Birmingham, collected data on 196 pregnancies in which the mother had taken valproate;

London SE11
Pippa Oakeshott, MRCP, *general practitioner*

Addenbrooke's Hospital, Cambridge CB2 2QQ
Gillian M Hunt, MB, *clinical assistant*

Correspondence to: Dr P Oakeshott, Mawbey Brough Health Centre, 39 Wilcox Close, London SW8 2UD.

Br Med J 1989;298:1300-1

157 were normal, but the 39 abnormal pregnancies included nine with spina bifida.[8] It was suggested that women who have taken valproate in early pregnancy might be counselled about the risk of spina bifida and offered amniocentesis.[9,10]

In 1983 the Centers for Disease Control analysed the data from Italy, France, and the United Kingdom and concluded: "Sodium valproate should be considered a human teratogen."[1] The Centers for Disease Control estimated the risk to a pregnant woman treated with valproate of having a child with spina bifida to be 1-2%, which is similar to the recurrence risk for spina bifida. Robert and Rosa similarly calculated the risk of spina bifida to be 40 times the expected rate after exposure to valproate.[11]

In 1986 Lindhout and Schmidt published a prospective study of exposure to valproate in utero and neural tube defects.[12] One hundred and twenty epileptic mothers receiving valproate alone produced three infants with neural tube defects; 273 epileptic mothers taking valproate and other drugs also produced three infants with neural tube defects. The results confirmed that "Valproate exposure during the first trimester of pregnancy is causally associated with a considerably increased risk of neural tube defects of 1·5%." More recently Khoury and Holtzman compared the teratogenicity of valproate with thalidomide.[13] They calculated the relative risks or strengths of the teratogens as 20-25 and 175 respectively and concluded that valproate is a strong teratogen.

The Committee on Safety of Medicines has received 97 reports by the yellow card system of fetal abnormalities possibly associated with mothers taking valproate during pregnancy (Committee on Safety of Medicines, personal communication, 1988). Of these, 26 were spina bifida. A further 20 cases were multiple malformations or hydrocephalus, which may have included some cases of spina bifida. The remaining 51 cases were of 25 other anomalies, most of which were less serious.

The induction of spina bifida by valproate has been confirmed by many animal studies, and valproate was the drug chosen by Michejda and McCullough to provide an animal model for research on spina bifida.[14] They gave high doses of valproate to three pregnant monkeys for three days corresponding to the critical period of neural tube formation. One miscarried early but both the other fetuses developed spina bifida.

Any woman with epilepsy requiring treatment has a risk of having a child with a congenital malformation or mental retardation two to three times greater than average because of both her disease and its treatment.[15] All epileptic drugs carry specific risks, and sodium valproate is a first choice anticonvulsant.[16] It may cause a characteristic pattern of facial malformations in the fetus, but there is no substantial evidence that it causes any severe malformation other than spina bifida, for which screening is clearly essential.[17]

As shown by our three cases, few general practitioners seem to be aware of the risk of spina bifida due to valproate. In one study of general practitioners (including nine lecturers in general practice), most of whom were attending a postgraduate course, only four out of 55 knew of the risk of spina bifida, though most would have investigated the side effects. Consulting the British data sheet on sodium valproate, however, would not have helped, as this completely fails to mention the risk of spina bifida and merely states that the drug is teratogenic in animals and that "pregnancies should be monitored."[18] Even the *British National Formulary* reference to valproate does not mention spina bifida except separately in the section on prescribing in pregnancy, where it states that an increased risk of neural tube defects has been reported but fails to recommend specific screening.[19]

This contrasts with the United States, where the product information clearly states that the risk of women exposed to valproate having children with spina bifida is roughly 1-2%.[20] Increased awareness of the risk and the fact that in America valproate is used only for absence seizure disorders and is thus less commonly prescribed may have reduced the number of American babies born with spina bifida due to exposure to the drug in utero.[17]

The prenatal diagnosis of spina bifida in a mother treated with valproate enables an affected pregnancy to be terminated if she wishes. In France since 1983 women taking valproate during the first trimester have been counselled and offered aminotic fluid examination and fetal ultrasound.[5] When done at 16-18 weeks of gestation this should detect 93-95% of all neural tube defects.[21,22] In three years three cases of spina bifida were thus diagnosed and the pregnancies terminated. One other case escaped screening.

The three French cases of spina bifida which were diagnosed in utero and subjected to termination contrast with the three cases in our series, in which the infants were born during the same period (1983-6) when no special screening was done. They underline the need for awareness of the teratogenicity of valproate and for counselling and the offer of prenatal diagnosis of spina bifida for pregnant women using the drug.

Finally, as it is not so much a case of prescribing in pregnancy as a woman becoming pregnant while taking the drug, possibly general practitioners should review their routine repeat prescriptions of sodium valproate to epileptic women of childbearing age.

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(Accepted 15 March 1989)

Reckitt & Colman Pharmaceuticals

142/10/2501

17 July 1991

The Director General of Health
Medicines & Benefits
Department of Health
P O Box 5013
WELLINGTON

Dear Sir,

re: Valproate/Spina bifida

Sanofi, the manufacturer of Epilim (Sodium Valproate), has recently forwarded to us some preliminary information concerning a prospective study into the outcome of pregnancies in women receiving anticonvulsants, which was conducted by Professor Lindhout, Erasmus University, Rotterdam.

It is expected that the results will be published in due course, but it is felt appropriate that we submit the preliminary information at this stage. A CIOMS form is enclosed.

Our reference is: UEP 1993

Yours faithfully,
RECKITT & COLMAN PHARMACEUTICALS

[redacted]

Division of Reckitt & Colman (New Zealand) Limited
Private Bag, Avondale, Auckland 7, New Zealand. ☎ (09) 884-129. Tx N.Z. 21190. Fax (09) 884-648

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. Patient Initials (first, last)	1a. Country	2. Date of Birth Day	Month	Year	2a. Age Years	3. Sex	4 – 6 Reaction Onset Day	Month	Year
6 Cases	NL								85–90

7+13. Describe Reaction(s) (including relevant tests/lab data)

Spina bifida

In a five year prospective study of 297 pregnant women treated with anticonvulsants in the Rotterdam area, 92 received valproate (60 valproate monotherapy, 32 in association with other drug(s)). Systematic measurement of amniotic fluid alpha–foetoprotein level was performed before week 22 of pregnancy. Spina bifida was detected in 5 pregnancies (including one set of twins). Four of the mothers had received valproate monotherapy, one valproate and carbamazepine.

The cases were not evenly distributed: the study recruited between 1985 and 1990, but no cases were detected before 1989. Five cases were detected over a nine month period.

The investigator has reported to the company that this represents, in his study, an incidence of 6.3% of cases of spina bifida in the foetuses of women treated with valproate and that the 95% confidence interval, 0.9–11.6% does not conflict with previous publications.

8 – 12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] Patient died
- [ ] Involved or prolonged inpatient hospitalisation
- [ ] Involved persistence or significant disability or incapacity
- [ ] Life threatening

II. SUSPECT DRUG(S) INFORMATION

14. Suspect Drug(s) (include generic name)

Sodium valproate
with Carbamazepine (one mother)

20. Did reaction abate after stopping drug? [ ] Yes [ ] No [✓] NA

15. Daily dose (s) Not confirmed *

16. Route(s) of administration indirect via mother

21. Did reaction reappear after reintroduction? [ ] Yes [ ] No [✓] NA

17. Indication(s) for use Epilepsy

18. Therapy Dates (from/to)

19. Therapy Duration

III. CONCOMITANT DRUGS AND HISTORY

22. Concomitant Drug(s) and Dates of Administration (Exclude those used to treat reaction)

23. Other relevant history (e.g. diagnosis, allergies, pregnancy with last month of period, etc)

IV. MANUFACTURER INFORMATION

24a. Name and Address of Manufacturer

24b. MFR Control No.

24c. Date Received by Manufacturer

24d. Report source
- [✓] Study (unpublished article)
- [ ] Literature
- [ ] Health professional

Date of this report: 19.6.91

25a. Report type
- [✓] Initial
- [ ] Follow up

This study was conducted by Professor Lindhout, Department of Clinical Genetics, Erasmus University, Rotterdam, Netherlands

Limited information has been made available in advance of publication. However it is considered likely that 4 of these pregnancies are those reported as apparent spontaneoous reports (labelled) in a letter in The Lancet (Nov 1990) concerning sulproston. * There is some conflicting information on the dosage received by the patients and we are informed that the investigator reported to the parent company that the mean dose of valproate received by these mothers was much higher (1640±136mg) than that received by other women in the study (941±48mg/day)

Our reference number is UEP 1993

Department of Health
TE TARI ORA

133 Molesworth St
Wellington
New Zealand
P.O. Box 5013, Wellington
Phone (04) 496 2000
Fax (04) 496 2340

142/70/2501
2501/1
2501/2
2501/3
2501/4
2501/5

18 October, 1991

[redacted]
Group Product
Reckitt & Colman (NZ) Ltd
Private Bag
Avondale
AUCKLAND 7

Dear [redacted]

Data Sheet for Epilim (sodium valproate) products

I have been asked to assess the data sheet for your Epilim medicines. The draft we have on our files are dated January 1989.

In June 1989 Dr Ronaldson wrote to Reckitt & Colman (NZ) requesting inclusion of the risk of spina bifida during pregnancy in the data sheet. This was shortly after your CMN submission to update the data sheet. There is no indication that your updates had been examined at that time.

In order to not repeat the assessment, I would greatly appreciate it if you could send me your latest data sheets on the medicines.

Yours sincerely

Khay Ooi

Khay Ooi
Scientist
Therapeutics Section

P.O. Box 5013, Wellington N.Z. 21190. Fax (09) 884-648

PL 0623/0061

APPLICATION FOR AN ABRIDGED PRODUCT LICENCE FOR

EPILIM CR 200

PART III–IV

PHARMACO–TOXICOLOGICAL AND

CLINICAL DOCUMENTATION

VOLUME 1

APPLICANT:

SANOFI UK LTD
FLOATS ROAD
WYTHENSHAWE
MANCHESTER
M23 9NF

ARCHIVE REF: W/LA40220/176

DATE SUBMITTED: JANUARY 1992

[redacted]
out of scope

PART IIIC REPRODUCTION STUDIES

A fertility and general reproductive performance study (Data on file, 1977 report No RC 7793), was carried out in male and female rats to assess the possible effects of sodium valproate on male fertility, the oestrous cycle, ovulation, implantation, parturition, lactation and postnatal growth and survival of progeny.

Males were treated by intragastric administration of valproic acid for 60 days before the mating period and then over the mating period, females for 14 days prior to mating until day 21 post partum. Doses were 65, 150 and 350 mg/Kg/day as valproic acid.

Virtually all the rats proved to be fertile but some delays in parturition were seen. Litter sizes at the highest dose (350 mg/Kg/day) were slightly reduced and all the offspring from these litters died very shortly after birth due to an absence of maternal care.

A further study using the same dosages but treating only the female rats was carried out to attempt to separate prenatal from postnatal toxicities. Parturition was again delayed in the treated rats. A low survival index and severely reduced weight gain was seen in the offspring of dams treated with the highest dosage (350 mg/Kg/day). Control pups transferred to high dose mothers died shortly after transfer indicating post natal toxicity possibly due to high levels of valproic acid in the milk. But a loss of approximately 30% of pups very soon after birth also suggests pre- or peri- natal toxicity at the higher dose levels.

In a third study of peri- and post- natal development using oral doses of 65, 150 and 350 mg/Kg/day valproic acid in female rats from 15th day of gestation until 21 days post partum (Data on file 1977, report RC 7796), a dose related delay in onset of parturition was again observed but there was no effect on difficulty or duration of parturition. Post natal growth and survival were good except in the litters of two rats on the highest dose.

To study the effect of valproic acid on development of the reproductive tract and on sexual maturation, Cohn et al, 1982, injected albino male rats with valproic acid for three months immediately after weaning. A decrease in prostate and epididymal weight was found together with a diminished sperm content and motility.

Teratogenicity

Sodium valproate has been shown to be teratogenic in mice, rats, and rabbits.

In mice dose related effects were noted at 200 mg/Kg/day sodium valproate and greater in one study (Miyagawa et al, 1971) and at 600 mg/Kg/day in another (Tucker, 1973). Increased foetal resorptions, retarded foetal growth and frank maldevelopments occurred. Foetal abnormalities seen included cleft palate, exencephaly, open eye and rib and vertebral malformations.

A third study (Data on file, 1976, study no 75-354) using oral valproic acid showed an increased incidence of skeletal abnormalities at 150 mg and 350 mg/Kg/day. A "no teratogenic effect" dosage was considered to be 65 mg/Kg/day.

In rats, two studies using sodium valproate showed a significant increase in resorption and depression of foetal weight at 400 and 600 mg/Kg/day (Miyagawa et al, 1971; Tucker, 1973); skeletal defects involving ribs and vertebrae were also noted. In one study (Tucker 1973) sodium valproate was teratogenic at all dose levels, (150 mg/Kg/day was the lowest dosage tested). A third study (Data on file 1976, study 75-356) using oral valproic acid found a "no teratogenic effect" dosage of 65 mg/Kg/day. Increased skeletal defects of ribs and vertebrae were noted at 150 mg and 350 mg/Kg/day.

Two independent investigations were carried out in rabbits. In the first study (Tucker, 1973) using sodium valproate all foetuses were resorbed at 400 mg/Kg/day doses. Sodium valproate appeared to cause abnormal development at 315 mg/Kg/day but to be nonteratogenic at 252 mg/Kg/day. Defects included kidney agenesis, and fused ribs and lumbar vertebrae.

In the second study (Data on file, 1976 study no 75-355) using valproic acid, the highest dosage 350 mg/Kg/day group showed significant maternal deaths and embryolethality. There was a dose related trend toward diminished foetal weight across all the dosages tested. Major developmental abnormalities including cleft palate, exencephaly, umbilical hernia, fused ribs and kidney agenesis were seen in offspring of rabbits treated with 350 mg/Kg/day valproic acid.

There are, however, rare reports of stupor (Sackellares et al 1979), sometimes accompanied by altered behaviour, hallucinations or convulsions (Marescaux et al 1982) and occasionally progressing to coma (Gastaut and Iemolo 1982) in patients whose serum drug and ammonia levels are not excessive. The mechanism is not known but a direct intrinsic sedative action of valproate on the brain seems to be implicated (Sackellares et al 1979, Gastaut and Iemolo 1982).

5. Pregnancy and Lactation

Valproate crosses the human placenta in pregnancy (Dickinson et al, 1979; Alexander, 1979; Froescher et al, 1981) and is also excreted in the semen of men taking the drug and into breast milk of lactating women (Nau et al, 1981).

There have been reports of various congenital abnormalities in children born to mothers who have taken valproate in pregnancy. These have included congenital heart disease, oral clefts, hypospadias, facial dysmorphism, digital and limb defects.

However, congenital malformations are estimated to occur in 2 - 3% of all live births in the general population, and this incidence is probably higher in the offspring of women with epilepsy, more so if they have been exposed to antiepileptic drugs.

Published literature involving retrospective, case control, and pooled prospective studies have indicated that there may be an increased incidence of neural tube defect, specifically spina bifida in the offspring of patients taking valproate in early pregnancy.

The early estimates of risk came from the figures of Robert and Gibaud 1982 and are given as 1.2%. Bjerkedal 1982 used pooled data, including Robert and Gibaud's numbers, from a variety of centres and calculated a risk of 1%. However Castilla 1983 stated that his data from South America was too late to be included in Bjerkedal's analysis, but states that this data was negative for an association between spina bifida and valproate. This was the basis of the 1983 WHO statement as being in the region of 1.2.%.

Jeavons 1982 reviewed published and unpublished data from several countries and found that 68 abnormal babies including 9 neural tube defects occurred in 344 reported pregnancies in women taking valproate. 28 of the abnormalities occurred in women receiving valproate monotherapy.

Lindhout and Schmidt 1986 sent a questionnaire to 18 birth defect centres and received 13 replies, and on the figures given, they estimate the risk to be 1.5% with a 95% confidence interval of 0.42 - 3.0. From this published data, Lammer 1987 quotes the risk for spina bifida as 1%-2%.

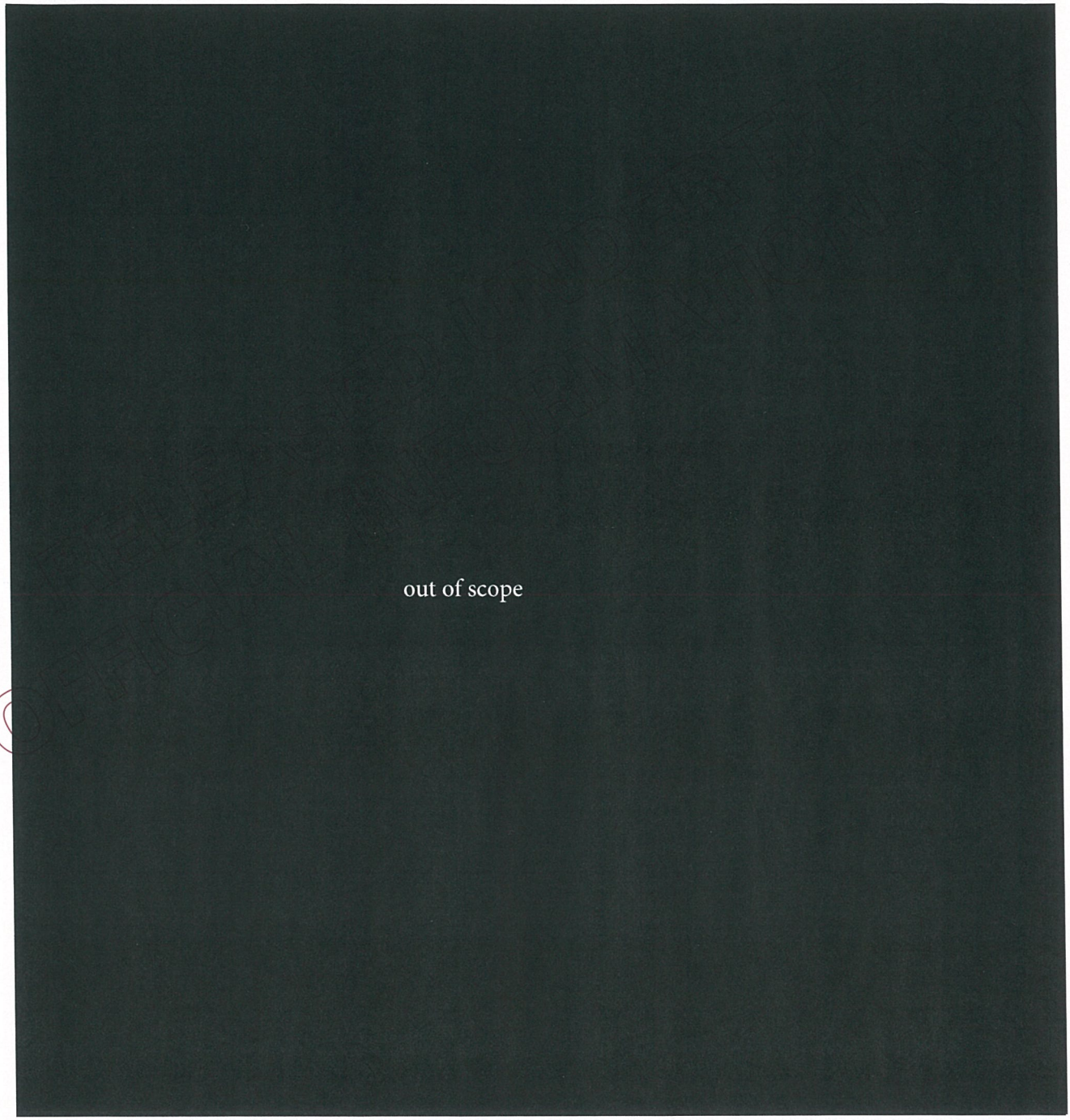
McCrae 1982 questioned the accuracy of the original conclusions, basing his comments on the small number of patients involved, and on the influence of bias involved in the collection of data. Since these original estimates have been widely quoted following the original papers, little work has been published to allow a more accurate assessment of the risk to be made.

Also these findings from birth defect registries were recently questioned in a leading article in the Lancet (December 17th 1988) which reviewed valproate, spina bifida and birth defect registries and considered that such important findngs should be supported by high quality evidence, and that such evidence is lacking, as none of the main results have been presented in a full paper with discussion of the epidemiological issues essential to interpretation of the data. In view of these comments and the available evidence the company estimates the evidence as possibly being in the region of about 1%.

Nevertheless, it should be borne in mind that uncontrolled epilepsy may be damaging, if not life-threatening, to both mother and foetus. It is generally accepted (WHO, 1983; Hopkins, 1987) that where the patient with severe epilepsy, or otherwise intractable seizures becomes pregnant, valproate monotherapy should be continued, together with appropriate counselling, and the facilities for antenatal monitoring (Cleland 1991).

Breast feeding

Sodium valproate is excreted into breast milk in very low concentrations, 0.17 - 5.4% of the concentration in maternal plasma (Nau et al, 1981; Dickinson et al, 1979; Alexander, 1979). If maternal plasma levels are within the range 50-100 µg/ml it would be estimated that during breast feeding steady state plasma levels in the newborn would be 10 - 15% of maternal plasma levels and therefore unlikely to affect the baby adversely (Rimmer and Richens, 1985). No reports linking the use of valproic acid with adverse effects in the nursing infant have been located (Briggs et al, 1986)



EPILIM CR 500

PATIENT INFORMATION LEAFLET

I confirm that the proposed Epilim CR Patient Information leaflet is in accordance with the product licence application (0623/0062).

[redacted]

CLINICAL RESEARCH PHYSICIAN

What You Should Know About

EPILIM [R] CR

Please read this carefully before you start to take your medicine. If you have any questions or are not sure about anything ask your doctor or pharmacist.

The name of your medicine is Epilim CR. It contains a mixture of Sodium Valproate and valproic acid. This is one of a group of medicines called "anticonvulsant or anti-epileptic agents" which are used to treat epilepsy.

Things to remember about Epilim CR

1. Before taking your medicine read the back of this leaflet.
2. Take your medicine as directed by your doctor. Read the instructions on the label carefully.
3. Epilim CR can sometimes cause side effects. See "After taking your medicine" on the back of this leaflet.
4. Do not stop taking your medicine suddenly. Ask your doctor first.
5. Tell medical staff you are taking this medicine, for example, if you go into hospital or see a dentist or another doctor.
6. If you are likely to become pregnant, tell your doctor.

You will find more about Epilim CR on the back of this leaflet.

Continued from overleaf

BEFORE TAKING YOUR MEDICINE

DO NOT take Epilim CR without first talking to your doctor again if you have any of these

- Liver disease
- A family history of severe liver disease
- An allergy to sodium valproate (Epilim CR)

You should also tell your doctor if you can answer YES to any of the following questions. He may need to give you special instructions.

- Are you pregnant or likely to become pregnant?
- Are you diabetic?
- Are you taking other medicines to control your epilepsy?
- Are you taking any medicine regularly which reduces blood clotting (eg anticoagulant, aspirin).
- Are you taking antidepressants or other medicines to alter your mood or behaviour

TAKING YOUR MEDICINE

- Take your medicine regularly, as directed by your doctor. This is particularly important with anticonvulsants to make sure that you are getting the best control from your medication.
- Look at the label on your medicine, it will tell you when to take it. If it does not, or you are not sure, ask your doctor or pharmacist for advice.
- Swallow the tablets whole with a drink of water, usually after meals.
- If you forget to take a dose at the correct time take it as soon as you remember then go on as before.
- If you accidentally take an overdose contact your nearest hospital casualty department or tell your doctor immediately.
- Keep taking your medicine until your doctor tells you to stop. Do not stop taking the tablets just because you feel better. If you stop them your condition may get worse.

AFTER TAKING YOUR MEDICINE

- Make sure you keep your regular check up appointments. They are very important as your dosage may need to be changed.

- If you go into hospital or visit another doctor or a dentist tell them you are taking Epilim CR.

- Epilim CR can affect the liver in a very small number of patients. You should tell your doctor IMMEDIATELY if you develop a sudden illness, especially if it is within the first six months of treatment and particularly if it includes repeated vomiting, extreme tiredness, loss of appetite, jaundice, swelling, abdominal pain or worsening of your epilepsy.

- Epilim CR may sometimes cause minor stomach upsets, increased appetite or weight gain. You need only consult your doctor about these if symptoms become troublesome.

- Occasionally Epilim CR can affect the hair. Any loss of hair is usually temporary but when it grows back it may be more curly than before,

- Epilim CR can also have other effects. You should report any of the following symptoms to your doctor

  Severe stomach pains
  Abnormal bleeding or a tendency to bruise more easily
  Irregular or missed periods
  Shakiness or problems with balance
  A rash or anything else which is unusual or unexpected

- Epilim CR may affect your condition if you become pregnant and in these circumstances it is important to consult your doctor promptly.

STORING YOUR MEDICINE

- Keep your tablets in a dry place below 30°C and make sure children cannot reach them. Your tablets could harm them.

- Keep your tablets in their protective foil until you are ready to take them. If you remove them from the foil too soon they may go soft and spoil.

- If your doctor decides to stop the treatment, return any leftover tablets to the pharmacist. Only keep them if your doctor tells you to.

WHAT'S IN YOUR MEDICINE

Epilim CR tablets are lilac and contain a mixture of Sodium Valproate BP and valproic acid. They are available in three sizes containing the equivalent of 200mg, 300mg, or 500mg Sodium Valproate.

This leaflet provides a summary of the information available on your medicine. For further information consult your doctor or pharmacist.

THIS LEAFLET APPLIES TO EPILIM CR TABLETS ONLY

REMEMBER: This medicine is for YOU. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet has been produced in accordance with guidelines issued by the Association of the British Pharmaceutical Industry.

The Product Licence Holder is:

Sanofi UK Ltd
Floats Road
Wythenshawe
Manchester
M23 9NF

Epilim CR 200 PL xxxx/xxxx

Epilim CR 500 PL xxxx/xxxx

The Manufacturer and Distributer is:
Sanofi Winthrop Ltd
Onslow Street
Guildford
Surrey
GU1 4YS

PROPOSED
DATA SHEET FOR EPILIM CR

Data Sheet

EPILIM [R] CR

Presentation

1. Epilim CR 200. A lilac coloured, controlled release tablet containing a mixture of Sodium Valproate BP and valproic acid equivalent to 200mg Sodium Valproate.

2. Epilim CR 500. A lilac coloured, controlled release tablet containing a mixture of Sodium Valproate BP and valproic acid equivalent to 500mg Sodium Valproate.

Uses

In the treatment of generalised, partial or other epilepsy. In women of childbearing age Epilim should be used only in severe cases or in those resistant to other treatment.

Dosage and Administration

Epilim CR is a controlled release formulation of Epilim which reduces peak concentration and ensures more even plasma concentrations throughout the day.

Epilim CR is to be given twice daily. The tablets must be swallowed whole and not crushed.

The dosage for each patient should be titrated to establish seizure control. If Epilim CR is to be substituted for other Epilim (valproate) products, the dosage may require retitration and the patient should be closely monitored during the changeover period.

Daily dosage requirements vary according to age and body weight.

Monotherapy

Usual requirements are as follows:-

Adults: Dosage should start at 600mg daily increasing by 200mg at three day intervals until control is achieved. This is generally within the dosage range 1000mg to 2000mg per day, ie 20-30mg/kg body weight. Where adequate control is not achieved within this range the dose may be further increased up to 2500mg per day.

Children over 20kg: Initial dosage should be 400mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35mg/kg body weight per day.

Children under 20kg: An alternative formulation of Epilim should be used in this group of patients, to facilitate dose titration.

Use in the elderly: Although the pharmacokinetics of valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Combined Therapy

In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, eg phenytoin, phenobarbitone, and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Epilim CR. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

General Considerations

Optimum dosage is mainly determined by seizure control. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected, see Further Information.

Contra Indications, Warnings, Etc

Contra-Indications: Hypersensitivity to sodium valproate. Active liver disease, family history of severe hepatic dysfunction, particularly drug related.

Side Effects

Hepatic: Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children, particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation. The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2-12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis eg prothrombin time may be most relevant.

Routine measurement of liver function should be undertaken before therapy and periodically during the first six months, especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision. Raised liver enzymes are not uncommon during treatment with valproate and are usually transient or respond to reduction in dosage. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function, including prothrombin time, should be monitored until they return to normal. However an abnormally prolonged prothrombin time, particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Metabolic: Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. This is usually transient, but may occasionally present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Epilim CR should be discontinued. Oedema has been rarely reported.

Pancreatic: There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate, usually within the first six months of therapy. Patients experiencing acute abdominal pain should have the serum amylase estimated; if these levels are elevated treatment should be discontinued.

Haematological: Valproic acid inhibits the second stage of platelet aggregation. Reversible prolongation of bleeding time and thrombocytopenia have been reported, but are usually associated with doses above those recommended. Prior to initiation of therapy and also before surgery, clinicians should assure themselves that there is no undue potential for bleeding complications. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations. Red cell hypoplasia and leucopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Neurological: Ataxia and tremor have been occasionally reported and appear to be dose-related effects.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Coma has very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur: this is generally beneficial but occasional aggression, hyperactivity and behavioural deterioration have been reported.

Gastro-intestinal: Increase in appetite may occur and an increase in weight is not uncommon. Minor gastric irritation and, less frequently, nausea may occur in some patients at the start of treatment, but these problems can usually be overcome by administering Epilim CR with or after food. If necessary the use of enteric coated Epilim tablets may be considered.

Dermatological: Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Rashes have been rarely reported.

Rarely, signs of an immune disorder have occurred, therefore caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus.

Endocrine: There have been isolated reports of irregular periods or amenorrhoea. Very rarely gynaecomastia has occurred.

Drug Interactions

Like many other drugs, valproate may potentiate the effect of neuroleptics, monoamine oxidase inhibitors and other antidepressants. The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy or oral contraceptive agents does not appear to be a problem.

Caution is recommended when administering anticonvulsants and other products which have anticoagulant properties (eg warfarin and salicylates). Valproate decreases protein binding of warfarin but this may not lead to clinically significant effects.

Phenytoin levels may be affected by valproate and these should be monitored, particularly the free form.

Dosage of Epilim CR may require adjustment when used in combination with other anticonvulsants. See Dosage, Combined Therapy Section.

Diabetic Patients

Valproate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

Women of Childbearing Age

An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and, if indicated, amniocentesis.

In all pregnancies monotherapy is to be recommended and dosage reviewed. The benefits of antiepileptic therapy during pregnancy must be evaluated against the possible risks and patients should be informed of these and the need for screening.

Breast Feeding

The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma levels. There appears to be no contra-indication to breast feeding by patients on valproate. The decision to allow the patient to breast feed should be take with regard to all the known facts.

Overdosage

Cases of accidental and suicidal valproate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose, ie with plasma concentrations 10 to 20 times maximum therapeutic levels there may be serious CNS depression and respiration may be impaired. Full recovery is usual following treatment including induced vomiting, gastric lavage, assisted ventilation, and other supportive measures.

Pharmaceutical Precautions

Epilim CR tablets are hygroscopic and must be kept in their protective foil until taken: they should be stored in a dry place below 30 C.

Legal Category
POM

Package Quantities
Epilim CR tablets are packed in foil, in cartons of 100 tablets.

Further Information

Epilim CR is a controlled release formulation of Epilim which reduces peak concentration and ensures more even plasma concentrations throughout the day.

The beneficial effects of Epilim may not be clearly correlated with the total plasma valproic acid levels. However, in those cases where measurement of plasma levels is considered necessary, the pharamacokinetics of Epilim CR make the measurement of plasma levels less dependent upon time of sampling.

The reported effective range is usually between 40-100mg/litre (278-694micromol/litre) depending on time of sampling and presence of co-medication.

The percentage of free drug then is usually between 6% and 15% of the total levels. Above this range an increased incidence of adverse effects may occur.

The half life of sodium valproate is usually reported to be within the range 8-20 hours.

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

Product Licence Numbers, Names and Addresses

Epilim CR 200	0623/xxxx
Epilim CR 500	0623/xxxx

Sanofi Winthrop Ltd
1 Onslow Street
Guildford
Surrey
GU1 4YS

Telephone: 0483 505515
Telefax: 0483 35432

Date of Preparation
--/--/92

sanofi aventis

Because health matters

RECEIVED
03 MAR 2010

Regulatory Affairs Dept

26 February 2010

Attn. Ms Abby Cutfield
Advisor, Pharmacovigilance
Clinical Risk Management
MEDSAFE
PO Box 5013
Wellington
NEW ZEALAND

Dear Abby,

RE: **REVIEW OF THE EPILIM DATA SHEET REGARDING USE IN PREGNANCY**

Medsafe File No.'s: TT50-2501/1, TT50-2501/1a, TT50-2501/3, TT50-2501/4, TT50-2501/5, TT50-2501/7, TT50-2501/6

I refer to your letter dated the 14th of January 2010 regarding the recommendations made by the Medicines Adverse Reactions Committee (MARC) at its December 2009 meeting. Specifically, the MARC recommended that the Precautions section of the Epilim data sheets be updated to improve the clarity of the information regarding the use of sodium valproate in pregnancy.

Sanofi-aventis has reviewed the proposal and accepts to implement all suggested changes. Accordingly, enclosed please find the proposed Data Sheets for Epilim and Epilim IV (tracked and clean copies) for your review.

Following reception of your approval of the proposed changes a Changed Medicine Notification will be submitted to Hazel Tompson, as instructed in your letter.

Sanofi-aventis corporate headquarters intend to produce a booklet regarding Epilepsy and Pregnancy for global distribution. This booklet will cover, amongst other topics, the use of sodium valproate in pregnancy. Sanofi-aventis believes that a non-product specific booklet regarding Epilepsy and Pregnancy will be more useful for both doctors and patients. This booklet is expected to be available in the last quarter of 2010.

Should you require further information, please do not hesitate to contact me directly on [redacted]

Yours sincerely,

[redacted]

List of Attachments

Attachment 1: Epilim Data Sheet (highlighted and clean copies)
Attachment 2: Epilim IV Data Sheet (highlighted and clean copies)

sanofi-aventis australia pty ltd ABN 31 008 558 807
Talavera Corporate Centre, Building D, 12-24 Talavera Road, Macquarie Park, NSW 2113 - Tel: ++61 (0) 2 8666 2000 – Fax: ++61 (0) 2 8666 3055 -
www.sanofi-aventis.com.au

[redacted]

8 March 2010

[redacted]
Senior Regulatory Affairs Associate
Sanofi-Aventis Australia Pty Ltd
Locked Bag 2227
North Ryde Business Centre
NSW
AUSTRALIA 1670

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

TT50-2501/1, TT50-2501/3, TT50-2501/4, TT50-2501/5, TT50-2501/7
Epilim EC, Epilim Liquid, Epilim Crushable Tablet, Epilim IV, Epilim Syrup

Dear [redacted]

Re: Review of the Epilim data sheet regarding use in pregnancy

Thank you for your letter dated 26 February 2010 in response to the recommendation of the Medicines Adverse Reactions Committee to improve the clarity of the information provided in the Epilim data sheets regarding use in pregnancy.

I note that Sanofi-Aventis has accepted the wording suggested by Medsafe and intends to make the requested changes to the Epilim and Epilim IV data sheets.

I can confirm that the proposed updated data sheets, as you provided in your letter, are acceptable in terms of the wording in the *Use in Pregnancy* sections. Please proceed with submitting the Changed Medicine Notifications for these changes to Hazel Thomson at Medsafe.

Please keep Medsafe informed of the progress of the global booklet regarding epilepsy and pregnancy. Please forward Medsafe a copy of the booklet for review prior to its distribution in New Zealand.

Kind regards,

Abby Cutfield
Pharmacovigilance Advisor
Medsafe
[redacted]

[redacted]

From: [redacted]
Sent: Tuesday, 20 April 2010 2:29 PM
To: [redacted]
Subject: Re: FW: Review of gingival disorders associated with the use of sodium valproate

Dear [redacted]

Thank you for your e-mail.

I can confirm that Medsafe is satisfied with Sanofi-Aventis' intentions to update the Epilim data sheets in the immediate future with regard to the pregnancy warnings (as requested by the MARC) and the interaction with carbapenem antibiotics (as requested by Medsafe).

I can confirm that Medsafe has granted Sanofi-Aventis with an extension to complete the review of the risk of gingival disorders associated with the use of sodium valproate, and that a response is expected to be received by Medsafe by the end of June 2010.

Kind regards,
Abby

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

[redacted]

02/12/2014 11:54 a.m.

To: [redacted]
cc:
bcc:

Subject: Epilim

Dear [redacted]

Medsafe has noted the recommendations of the recent PRAC review of use of Epilim in pregnancy. Whilst the proposed updates to the SPC are consistent with the NZ data sheet we would like to discuss with you whether Sanofi is considering any changes to the NZ data sheet as a result.
I would also be grateful if you could provide me with any unpublished information that was relevant to the PRAC discussions.
I would be grateful if you could call me on the number below
Kind regards
Susan

Susan Kenyon
Principal Technical Specialist (Pharmacovigilance)
Clinical Risk Management
Medsafe
Ministry of Health
[redacted]

[redacted]

To: [redacted]
cc:
bcc:

04/12/2014 10:50 a.m.

Subject: EU Update on Epilim review

Dear Susan

Thank you for your time on the phone, as discussed I have attached the summary of the outcomes of the EU review.

The CMDh has now endorsed the recommendations from the PRAC review to strengthen the warnings on the use of valproate medicines in women of child bearing age due to the risk of malformations and
developmental problems in babies who are exposed to valproate in the womb. The warnings aim to ensure that
patients are aware of the risks and that they take valproate only when clearly necessary.

A variation to implement the recommendations in the EU will be submitted by mid to end January 2015 in accordance with the agreed timetable. The documentation will also support the planned CCDS update to align the Medsafe Datasheet text with the EU SmPC changes with TGA submission planned for February.

If you require any further information or clarification, please let me know.

Kind regards

[redacted]

SANOFI

02-cmdh-comm-21nov14.pdf

SANOFI

February 2015
Ref: 0012-sacn-ccdsv16-17-update-27feb15

The Manager
Medsafe
PO Box 5013
Wellington
New Zealand

Dear Sir/Madam,

Re: Self Assessable Change Notification for

EPILIM 100 CRUSHABLE, Tablet 100mg	**(TT50-2501/4)**
EPILIM EC, Tablet, modified release 200mg	**(TT50-2501/1)**
EPILIM CR, Tablet, modified release 300mg	**(TT50-2501/6)**
EPILIM EC, Tablet, modified release 500mg	**(TT50-2501/1a)**
EPILIM INTRAVENOUS, Injection, solution 100mg/mL	**(TT50-2501/5)**
EPILIM LIQUID, Solution, oral 200mg/5mL (sugar free)	**(TT50-2501/3)**
EPILIM, Syrup 200mg/5mL	**(TT50-2501/7)**

Data sheet - miscellaneous changes
Please find enclosed a Self Assessable Change Notification (SACN) for the above products containing sodium valproate.

We have updated the Data sheet in accordance with the latest Company Core Data Sheets (CCDSv16 and 17). Please note that 17 was issued 2 weeks following 16 hence the Data sheet document contain changes from both, which implement recommendations following two PRAC reviews in the EU as outlined below.

- Review of available data on the effects of valproate exposure during pregnancy which recommended strengthening the restrictions on the use of valproate medicines due to the risk of malformations and developmental problems in children exposed to valproate in the womb.

  As agreed with the TGA implementation of the recommendations from this comprehensive safety review, which included consultation with specialists, experts, patients and families, address the original TGA request, issued following review of the latest NEAD study results, to expand the information on developmental delay in the 'Use in Pregnancy Section' in the DS.

- Review of mitochondrial toxicity which concluded that the evidence is sufficient to support a causal association between valproate and aggravation of underlying mitochondrial diseases, including risk of hepatotoxicity occurring mainly in patients suffering from POLG (polymerase gamma) Mutations attachment

Specifically we have included more information in the Contraindications, Precautions, Interactions with other medicines and Adverse Effects sections. The CMI has been updated to align with the

sanofi-aventis australia pty ltd trading as Sanofi ABN 31 008 558 807
Talavera Corporate Centre, Building D, 12-24 Talavera Road, Macquarie Park, NSW 2113
Tel: +61 (0) 2 8666 2000 – Fax: +61 (0) 2 8666 3000 - www.sanofi.com.au

SANOFI

uide for Healthcare profes

This Guide is provided as par

revisions to the DS and as part of implementation of the revised DS and CMI two risk minimization tools a Guide for Healthcare Professionals (HCP) and a Patient Information Booklet have also been developed:

- The HCP Guide is designed to inform of the risks associated with the use of valproate by women of childbearing potential and during pregnancy. It provides up-to-date information about the risk of neurodevelopmental disorders in children of women who have taken valproate during pregnancy in addition to the known risk of congenital malformations in exposed babies.

- The Patient booklet is intended to ensure patients of child bearing age are adequately informed of the risks during pregnancy

The information to be provided in each tool is provided for reference. The tools will be distributed via standard channels together with the updated DS with both electronic and hard copy options to optimize access.

In support of this SACN, the following documentation has been provided:

Module 1

1.2 Completed CMN A Form and Therapeutic Product Database Reports
1.3.1.1 Proposed DS Documents (clean copies)
1.3.1.2 Proposed Annotated DS documents
1.3.1.3 Data Sheet Declarations
1.3.1.4 Source Document - Australian Product Information document dated 26 February 2015
1.3.2.1 Proposed CMI Documents (clean copies)
1.3.2.2 Proposed Annotated CMI documents
Attachment 1 – HCP Guide and Patient Booklet

An assurance is provided that no aspects of the Data Sheet or pharmaceutical data have been changed, including manufacturing procedures and equipment and raw material and finished product specifications, other than the changes nominated in this SACN and the changes made to the Data Sheet are supported by data in the possession of Sanofi.

If you have any queries, please do not hesitate to contact me directly on [redacted]

Yours faithfully,

[redacted]

ll two risk minimization
klet have also been

de for Healthcare professionals

This Guide is provided as part of the risk minimisation measures developed for valproate to inform valproate prescribers of the risks associated with the use of valproate by women of childbearing potential and during pregnancy.

The Guide will provide up-to-date information about the risk of neurodevelopmental disorders in children of women who have taken valproate during pregnancy in addition to the known risk of congenital malformations in exposed babies.

This guide should be used with the Patient information booklet. To learn more about valproate, please read the complete Product Information before prescribing valproate.

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A. FEMALE CHILD

After medical evaluation,

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WHAT YOU SHOULD KNOW ABOUT THE RISKS OF VALPROIC ACID USE I FEMALE PATIENTS

VALPROATE contains valproic acid, an active ingredient with known teratogenic effects which may result in congenital malformations. Available data also show that in utero exposure to valproate can be associated with an increased risk of developmental disorders. These risks are briefly described below.

1. CONGENITAL MALFORMATIONS

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29), which represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2-3%[1]. Available data show the risk is dose dependent. The risk is greatest at higher doses (above 1 g daily). A threshold dose below which no risk exists cannot be established based on available data.

The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

2. DEVELOPMENTAL DISORDERS

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 available 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[2-5] in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics[9]. Although the role of confounding cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population[7].

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD)[8].

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IC ACID USE IN

...ient of female Patients with valproate

A. FEMALE CHILD FIRST PRESCRIPTION

After medical evaluation, you are considering prescribing valproate to your patient:

- Confirm that treatment with valproate is appropriate for your patient (i.e. all other treatments have been tried and failed).

- Discuss the following topics with your patient and relevant family members/care-givers:
  - Risks to pregnancy that are associated with the underlying condition;
  - Risks related to treatment, including risks related to valproate in case of pregnancy;
  - Need for an effective contraception method to avoid unplanned pregnancy.
  - Need for regular review of treatment

- Assess the most appropriate timing to provide advice on effective contraception methods and refer your patient to a specialist if needed.

- Ensure that your patient/family members/caregivers of the patient have understood the potential consequences in case of pregnancy and has/have an adequate level of understanding of the risks.

- A document has been developed to help you:
  - A Patient information booklet (Annex 1) which summarizes the teratogenic safety information and highlights key points for treatment management:
    - Read it, as it may help you to deliver appropriate information to your patient
    - Give one copy to your patient

- Advise your patient to contact you immediately
  - If she becomes pregnant or thinks she might be pregnant.

- Plan to review the need for treatment when she becomes capable of pregnancy.

B. WOMEN OF CHILDBEARING AGE WHO ARE NOT PLANNING PREGNANCY

After medical evaluation, you are considering prescribing valproate to your patient:

- Confirm that treatment with valproate is appropriate for your patient (i.e. all other treatments have been tried and failed).

- Discuss the following topics with your patient:
  - Risks to pregnancy that are associated with the underlying condition;
  - Risks related to treatment, including risks related to valproate in case of pregnancy;
  - Need for an effective contraception method to avoid unplanned pregnancy.
  - Need for regular review of treatment

- Assess the relevance of preconception counseling.

- Ensure that your patient has understood the potential risks to the child of using valp during pregnancy and has an adequate level of understanding of the risks, and that she to comply with the conditions for pregnancy.
  For this, the following document has been developed to support you:
  - A Patient information booklet (Annex 1) which summarizes the teratogenic safety information and highlight key points of treatment management
    - Give one copy to your patient

- Advise your patient to contact you
  - If she becomes pregnant or thinks she might be pregnant;
  - in case of any adverse events associated with her treatment.

C. WOMAN OF CHILDBEARING AGE WHO IS PLANNING PREGNANCY

- Remind your patients of teratogenic risks and risks of developmental disorders that can be seriously debilitating when taking valproate but also the risks of untreated seizures or bipolar disorder.

- Reassess the benefit/risk of valproate therapy, whatever the indication:
  - Consider if stopping treatment or switching to an alternative is possible.
  - If further to a careful evaluation of the risks and benefits, valproate treatment is to be continued, it is recommended to divide the daily dose into several small doses to be taken throughout the day at the lowest effective dosage possible. The use of a prolonged-release formulation may be preferable to other treatment forms.
  - Both valproate monotherapy and valproate polytherapy are associated with congenital malformations. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of abnormal pregnancy outcome than valproate monotherapy.
  - Folic acid supplementation may decrease the general risk of neural tube defects but the evidence does not suggest that it reduces the risk of birth defects associated with in utero valproate exposure.

- Consider referring your patient to specialists for preconception advice.

- Ensure that your patient has understood the potential risks to the pregnancy, and has an adequate level of understanding of the risks
  - A Patient information booklet (Annex 1) should be given to the patient which summarizes the risks:
    - Give one copy to your patient

- Advise your patient to contact their family doctor as soon as she becomes pregnant or thinks she might be pregnant in order to initiate appropriate pregnancy monitoring, including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations.

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MAN WITH UNPLANNED PREGNANCY

- Schedule an urgent consultation with your patient to review treatment as soon as possible to reconsider the benefits and risks of valproate.
- Tell her to keep taking her treatment until you have seen her, unless you are able to give other advice based on your assessment of the situation.
    - If further to a careful evaluation of the risks and benefits, valproate treatment is to be continued, it is recommended to divide the daily dose into several small doses to be taken throughout the day at the lowest effective dosage possible. The use of a prolonged-release formulation may be preferable to other treatment forms.
    - Both valproate monotherapy and valproate polytherapy are associated with congenital malformations. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of abnormal pregnancy outcome than valproate monotherapy.
    - Folic acid supplementation may decrease the general risk of neural tube defects but the evidence does not suggest that it reduces the risk of birth defects associated with in utero valproate exposure.
    - Ensure that your patient:
        - has truly understood the risks related to valproate in case of pregnancy
        - has received the Patient information booklet (Annex 1)
- Initiate specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Summary

A. FEMALE CHILD FIRST PRESCRIPTION

1. **Explain potential risks of the disease itself for the unborn child and the risks associated with use of sodium valproate in pregnancy**
2. **Assess your patient's need for treatment with sodium valproate**
3. **Inform your patient about the need to use effective contraception as soon as it is relevant**
4. **Ensure that your patient has received the Patient information booklet**
5. **Where applicable, advise your patient to contact you immediately if she becomes pregnant or thinks she might be pregnant.**

B. WOMEN OF CHILDBEARING AGE WHO ARE NOT PLANNING PREGNANCY

1. **Explain potential risks of treatment and of untreated disease for the unborn child**
2. **Assess your patient's need for treatment with valproate**
3. **Inform your patient about the need to use effective contraception**
4. **Ensure that your patient has received the Patient information booklet**
5. **Advise your patient to contact you immediately if she becomes pregnant or thinks she might be pregnant.**

C. WOMAN OF CHILDBEARING AGE WHO IS PLANNING PREGNANCY

1. **Explain potential risks of the disease itself on the unborn child, independent fr valproate's own risks.**
2. **Re-assess benefit/risk of patient's therapy**
3. **Adapt current treatment**
4. **Advise your patient to contact you when she becomes pregnant or thinks she might be pregnant**
5. **Ensure that your patient has received the Patient information booklet**

D. WOMAN WITH UNPLANNED PREGNANCY

1. **Inform her to keep taking her treatment until you have seen her**
2. **Schedule an urgent consultation**
3. **Re-assess the benefit/risk of her therapy**
4. **Ensure that your patient has understood the risks related to valproate in case of pregnancy**

References

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2. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L et al. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia 2010 October;51(10):2058-65.
3. Cummings et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011;96:643-647
4. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. NEJM 2009;360 (16): 1597- 1605
5. Thomas S.V et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy and Behaviour 2008 (13);229-236
6. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J,Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244-52
7. Christensen J et al. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA 2013;309(16):1696-1703
8. Cohen M.J et al. Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioural Functioning at age 3 years. Epilepsy Behav. 2011; 22(2):240-246
9. Meador K et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 (NEAD study): a prospective observational study. Lancet Neurol. 2013 March;12(3): 244-252

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Patient Information booklet

epi-hcp-tool-v1-d1-26feb15 Date of preparation February 2015

ANT INFORMATION BOOKLET –VALPROATE

The information in this booklet is for women who are being prescribed valproate and are able to get pregnant (of child-bearing age). If you have any questions talk to your doctor or pharmacist.

There is a lot of information and it is recommended that you show this booklet to friends and family to help you discuss and understand your treatment.

- **Keep this booklet. You may need to read it again.**

RISKS TO THE UNBORN CHILD

Valproate can be harmful to unborn children when taken by a woman during pregnancy.

Whether taken on its own or with another epilepsy medicine, valproate seems to carry a higher risk if taken during pregnancy than other epilepsy medicines. The higher the dose, the higher the risks but all doses carry a risk.

It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects include *spina bifida* (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.

If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in ever 100 born to women who don't have epilepsy.

It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk , intellectually less able than other children, and have difficulty with language and memory.

Autistic spectrum disorders and childhood autism are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to be at risk of developing symptoms of Attention Deficit Hyperactivity Disorder (ADHD).

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it it unlikely that it will reduce the risk of birth defects associated with valproate use.

If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.

Before prescribing this medicine to you, she or he will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.

FIRST PRESCRIPTION

If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- **Make sure you are using an effective method of contraception**
- **Tell your doctor at once if you are pregnant or think you might be pregnant.**

CONTINUING TREATMENT AND NOT TRYING FOR A BABY

If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- **Make sure you are using an effective contraception**
- **Tell your doctor at once if you are pregnant or think you might be pregnant.**

CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY

If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should discuss with your doctor well before you become pregnant so that you can put several actions in place so your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your doctor may need to change the dose of valproate or switch you to another medicine before you start trying for a baby. If you become pregnant, you will be monitored very closely both for the management of your epilepsy/ bipolar disorder as well to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it it unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- **Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy/ bipolar disorder is controlled and the risks to your baby are reduced**
- **Tell your doctor at once when you know or think you might be pregnant.**

AN UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT

Babies born to mothers who have been treated with valproate are at risk of birth defects and problems with early development which can be debilitating. If you are taking valproate and you think you are

explained the risk
will need to make su
o your doctor or family

or might be pregnant contact your doctor at once. Do not stop taking your epilepsy/ bipolar er medicine until your doctor tells you to.

sk your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it it unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- **Tell your doctor at once if you know you are pregnant or think you might be pregnant.**
- **Do not stop taking valproate unless your doctor tells you to.**

epi-pt-tool-v1-d1-26feb15 Date of preparation: February 2015

[redacted]

18/03/2015 10:54 a.m.

To: [redacted]
cc:
bcc:

Subject: Epilim- CMN and educational materials

Hi [redacted]
We have taken a look at the CMN and text for the educational materials and they look good.
Do you know when the final version of the educational materials will be available?
We would like to make them available on the Medsafe website to make sure there is easy access.
We were thinking of publishing an alert communication at the same time to ensure people are aware that they are available.
This will also refer to our earlier Prescriber Update article.
We will of course let you see the text prior to publication.
Kind regards
Susan

Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health [redacted]

MEDSAFE

[redacted]

[redacted]

13/05/2015 09:21 a.m.

To: [redacted]
cc:
bcc:

Subject: Epilim alert communication

Hi [redacted]
Please find the draft Epilim alert communication for your comments.
There is no publication date at this stage as we will wait for your educational materials to be ready.
Please give me a call if you need any further information
Kind regards
Susan

Epilim alert communication.docx

Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management |
Medsafe | Ministry of Health | [redacted]

[redacted]

[redacted]

To: [redacted]
cc:
bcc:

28/05/2015 05:35 p.m.

Subject: Request for additional information for Valproic acid- (Sanofi Reference number 2015SA022999)

Dear Colleagues

On the 24 February 2015 we retrieved a Valproate adverse event report (report number 113878) from the SMARS website . Please find attached the report for your reference .

The events reported were:

- Autism
- Developmental delay
- Foetal anticonvulsant syndrome
- Premature separation of Placenta

We would appreciate it if you could provide us with any additional information for this case, if available.

Kind regards

[redacted]

02-2015sa022999-valproate-ini.pdf

[redacted]

29/05/2015 11:35 a.m.

To: [redacted]
cc:
bcc:

Subject: Re: Request for additional information for Valproic acid- (Sanofi Reference number 2015SA022999)

Dear [redacted]
Thank you for your email.
This case was provided to Medsafe by ACC, therefore the details are limited (from a pharmacovigilance perspective)
The commentary was:
Clinical records indicate that the client developed foetal valproate syndrome and autism
spectrum disorder as a result of sodium valproate exposure in-utero.
At the time of pregnancy, the client's mother was managing her epilepsy with sodium valproate [redacted] During this time, she was taking folic
acid and was recorded as not having had any seizures. Antenatal ultrasounds showed intra-uterine growth retardation, with no other abnormalities. Male child was born on
[redacted]
External clinical advice (ECA) in paediatric neurology states that at the time of the
mother's pregnancy, the knowledge of the consequences of in-utero valproate exposure
was relatively unknown and it would have been difficult to judge the outcome.

We have no further information on this case.
I hope this information is of use to you.
Kind regards
Susan Kenyon
Medsafe Pharmacovigilance Team

Dear Colleagues On the 24 Februa... 28/05/2015 05:36:27 p.m.

From:
To: [redacted]
Cc:
Date: 28/05/2015 05:36 p.m.
Subject: Request for additional information for Valproic acid- (Sanofi Reference number 2015SA022999)

Dear Colleagues

On the 24 February 2015 we retrieved a Valproate adverse event report (report number 113878) from the SMARS website . Please find attached the report for your reference .

The events reported were:

- Autism
- Developmental delay
- Foetal anticonvulsant syndrome
- Premature separation of Placenta

We would appreciate it if you could provide us with any additional information for this case, if

available.

Kind regards

[redacted]

[attachment "02-2015sa022999-valproate-ini.pdf" deleted by Susan Kenyon/MOH]

[redacted]

To: [redacted]
cc:
bcc:

16/09/2015 05:49 p.m. Subject: Link to Valproate Educational Materials - Risk in Pregnancy

Dear Susan,

Thank you for updating us on Medsafe's activities around valproate. As discussed, here is the link to the website:
http://www.sanofi.com.au/l/au/en/layout.jsp?cnt=613DE812-F0B4-42F1-AE18-D9A0B9B86DF8

I will wait to hear from you prior to the dissemination of Medsafe's safety alert.

Kind regards,

[redacted]

SANOFI

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

21/09/2015 06:10 p.m. Subject: RE: Link to Valproate Educational Materials - Risk in Pregnancy

Thanks Susan for letting me know.

Kind regards,

[redacted]

SANOFI

From: [redacted]
Sent: Monday, 21 September 2015 3:43 PM
To: [redacted]
Cc:
Subject: Re: Link to Valproate Educational Materials - Risk in Pregnancy

Hi [redacted]
Just to confirm - it looks like the Alert communication will be published on 28 September
Kind regards
Susan
Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health | [redacted]

MEDSAFE

[redacted]

From: [redacted]
To:
Cc:
Date: 16/09/2015 05:49 p.m.
Subject: Link to Valproate Educational Materials - Risk in Pregnancy

Dear Susan,

Thank you for updating us on Medsafe's activities around valproate. As discussed, here is the link to the website: http://www.sanofi.com.au/l/au/en/layout.jsp?cnt=613DE812-F0B4-42F1-AE18-D9A0B9B86DF8

I will wait to hear from you prior to the dissemination of Medsafe's safety alert.

Kind regards,

[redacted]

SANOFI

[redacted] 13/05/2016 03:44 p.m.

To: [redacted]
cc:
bcc:

Subject: Fw: Commercial in Confidence - RE: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Hi
I spoke to Sanofi today as we agreed yesterday.
Below is a summary of a meeting held between the NZ branch and FACS.
To note the 'toolkit' is the property of Sanofi not MHRA. They are updating but text is pretty much the same as we currently have, has already been sent for printing. They will be providing yearly training for providers/prescribers and monitoring this. The change to the packaging is awaiting TGA approval.
thanks
Susan

Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health | [redacted]

MEDSAFE [redacted]

----- Forwarded by Susan Kenyon/MOH on 13/05/2016 03:39 p.m. -----

From: [redacted]
To:
Date: 13/05/2016 03:34 p.m.
Subject: Commercial in Confidence - RE: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Dear Susan,

Please find below summary of the Epilim events as discussed.

NZ Affiliate met with the NZ patient group on the 9 May 2016. Prior to the meeting Denise sent an email to our NZ colleagues. Excerpt from that email highlighted below

One of the areas that will be getting discussed during the meeting, is the lack of consistency between the international Epilim box insert information and NZ's CMI
http://www.medsafe.govt.nz/consumers/cmi/e/Epilim.pdf .
So in preparation for this meeting I have attached the UK and USA inserts. I realise they are from the same provider, with just the Epilim name changed to Depakote in the USA.

We did a quick assessment - The UK PIL contains additional information, however this information is included in our patient information booklet, with the only difference being we do not discuss the types of birth defects that can occur. Instead we have taken the approach to tell their patients to discuss the risks and benefits with their doctor.

Summary of the discussion held at the meeting (sent by our NZ colleague)

They wanted to see where Sanofi were at but also to let us know what they are doing.

- ACC, FACS, Medsafe, PHARMAC, Pharmaceutical Society, neurologists and other interested parties are apparently working as a group to ensure prescribers improve communication and monitoring of female patients. NZ Sanofi inquired if they have

considered including someone from Industry – Dee will check and revert if the group think that is appropriate.

- They are focussing on Epilim. Dee from ACC said that they have 14 cases with a lifetime cost of $20million and want to minimise the risk.
- They have seen the Dear HCP letter, card (which Denise recognised as part of the MHRA patient kit which is what they are hoping to introduce in NZ)
- Sanofi agreed to include both ladies in the mailout when it goes. They will provide us with some other organisations that should receive the mailout.
- Sanofi advised Q2/Q3 for the mailout – we will do asap.
- Sanofi advised end 2016 for new packaging (explained awaiting TGA approval for packaging and then introduction of new packaging can take up to 6 months).
- Sanofi discussed a pop up in the prescribing software and in the dispensing software and asked for assistance in getting this sorted out (Sanofi having problems getting MedTech to respond to request).
- Sanofi discussed original pack dispensing versus repackaging and this appears to happen a lot in NZ so looking at what we could do – suggestion that we have a "Cautionary Advisory Label" which is either stuck on to the box, or printed with the label (due to space restrictions might need to be a second label but that might be possible in the dispensing software. I think they were going to discuss with Pharmacy Guild or Pharmaceutical Society.
- Comment from our NZ colleague – "With regard to the CMI, we did cover off that there is a standard format and I suggested that while there was a lot more information in the UK version I had some doubt as to whether we have the health literacy here to understand the text – this is an area of considerable concern in NZ. Denise did agree but I think still wants more text".

As discussed, will send the updated patient toolkit to Medsafe next week, prior to the 20 May meeting.

Many thanks & kind regards

[redacted]

SANOFI

[redacted]

From: [redacted]
Sent: Monday, 2 May 2016 7:13 AM
To: [redacted]
Subject: Re: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Thanks [redacted] - very helpful
Kind regards
Susan
Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health | [redacted]

From: [redacted]
To:
Date: 29/04/2016 07:29 p.m.
Subject: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Dear Susan,

Appreciate your time earlier today to discuss the implementation of the Epilim patient toolkit.

Listed below are some key points

- Sanofi Global has mandated the implementation of a Patient Card worldwide as a new additional risk minimization measure in addition to the risk minimization measures already being implemented.
- Sanofi has a plan in place for implementing the Patient toolkit
- Updates/amendments to patient materials are in progress
- Notification along with the patient toolkit will be sent to Medsafe by the end of May 2016
- NZ Affiliate will be meeting with the NZ patient group on the 9 May 2016

Additionally, application to register the "pregnancy warning statement" on the Epilim packaging was submitted to Medsafe on the 15 April 2016.

Kind regards

[redacted]

Sanofi, Talavera Corporate Centre Building D, 12-24 Talavera Road, Macquarie Park, NSW 2113 – Australia

[redacted]

[redacted]

Sanofi, Talavera Corporate Centre Building D, 12-24 Talavera Road, Macquarie Park, NSW 2113 – Australia

SANOFI

Depakote Information.pdf PIL UK Epilim.pdf

[redacted] 12/05/2016 09:47 a.m.

To: [redacted]
cc:
bcc:

Subject: Re: Fw: 20 May 2016 - FACS Meeting Agenda and Papers

Hi
I'll contact the company
1- The toolkit is the property of Sanofi
2- The text of the toolkit is non-negotiable, this has already been confirmed by the company
3. The text seems to be the same as that used in the current brochures available on the Sanofi website and linked in our alert communication on Epilim.
http://www.sanofi.com.au/l/au/en/layout.jsp?cnt=613DE812-F0B4-42F1-AE18-D9A0B9B86DF8
4- There doesn't appear to be any representation of Midwives, obstetrics or GPs at the meeting
5 This information has been in the data sheet for a long time
6 No evidence has been presented that this is currently a problem in NZ - all the recent notified cases to CARM have been through ACC and the children are relatively old. Ideally we need better information on the magnitude of the problem - particularly if considering how best to alert healthcare professionals

Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health [redacted]

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

[redacted]

Rowan Pollock Rowan Pollock | Senior Advisor Ph... 12/05/2016 09:12:13 a.m.

From: [redacted]
To:
Date: 12/05/2016 09:12 a.m.
Subject: Fw: 20 May 2016 - FACS Meeting Agenda and Papers

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

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

[redacted]

----- Forwarded by Rowan Pollock/MOH on 12/05/2016 09:11 a.m. -----

From: [redacted]
To:
Date: 11/05/2016 05:02 p.m.
Subject: Fw: 20 May 2016 - FACS Meeting Agenda and Papers

Hi Rowan

FYI below. Can someone please take a look at the toolkit and let me know if we need changes in NZ? Meeting is Friday week

Thanks

Chris

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

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

----- Forwarded by Chris James/MOH on 11/05/2016 05:01 p.m. -----

From:
To:
Cc:
[redacted]

Date: 11/05/2016 01:43 p.m.
Subject: 20 May 2016 - FACS Meeting Agenda and Papers

Good Afternoon Everyone

Please find attached the agenda and papers for the FACS project team meeting on 20th May, at the Brentwood Hotel at 16 Kemp St, Kilbirnie, Wellington.

If you are travelling from Wellington Airport, when you land, please call 0508 273 689 and the free Brentwood Shuttle will come and pick you up. If you are driving, there is free parking at the Brentwood.

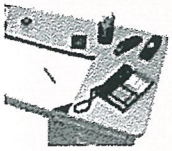
Please give me a call on [redacted] if you have any questions.

Many thanks
Ginette

Ginette Spence, Project Manager, ACC
[redacted]
ACC / Enterprise Programme Management Office / Justice Centre - Level 13
PO Box 242 / Wellington 6011 / New Zealand / www.acc.co.nz

Disclaimer:

"This message and any attachments may contain confidential and privileged information. If you believe you have received this email in error, please advise us immediately by return



[redacted]

16/06/2016 11:47 a.m.

To: [redacted]
cc:
bcc:

Subject: Re: Fw: FACS Toolkit Documents

Thanks Susan - sounds like a few issues for them to work through

Chris

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

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY

Susan Kenyon Hi I've put all these documents in m... 16/06/2016 09:44:31 a.m.

From: [redacted]
To:
Cc:
Date: 16/06/2016 09:44 a.m.
Subject: Re: Fw: FACS Toolkit Documents

Hi
I've put all these documents in my G drive under Epilim, along with the company versions for comparison.
These are the ANZ versions which have the same text as the UK version for hcp - not sure about consumers.
I put some specific comments on a couple of the docs.
These are just some quick comments....

Is there a copyright issue - they have copied some bits from the toolkit verbatim?

In general their version of the consumer leaflet is better written than the hcp but neither are as well written as the company documents. They also have issues with format presentation language and grammar.
For example: sodium valproate is a known teratogenic (in the hcp booklet)
The risk data is not provided in a consistent way - percent versus 1 in x etc
The tone of the hcp booklet appears to demonstrate a them and us mentality rather than this is to help you
All the documents need dating and version control
They have included a two page list of anomalies that may or may not be linked to valproate - this is too much for GPs (and this list is a mix of scientific terms and consumer language).
They talk about risk benefit ratios!
Use of drug rather than medicine

hcp booklet - In the different advice sections for women thinking of having a baby and those not planning etc Some of the advice seems to be in incorrect sections - unless they take the view that women have the idea that they will have a baby 10 years in the future?
The text around folic acid makes no sense - 'The folic acid supplementation reduces risk in the general population of neural tube defects, however there is evidence showing that it does not reduce the risks of birth defects associated with exposure to sodium valproate in utero'
The references are not referred to in the text.

The wallet card is not as good as the company's - doesn't encourage reporting of ADRs for example

The poster - not very attractive- incorrect - the oesophagus does not directly link to a baby - misleading as congenital abnormalities form before the fetus looks like a baby and possible offensive to some cultures?

In the patient information the indications for epilim include off-label use - would this contravene advertising regs? - use of antiepileptic drug (AED) and then AED used throughout should keep using antiepileptic medicine - people don't read leaflets from start to finish

thanks
Susan

Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health [redacted]

Rowan Pollock Hi Please see below for draft FAC... 15/06/2016 03:39:59 p.m.

[redacted]

14/01/2016 04:01 p.m.

To: [redacted]
cc:
bcc:

Subject: Epilim Labelling

Dear [redacted]

I am not sure if I am contacting the correct person, please could you pass on my query if not.

We have had a query about labelling changes on the packaging of Epilim in the UK.
There will soon be a warning for women on the box that the medicine may harm an unborn baby, that they use effective contraception or they talk to their doctor if thinking about pregnancy or if already pregnant.

Could you please let me know if any changes are to be implemented in New Zealand?

Kind regards
Rowan

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

MEDSAFE

[redacted]

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

19/01/2016 08:09 a.m. Subject: RE: Epilim Labelling

Dear Rowan,

We have received your email below. Please note that [redacted] has left Sanofi and I am now the pharmacovigilance contact for Sanofi.

I have forwarded your query to our Regulatory Affairs team who can provide a response to you. Please note that our national sales conference is currently underway so you may not receive a response until the end of the week.

Kind regards,

[redacted]

SANOFI

From: [redacted]
Sent: Tuesday, 19 January 2016 6:00 AM
To: [redacted]
Cc: Adverse Events PH/AU
Subject: Fw: Epilim Labelling

Dear [redacted]

I was wondering if firstly, the below email was received and secondly, if there was any response?

Many thanks
Rowan

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

MEDSAFE [redacted]

----- Forwarded by Rowan Pollock/MOH on 19/01/2016 07:56 a.m. -----

From: [redacted]
To: [redacted]
Date: 14/01/2016 04:01 p.m.
Subject: Epilim Labelling

Dear [redacted]

I am not sure if I am contacting the correct person, please could you pass on my query if not.

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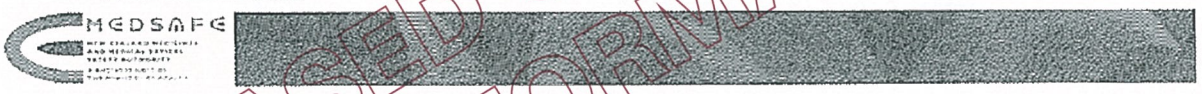
There will soon be a warning for women on the box that the medicine may harm an unborn baby, that they use effective contraception or they talk to their doctor if thinking about pregnancy or if already pregnant.

Could you please let me know if any changes are to be implemented in New Zealand?

Kind regards
Rowan

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



[redacted]

19/01/2016 08:11 a.m.

To: [redacted]
cc:
bcc:

Subject: RE: Epilim Labelling

Dear [redacted]

Thank you for letting me know.

Kind regards
Rowan

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

MEDSAFE [redacted]

Dear Rowan, We have received yo... 19/01/2016 08:09:20 a.m.

From: [redacted]
To:
Cc:
Date: 19/01/2016 08:09 a.m.
Subject: RE: Epilim Labelling

Dear Rowan,

We have received your email below. Please note that [redacted] has left Sanofi and I am now the pharmacovigilance contact for Sanofi.

I have forwarded your query to our Regulatory Affairs team who can provide a response to you. Please note that our national sales conference is currently underway so you may not receive a response until the end of the week.

Kind regards,

[redacted]

SANOFI

From: [redacted]
Sent: Tuesday, 19 January 2016 6:00 AM
To: [redacted]

Cc: [redacted]
Subject: Fw: Epilim Labelling

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I was wondering if firstly, the below email was received and secondly, if there was any response?

Many thanks
Rowan

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

----- Forwarded by Rowan Pollock/MOH on 19/01/2016 07:56 a.m. -----

From: [redacted]
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Date: 14/01/2016 04:01 p.m.
Subject: Epilim Labelling

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Could you please let me know if any changes are to be implemented in New Zealand?

Kind regards
Rowan

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

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

19/01/2016 04:30 p.m. Subject: RE: Epilim Labelling

Dear Rowan,

We are in the process of updating our labelling with a pregnancy warning. This should be submitted to Medsafe next month. Please make sure the enquirer is aware that although it is being submitted next month it may take several months for the stock on the shelves to reflect this change.

Kind regards,

[redacted]

SANOFI

From: [redacted]
Sent: Tuesday, 19 January 2016 9:06 AM
To: [redacted]
Subject: FW: Epilim Labelling

From: [redacted]
Sent: Tuesday, 19 January 2016 6:06 AM
To: [redacted]
Cc: [redacted]
Subject: FW: Epilim Labelling

Dear [redacted] and team,

Could you kindly respond to Medsafe's query below?

Many thanks,

[redacted]

SANOFI

From: [redacted]
Sent: Tuesday, 19 January 2016 6:00 AM
To: [redacted]
Cc: Adverse Events PH/AU
Subject: Fw: Epilim Labelling

Dear [redacted]

I was wondering if firstly, the below email was received and secondly, if there was any response?

Many thanks
Rowan

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

MEDSAFE [redacted]

----- Forwarded by Rowan Pollock/MCH on 19/01/2016 07:56 a.m. -----

From [redacted]
To
Date 14/01/2016 04:01 p.m.
Subject Epilim Labelling

Dear [redacted]

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There will soon be a warning for women on the box that the medicine may harm an unborn baby, that they use effective contraception or they talk to their doctor if thinking about pregnancy or if already pregnant.

Could you please let me know if any changes are to be implemented in New Zealand?

Kind regards
Rowan

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

MEDSAFE [redacted]

[redacted]

To: [redacted]
cc:
bcc:

29/04/2016 07:29 p.m.

Subject: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Dear Susan,

Appreciate your time earlier today to discuss the implementation of the Epilim patient toolkit.

Listed below are some key points

- Sanofi Global has mandated the implementation of a Patient Card worldwide as a new additional risk minimization measure in addition to the risk minimization measures already being implemented.
- Sanofi has a plan in place for implementing the Patient toolkit
- Updates/amendments to patient materials are in progress
- Notification along with the patient toolkit will be sent to Medsafe by the end of May 2016
- NZ Affiliate will be meeting with the NZ patient group on the 9 May 2016

Additionally, application to register the "pregnancy warning statement" on the Epilim packaging was submitted to Medsafe on the 25 April 2016.

Kind regards

[redacted]

[redacted]

SANOFI

[redacted]

To: [redacted]
cc:
bcc:

13/05/2016 03:33 p.m.

Subject: Commercial in Confidence - RE: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Dear Susan,

Please find below summary of the Epilim events as discussed.

NZ Affiliate met with the NZ patient group on the 9 May 2016. Prior to the meeting Denise sent an email to our NZ colleagues. Excerpt from that email highlighted below

One of the areas that will be getting discussed during the meeting, is the lack of consistency between the international Epilim box insert information and NZ's CMI
http://www.medsafe.govt.nz/consumers/cmi/e/Epilim.pdf
So in preparation for this meeting I have attached the UK and USA inserts. I realise they are from the same provider, with just the Epilim name changed to Depakote in the USA.

We did a quick assessment - The UK PIL contains additional information, however this information is included in our patient information booklet, with the only difference being we do not discuss the types of birth defects that can occur. Instead we have taken the approach to tell their patients to discuss the risks and benefits with their doctor.

Summary of the discussion held at the meeting (sent by our NZ colleague)

They wanted to see where Sanofi were at but also to let us know what they are doing.

- ACC, FACE, Medsafe, PHARMAC, Pharmaceutical Society, neurologists and other interested parties are apparently working as a group to ensure prescribers improve communication and monitoring of female patients. NZ Sanofi inquired if they have considered including someone from Industry – Dee will check and revert if the group think that is appropriate.
- They are focussing on Epilim. Dee from ACC said that they have 14 cases with a lifetime cost of $20million and want to minimise the risk.
- They have seen the Dear HCP letter, card (which Denise recognised as part of the MHRA patient kit which is what they are hoping to introduce in NZ)
- Sanofi agreed to include both ladies in the mailout when it goes. They will provide us with some other organisations that should receive the mailout.
- Sanofi advised Q2/Q3 for the mailout – we will do asap.
- Sanofi advised end 2016 for new packaging (explained awaiting TGA approval for packaging and then introduction of new packaging can take up to 6 months).
- Sanofi discussed a pop up in the prescribing software and in the dispensing software and asked for assistance in getting this sorted out (Sanofi having problems getting MedTech to respond to request).
- Sanofi discussed original pack dispensing versus repackaging and this appears to happen a lot in NZ so looking at what we could do – suggestion that we have a "Cautionary Advisory Label" which is either stuck on to the box, or printed with the label (due to space restrictions might need to be a second label but that might be possible in the dispensing software. I think they were going to discuss with Pharmacy Guild or Pharmaceutical Society.

- Comment from our NZ colleague –"With regard to the CMI, we did cover off that there is a standard format and I suggested that while there was a lot more information in the UK version I had some doubt as to whether we have the health literacy here to understand the text – this is an area of considerable concern in NZ. Denise did agree but I think still wants more text".

As discussed, will send the updated patient toolkit to Medsafe next week, prior to the 20 May meeting.

Many thanks & kind regards

[redacted]

SANOFI

From: [redacted]
Sent: Monday, 2 May 2016 7:13 AM
To: [redacted]
Subject: Re: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Thanks [redacted] very helpful
Kind regards
Susan
Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health | [redacted]

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

[redacted]

From: [redacted]
To: <[redacted]
Date: 29/04/2016 07:29 p.m.
Subject: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

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- NZ Affiliate will be meeting with the NZ patient group on the 9 May 2016

Additionally, application to register the "pregnancy warning statement" on the Epilim packaging was submitted to Medsafe on the 15 April 2016.

Kind regards

[redacted]

[redacted]

SANOFI

immediately and delete this message.
****

This e-mail message has been scanned for Viruses and Content and cleared by the Ministry of Health's Content and Virus Filtering Gateway


Depakote Information.pdf PIL UK Epilim.pdf

[redacted]

To: [redacted]
cc:
bcc:

08/06/2016 07:29 p.m.

Subject: RE: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Dear Susan,

As communicated previously, Sanofi Global has mandated the implementation of a Patient Card worldwide as a new additional risk minimization measure in addition to the risk minimization measures already being implemented.

Attached is the following documents for your information and Medsafe files.

- Updated Patient Information Booklet
- Updated Guide for Healthcare professionals
- Patient card for New Zealand which is a new addition to the toolkit

The updates involve removal of the images in the brochures, however the content remains unchanged. The Patient Toolkit will be implemented this week.

Kind regards

[redacted]

SANOFI

From: [redacted]
Sent: Friday, 29 April 2016 5:29 PM
To: [redacted]
Subject: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

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Additionally, application to register the "pregnancy warning statement" on the Epilim packaging was submitted to Medsafe on the 15 April 2016.

Kind regards

[redacted]

[redacted]

SANOFI

SAANZ.VPA.16.05.0085 vFinal 1.0.pdfSAANZ.VPA.16.04.0080 vFinal 1.0.pdf

SAANZ.VPA.16.04.0081 vFinal 1.0.pdf

Key Facts – Valproate and Pregnancy

Name: Date:

- Valproate is an effective medicine used to treat epilepsy and bipolar disorder.
- Valproate can seriously harm an unborn child when taken during pregnancy and should not be taken by women and girls unless nothing else works.
- When taking valproate always use reliable contraception so you do not have an unplanned pregnancy.

▼ Please report any side effects you may get.
See www.medsafe.govt.nz/safety/reportaproblem.asp for how to report side effects.

What you must do

- Speak to your doctor if you are thinking about having a baby, and do **not** stop using contraception until you have done so.
- Tell your doctor immediately if you think you may be pregnant or know you are pregnant.
- Do not stop taking valproate unless your doctor tells you to as your condition may become worse.

Keep this card safe so you always know what to do.

SAANZ VPA 16.05.0085 May 2016

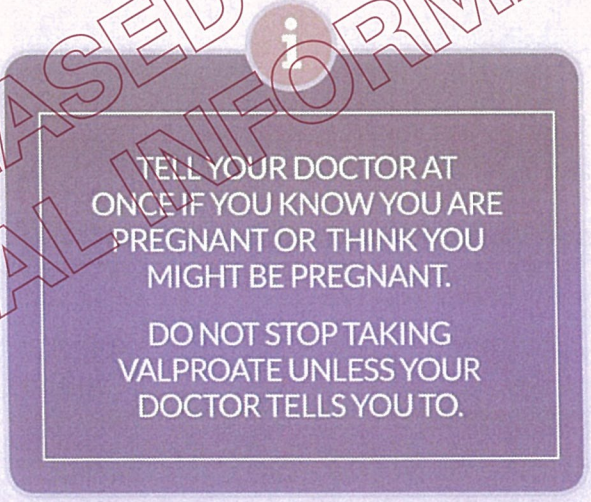
Patient Information booklet

VALPROATE

The information in this booklet is for women who are being prescribed valproate and are able to get pregnant (of child-bearing age). If you have any questions talk to your doctor or pharmacist.

There is a lot of information and it is recommended that you show this booklet to friends and family to help you discuss and understand your treatment.

Keep this booklet. You may need to read it again.



TELL YOUR DOCTOR AT ONCE IF YOU KNOW YOU ARE PREGNANT OR THINK YOU MIGHT BE PREGNANT.

DO NOT STOP TAKING VALPROATE UNLESS YOUR DOCTOR TELLS YOU TO.

A BEFORE YOU TAKE VALPROATE

Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child, you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product, if this is possible.

If you are a woman capable of becoming pregnant, your doctor should only prescribe valproate if nothing else works for you.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

B FIRST PRESCRIPTION

If this is the first time you have been prescribed valproate, your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

- ***Make sure you are using an effective method of contraception***
- ***Tell your doctor at once if you are pregnant or think you might be pregnant***

C CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY

If you are continuing treatment with valproate and you are now thinking of trying for a baby, you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should discuss your plan with your doctor well before you become pregnant, so that you can put several actions in place so your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your doctor may need to change the dose of valproate or switch you to another medicine before you start trying for a baby. If you become pregnant, you will be monitored very closely both for the management of your epilepsy/ bipolar disorder as well as to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Remember:

- ***Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy/ bipolar disorder is controlled and the risks to your baby are reduced***
- ***Tell your doctor at once when you know or think you might be pregnant***

D CONTINUING TREATMENT AND NOT TRYING FOR A BABY

If you are continuing treatment with valproate and you don't plan to have a baby, make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

- ***Make sure you are using an effective contraception***
- ***Tell your doctor at once if you are pregnant or think you might be pregnant***

E AN UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT

Babies born to mothers who have been treated with valproate are at risk of birth defects and problems with early development which can be debilitating. If you are taking valproate and you think you are pregnant or might be pregnant, contact your doctor at once. Do not stop taking your epilepsy/ bipolar disorder medicine until your doctor tells you to.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

SANOFI

Registered trademark of sanofi-aventis Australia Pty Ltd trading as Sanofi. ABN 310 008 558 807. Talavera Corporate Centre, Building D, 12-24 Talavera Road, Macquarie Park, NSW 2113
Tel: + 61 (0)2 8666 2000. Fax: + 61 (0)2 8666 3000.
James & Wells Tower, 56 Cawley Street, Ellerslie, Auckland
Tel: +64 (0)9 580 1810
Date of approval: May 2016 SAANZ.VPA.16.04.0080

Guide for Healthcare professionals

VALPROATE

This Guide is provided as part of the risk minimisation measures developed for valproate to inform prescribers of the risks associated with the use of valproate by women of childbearing potential and during pregnancy.

The Guide will provide up-to-date information about the risk of neurodevelopmental disorders in children of women who have taken valproate during pregnancy in addition to the known risk of congenital malformations in exposed babies.

This guide should be used along with the patient information booklet. To learn more about valproate, please read the complete Product Information before prescribing valproate.

WHAT YOU SHOULD KNOW ABOUT THE RISKS OF VALPROIC ACID USE IN FEMALE PATIENTS

VALPROATE contains valproic acid, an active ingredient with known teratogenic effects which may result in congenital malformations. Available data also show that in utero exposure to valproate can be associated with an increased risk of developmental disorders. These risks are briefly described on the next few pages.

1 CONGENITAL MALFORMATIONS

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29), which represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2-3%.[1] Available data show the risk is dose dependent. The risk is greatest at higher doses (above 1 g daily). A threshold dose below which no risk exists cannot be established based on available data.

The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

2 DEVELOPMENTAL DISORDERS

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 available 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[2-5] in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school-aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics.[9] Although the role of confounding cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.[7]

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).[8]

Treatment of female patients with valproate

A FEMALE CHILD FIRST PRESCRIPTION

After medical evaluation, you are considering prescribing valproate to your patient:

- **Confirm** that treatment with valproate is appropriate for your patient (i.e. all other treatments have been tried and failed).
- **Discuss** the following topics with your patient and relevant family members/care-givers:
  - Risks to pregnancy that are associated with the underlying condition;
  - Risks related to treatment, including risks related to valproate in case of pregnancy;
  - Need for an effective contraception method to avoid unplanned pregnancy;
  - Need for regular review of treatment.
- **Assess** the most appropriate timing to provide advice on effective contraception methods and refer your patient to a specialist if needed.
- **Ensure** that your patient/family members/caregivers of the patient have understood the potential consequences in case of pregnancy and has/have an adequate level of understanding of the risks.

A document has been developed to help you:

- A patient information booklet which summarises the teratogenic safety information and highlights key points for treatment management:
  - Read it, as it may help you to deliver appropriate information to your patient
  - Give one copy to your patient
- Advise your patient to contact you immediately if she becomes pregnant or thinks she might be pregnant.
- Plan to review the need for treatment when she becomes capable of pregnancy.

B WOMEN OF CHILDBEARING AGE WHO ARE NOT PLANNING PREGNANCY

After medical evaluation, you are considering prescribing valproate to your patient:

- **Confirm** that treatment with valproate is appropriate for your patient (i.e. all other treatments have been tried and failed).
- **Discuss** the following topics with your patient:
  - Risks to pregnancy that are associated with the underlying condition;
  - Risks related to treatment, including risks related to valproate in case of pregnancy;
  - Need for an effective contraception method to avoid unplanned pregnancy;
  - Need for regular review of treatment.
- **Assess** the relevance of preconception counseling.
- **Ensure** that your patient has understood the potential risks to the child of using valproate during pregnancy and has an adequate level of understanding of the risks, and that she agrees to comply with the conditions for pregnancy.

For this, the following document has been developed to support you:

- **A patient information booklet** which summarises the teratogenic safety information and highlights key points of treatment management
  - Give one copy to your patient.
- **Advise** your patient to contact you
  - If she becomes pregnant or thinks she might be pregnant;
  - In case of any adverse events associated with her treatment.

C WOMAN OF CHILDBEARING AGE WHO IS PLANNING PREGNANCY

- **Remind** your patients of teratogenic risks and risks of developmental disorders that can be seriously debilitating when taking valproate but also the risks of untreated seizures or bipolar disorder.
- **Reassess** the benefit/risk of valproate therapy, whatever the indication:
  - Consider if stopping treatment or switching to an alternative is possible.
  - If further to a careful evaluation of the risks and benefits, valproate treatment is to be continued, it is recommended to divide the daily dose into several small doses to be taken throughout the day at the lowest effective dosage possible. The use of a prolonged-release formulation may be preferable to other treatment forms.
  - Both valproate monotherapy and valproate polytherapy are associated with congenital malformations. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of abnormal pregnancy outcome than valproate monotherapy.
  - Folic acid supplementation may decrease the general risk of neural tube defects but the evidence does not suggest that it reduces the risk of birth defects associated with in utero valproate exposure.
- **Consider** referring your patient to a specialist for preconception advice.
- **Ensure** that your patient:
  - has truly understood the risks related to valproate in case of pregnancy;
  - has received the patient information booklet.
- **Advise** your patient to contact her family doctor as soon as she becomes pregnant or thinks she might be pregnant in order to initiate appropriate pregnancy monitoring, including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations.

D WOMAN WITH UNPLANNED PREGNANCY

- **Schedule an urgent consultation** with your patient to review treatment as soon as possible to reconsider the benefits and risks of valproate.
- **Tell her to keep taking her treatment** until you have seen her, unless you are able to give other advice based on your assessment of the situation.
  - If further to a careful evaluation of the risks and benefits, valproate treatment is to be continued, it is recommended to divide the daily dose into several small doses to be taken throughout the day at the lowest effective dosage possible. The use of a prolonged-release formulation may be preferable to other treatment forms.
  - Both valproate monotherapy and valproate polytherapy are associated with congenital malformations. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of abnormal pregnancy outcome than valproate monotherapy.
  - Folic acid supplementation may decrease the general risk of neural tube defects but the evidence does not suggest that it reduces the risk of birth defects associated with in utero valproate exposure.
- **Ensure** that your patient:
  - has truly understood the risks related to valproate in case of pregnancy;
  - has received the patient information booklet.
- **Initiate specialised prenatal monitoring** in order to detect the possible occurrence of neural tube defects or other malformations.

SUMMARY

A. FEMALE CHILD FIRST PRESCRIPTION

1. Assess your patient's need for treatment with sodium valproate
2. Explain potential risks of the disease itself for the unborn child and the risks associated with use of sodium valproate in pregnancy
3. Inform your patient about the need to use effective contraception as soon as it is relevant
4. Ensure that your patient has received the patient information booklet
5. Where applicable, advise your patient to contact you immediately if she becomes pregnant or thinks she might be pregnant

B. WOMEN OF CHILDBEARING AGE WHO ARE NOT PLANNING PREGNANCY

1. Assess your patient's need for treatment with valproate
2. Explain potential risks of treatment and of untreated disease for the unborn child
3. Inform your patient about the need to use effective contraception
4. Ensure that your patient has received the patient information booklet
5. Advise your patient to contact you immediately if she becomes pregnant or thinks she might be pregnant

C. WOMAN OF CHILDBEARING AGE WHO IS PLANNING PREGNANCY

1. Explain potential risks of the disease itself on the unborn child, independent from valproate's own risks
2. Re-assess benefit/risk of patient's therapy
3. Adapt current treatment
4. Advise your patient to contact you when she becomes pregnant or thinks she might be pregnant
5. Ensure that your patient has received the patient information booklet

D. WOMAN WITH UNPLANNED PREGNANCY

1. Inform her to keep taking her treatment until you have seen her
2. Schedule an urgent consultation
3. Re-assess the benefit/risk of her therapy and adapt current treatment as appropriate
4. Ensure that your patient has understood the risks related to valproate in case of pregnancy

References: 1. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. *Epilepsy Res.* 2008;81(1):1-13. 2. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L *et al.* Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010 October;51(10):2058-65. 3. Cummings *et al.* Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011;96:643-647. 4. Meador K *et al.* Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. *NEJM* 2009;360 (16): 1597- 1605. 5. Thomas S.V *et al.* Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy and Behaviour* 2008 (13):229-236. 6. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J,Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol.* 2013 Mar;12(3):244-52. 7. Christensen J *et al.* Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. *JAMA* 2013;309(16):1696-1703. 8. Cohen M.J *et al.* Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioural Functioning at age 3 years. *Epilepsy Behav.* 2011; 22(2):240-246. 9. Meador K *et al.* Fetal antiepileptic drug exposure and cognitive outcomes at age 6 (NEAD study): a prospective observational study. *Lancet Neurol.* 2013 March;12(3): 244-252.

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Tel: + 61 (0)2 8666 2000. Fax: + 61 (0)2 8666 3000.
James & Wells Tower, 56 Cawley Street, Ellerslie, Auckland
Tel: + 64 (0)9 580 1810
Date of approval: May 2016 SAANZ.VPA.16.04.0081

[redacted]

To: [redacted]
cc:
bcc:

09/06/2016 12:19 p.m.

Subject: RE: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Dear Susan,

According to our global mandate we are required to distribute hard copies of the Patient cards and educational materials (Guide for HCPs and Patient Information Booklet) to HCPs. Additionally, the education materials will also be on the Sanofi website (ANZ).

Yes, it would be much appreciated if Medsafe could link to the Sanofi website

Kind regards

[redacted]

SANOFI

From: [redacted]
Sent: Thursday, 9 June 2016 7:11 AM
To: [redacted]
Cc: Regulatory Affairs AU PH/AU
Subject: RE: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Hi [redacted]
Many thanks for sending these.
What where your plans re publication? - will you have them on your website?
Do you want us to link to them and/or have on our website?
Kind regards
Susan

Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health [redacted]

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

[redacted]

From: [redacted]
To:
Cc:
Date: 08/06/2016 07:30 p.m.
Subject: RE: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Dear Susan,

As communicated previously, Sanofi Global has mandated the implementation of a Patient Card worldwide as a new additional risk minimization measure in addition to the risk minimization measures already being implemented.

Attached is the following documents for your information and Medsafe files.

- Updated Patient Information Booklet
- Updated Guide for Healthcare professionals
- Patient card for New Zealand which is a new addition to the toolkit

The updates involve removal of the images in the brochures, however the content remains unchanged. The Patient Toolkit will be implemented this week.

Kind regards

[redacted]

SANOFI

From: [redacted]
Sent: Friday, 29 April 2016 5:29 PM

To: [redacted]
Subject: Epilim - Patient card Instruction for implementation as a new additional risk minimization measure

Dear Susan,

Appreciate your time earlier today to discuss the implementation of the Epilim patient toolkit.

Listed below are some key points

- Sanofi Global has mandated the implementation of a Patient Card worldwide as a new additional risk minimization measure in addition to the risk minimization measures already being implemented.
- Sanofi has a plan in place for implementing the Patient toolkit
- Updates/amendments to patient materials are in progress
- Notification along with the patient toolkit will be sent to Medsafe by the end of May 2016
- NZ Affiliate will be meeting with the NZ patient group on the 9 May 2016

Additionally, application to register the "pregnancy warning statement" on the Epilim packaging was submitted to Medsafe on the 15 April 2016.

Kind regards

[redacted]

[redacted]

SANOFI

[attachment "SAANZ.VPA.16.05.0085 vFinal 1.0.pdf" deleted by Susan Kenyon/MOH] [attachment "SAANZ.VPA.16.04.0080 vFinal 1.0.pdf" deleted by Susan Kenyon/MOH] [attachment "SAANZ.VPA.16.04.0081 vFinal 1.0.pdf" deleted by Susan Kenyon/MOH]

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SANOFI

29 March 2017
Ref: 0024-sacn-ccdsv22-pictogram-200mg-500mg-iv-artworks-29mar17

The Manager
Medsafe
PO Box 5013
Wellington
New Zealand

Dear Sir/Madam,

Re: Self Assessable Change Notification for
Epilim 100 Crushable Tablet 100mg (TT50-2501/4)
Epilim EC Tablet, modified release 200mg (TT50-2501/1)
Epilim EC Tablet, modified release 500mg (TT50-2501/1a)
Epilim Intravenous Injection, solution 100mg/mL (TT50-2501/5)

Labelling – Grade 1

Please find enclosed a Self Assessable Change Notification (SACN) for the above products containing sodium valproate. This notification relates to:

- addition of a pictogram
- addition of strength next to active ingredient, ensuring consistency with the presentation order of name, active ingredient, strength and dosage form across all Epilim products
- reformatting of text without change in meaning ensuring consistency in order of presentation across all Epilim products
- addition of label box (IV carton only)
- update to NZ Sponsor details
- update to packaging codes

Following the SACN for the addition of the 'Pregnancy Warning Statement' to all outer packaging of valproate-containing products last year, (Medsafe acknowledged 27 April 2016), we have been requested by our global colleagues to draw attention to this warning statement further by adding a pictogram and a red boxed warning. Sanofi wishes to implement this change worldwide as an additional risk minimisation measure in order to ensure consistency in the level of risk minimisation and access to the same patient information in all countries where Sanofi markets valproate-containing products.

In addition to the pictogram, we wish to take this opportunity to update the artworks with some extra changes that we have listed above. We would like to bring to your attention the change in presentation of the Epilim 100mg crushable tablets, (TT50-2501/4). The registered trade name in NZ is 'Epilim 100 Crushable' and in Australia is 'Epilim'. As this is a harmonised carton, it is our aim to be consistent with the presentation across all of our Epilim products with respect to the presentation order of name, active ingredient, strength and dosage form. Due to the inconsistency in the registered

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Talavera Corporate Centre, Building D, 12-24 Talavera Road, Macquarie Park, NSW 2113
Tel: +61 (0) 2 8666 2000 – Fax: +61 (0) 2 8666 3000 - www.sanofi.com.au

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trade names between both countries, we believe this proposed format change is the best presentation to keep with consistency and identifies the different components, (ie name, active ingredient, strength and dosage form), easily. To explain these requested changes in more detail, we have created a change table, which we have inserted between pages 4 and 5 of the application form. We believe the proposed changes, to all artworks listed overleaf, reinforce the outer box warning message and also improve the readability of the artworks.

Please note, our non-marketed 300mg controlled release tablet, (TT50-2501/6), has been omitted from this SACN. We provide the assurance that if a decision is made in the future to launch this product in New Zealand, the updated artwork will be submitted to Medsafe prior to commencement of supply. Further, we confirm that the approval for the above changes is not being sought at this time for our non-marketed presentation.

Module 1

1.2 Completed CMN A Form and Therapeutic Product Database Reports

1.3 Current and Proposed carton artworks

An assurance is provided that no aspects of the Data Sheet or pharmaceutical data have been changed, including manufacturing procedures and equipment and raw material and finished product specifications, other than the changes nominated in this SACN and the changes made to the Data Sheet are supported by data in the possession of sanofi.

If you have any queries, please do not hesitate to contact me directly on [redacted]

Yours faithfully,

[redacted]

(Place label here)

Please recycle carton only.

(B) EXP

Epilim® EC200
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.
Dosage: as directed by Physician.
The tablet must be swallowed whole, not chewed.
Keep tablets sealed in the blister until they are needed.
Do not use if blister pack is torn or damaged.
In Australia Consumer Medicine Information is available from your Pharmacist.
Store below 30°C, in a dry place.

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C14225

Distributed by:
sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park, NSW 2113
Freecall No: 1800 818 806

CODE NO: GO/DRUGS/349
sanofi-aventis new zealand limited
Auckland, New Zealand
Freecall No: 0800 283 684

Epilim EC200 sodium valproate
Each enteric-coated tablet contains sodium valproate 200 mg

PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Epilim® EC200
sodium valproate

Each enteric-coated tablet contains sodium valproate 200 mg

AUST R 15369
100 Tablets

SANOFI

Epilim EC200
sodium valproate
100 Tablets

SIL-0745814-2it-ANZ-EX

proposed

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Freecall No: 1800 818 806

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street,
Ellerslie, Auckland 1051
Freecall No: 0800 283 684

(Place label here)

(B)
EXP

541528

Epilim® EC200

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.

Please recycle carton only.

In Australia Consumer Medicine Information is available from your Pharmacist.
Dosage: as directed by Physician.
The tablet must be swallowed whole, not chewed.
Keep tablets sealed in the blister until they are needed.
Do not use if blister pack is torn or damaged.
Store below 30°C, in a dry place.

CODE NO. GO/DRUGS/349

9 319733 000470

C16355

PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Epilim® EC200
sodium valproate 200mg

Each enteric-coated tablet contains sodium valproate 200 mg

AUST R 15369

100 Tablets

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Epilim EC200 sodium valproate 200mg
Each enteric-coated tablet contains sodium valproate 200 mg

Epilim EC200
100 Tablets
sodium valproate 200mg

16-3tt-AUS-EX

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Depakote

Keep this medicine in a safe place where children cannot see or reach it.

Do not use Depakote after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment

6. Contents of the pack and other information

What Depakote 250mg Tablets contain

- Each 250mg tablet contains 269.1mg of the active substance, valproate semisodium (equivalent to 250mg of valproic acid)
- The other ingredients are: silicone dioxide, pregelatinised starch, povidone, titanium dioxide (E171), hypromellose , polyethylene glycol 6000, Methacrylic acid- ethyl acrylate copolymer (1:1), triethyl citrate, , vanillin, sunset yellow aluminium lake (E110).

What Depakote 500mg Tablets contain

- Each 500mg tablet contains 538.2mg of the active substance, valproate semisodium (equivalent to 500mg of valproic acid)
- The other ingredients are: silicone dioxide, pregelatinised starch, povidone, titanium dioxide (E171), hypromellose , polyethylene glycol 6000, Methacrylic acid- ethyl acrylate copolymer (1:1), triethyl citrate, vanillin, ponceau 4R aluminium lake (E124), indigotine aluminium lake (E132)

What Depakote looks like and contents of the pack

Depakote 250mg Tablets are oval orange gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.

Depakote 500mg Tablets are oval lilac pink gastro-resistant tablets supplied in Aluminium/aluminium blister packs containing 30, 60 or 90 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS
UK
Tel: 0845 372 7101
Fax: 01483 535432
email: uk-medicalinformation@sanofi.com

Manufacturer
Sanofi-aventis SA, Carretera C-35 (La Batlloria-Hostalric), Km 65.09
17404 Riells i Viabrea (Girona)

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in Feburary 2015

Avance bobina

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PACKAGE LEAFLET:
INFORMATION FOR THE USER

Depakote® 250mg and 500mg Tablets

Valproic acid (as valproate semisodium)

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Is this leaflet hard to see or read?
Phone 0845 372 7101 for help

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

WARNING
Valproate can cause birth defects and problems with early development of the child if it is taken during pregnancy. If you are a female of childbearing age you should use an effective method of contraception throughout your treatment.

Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet. Tell your doctor at once if you become pregnant or think you might be pregnant.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Depakote is and what it is used for

The name of your medicine is Depakote 250mg or 500mg tablets (called Depakote in this leaflet). Depakote contains a medicine called valproate semisodium. This belongs to a group of medicines called mood stabilisers. It works by stabilising the levels of chemicals in your brain that affect your mood.
Depakote can be used to manage or control mania (feeling highly excited, enthusiastic, being over-active and easily irritated or distracted) caused by bipolar disorder. Bipolar disorder is where the mood changes between feeling very high (mania) and very low (depression).
Depakote can be used when lithium can not be used.

2. What you need to know before you take Depakote

Do not take Depakote

x You are allergic (hypersensitive) to valproate semisodium or any of the other ingredients of Depakote (see Section 6: Contents of the pack and other information)
x Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
x You have liver problems
x You or a family member has ever had liver problems caused by taking a medicine
x You have a rare illness called porphyria which affects your metabolism
x If you have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome)

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Depakote.

Warnings and precautions

A small number of people being treated with mood stabilisers such as valproate semisodium have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Talk to your doctor or pharmacist before taking Depakote if:

▲ You are changing from another medicine that contains valproate
▲ The person taking this medicine is less than 18 years old
▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain.
▲ You have kidney problems
▲ You have problems with your pancreas
▲ You have an illness called 'systemic lupus erythematosus'. This is a disease of the immune system which affects the skin, bones, joints and internal organs
▲ You have a metabolic condition which results in too much ammonia in the blood (shown in blood tests)
▲ You have diabetes or are being tested for diabetes. This medicine may affect the results of urine tests
▲ You know that there is a genetic problem caused by a mitochondrial disorder in your family.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Depakote.

Weight gain

Taking Depakote may make you put on weight. Talk to your doctor about how this will affect you.

Other medicines and Depakote

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Depakote can affect the way some other medicines work. Also, some medicines can affect the way Depakote works.

In particular, do not take and check with your doctor if you are taking any of the following:

- Some medicines used for pain and inflammation called 'salicylates' such as aspirin.

The following medicines can affect the way Depakote works or Depakote can affect the way some of these medicines work:

- Some medicines used to treat fits (epilepsy) such as phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine and felbamate. Your doctor may change the dose of one of your medicines and monitor your treatment closely
- Medicines for depression
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine
- Zidovudine - used for HIV infection
- Carbapenem agents (antibiotics used to treat bacterial infections) such as panipenem, imipenem, meropenem, rifampicin and erythromycin. The combination of Depakote and carbapenems should be avoided because it may decrease the effect of your medicine
- Some medicines used for malaria such as mefloquine or chloroquine
- Medicines used for thinning the blood such as warfarin. Your doctor may change your dose of the blood thinning medicine and monitor your treatment closely.
- Temozolomide - used for cancer
- Cimetidine - used for stomach ulcers
- Colestyramine - used for lowering blood cholesterol levels

Taking Depakote with food and drink

Alcohol intake is not recommended during treatment.

Pregnancy, breast feeding and fertility

Important advice for women

- Valproate can be harmful to unborn children when taken by a woman during pregnancy.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include *spina bifida* (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk , intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

FIRST PRESCRIPTION

If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND NOT TRYING FOR A BABY

If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY

If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should talk to your doctor well before you become pregnant so that you can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your doctor may decide to change the dose of valproate or switch you to another medicine before you start trying for a baby.

If you do become pregnant you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your bipolar is controlled and the risks to your baby are reduced.
- Tell your doctor at once when you know or think you might be pregnant.

UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. If you are taking valproate and you think you are pregnant or might be pregnant contact your doctor at once. Do not stop taking your medicine until your doctor tells you to.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Tell your doctor at once if you know you are pregnant or think you might be pregnant.
- Do not stop taking valproate unless your doctor tells you to.

Make sure you read the patient booklet and sign the Acknowledgement of Risk form which should be given to you and discussed with you by your doctor or pharmacist.

Breast-feeding

If you are breast-feeding or planning to breast-feed, talk to your doctor or pharmacist before taking any medicine.

Driving and using machines

You may feel sleepy, confused or dizzy while taking this medicine.
If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of Depakote

Your medicine contains colours called **'sunset yellow aluminium lake (E110)'** and **'ponceau 4R aluminium lake (E124)'**. They may cause allergic reactions including asthma in some people. You are more likely to have an allergy if you are also allergic to aspirin.

3. How to take Depakote

Always take Depakote exactly as your doctor has told you. Your doctor will decide your daily dose. You should check with your doctor or pharmacist if you are not sure. Depakote treatment must be started and supervised by a doctor specialised in the treatment of bipolar disorders.

How to take your medicine

- Take this medicine by mouth
- Swallow the tablets whole with a drink of water. Do not crush or chew them
- This medicine can be taken with or after a meal
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor

How much to take

The normal dose is:

Adults including the elderly

- **Starting dose** is 750mg on the first day. This is usually taken as 2 or 3 divided doses
- **The usual dose is then increased to** between 1000mg and 2000mg each day
- Your doctor may decide to increase your dose depending on your illness

If you have kidney problems

- Your doctor may decide to lower your dose

Children and adolescents

Children and adolescents under 18 years of age:
Depakote should not be used in children and adolescents under 18 years of age for the treatment of mania

Tests

Your doctor may do regular blood tests and liver function tests before and during your treatment with this medicine.

If you take more Depakote than you should

If you or someone else has taken more Depakote than you should, talk to a doctor or go to your nearest hospital casualty department straight away. Remember to take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: being sick, headache, blurred eyesight due to pupils of the eyes becoming smaller, lack of reflexes, confusion and tiredness. You may also have weak or 'floppy' muscles, fits (seizures), loss of consciousness, behavioural changes and breathing difficulties such as fast breathing, shortness of breath or chest pain.

If you forget to take Depakote

If you forget to take a dose at the right time, take it as soon as you remember. Do not take a double dose to

If you stop taking Depakote

Keep taking your medicine until your doctor tells you to stop. Do not stop taking Depakote just because you feel better. If you stop, your illness may return.

When your doctor says that you can stop taking Depakote, your dose will be lowered gradually. Your doctor will help you to do this.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Depakote can cause side effects, although not everybody gets them. Side effects are more likely to happen at the start of treatment.

Allergic reactions

If you have an allergic reaction, stop taking Depakote and see a doctor or go to a hospital straight away. The signs may include: rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.

Stop taking Depakote and see your doctor or go to a hospital straight away if you notice a combination of any of the following serious side effects:

The following side effects may be signs of problems with your liver or pancreas and may show as a sudden illness:

- Feeling weak, general feeling of being unwell
- Loss of or decreased appetite (anorexia)
- Feeling drowsy, confused or tired
- Swelling of the feet and legs (oedema)
- Nausea (feeling sick)
- Vomiting (being sick)
- Stomach pain. Sometimes may be severe and reach through to your back
- Recurrence of fits (seizures) for patients with epilepsy
- Yellowing of the eyes or skin

The following side effects may be signs of problems with your blood cells

- Bruising more easily, spontaneous bruising or bleeding
- Frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Getting more infections than usual
- Feeling weak, tired, faint, dizzy or having an unusually pale skin

These could be caused by a blood disorder called 'thrombocytopenia'. It can be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots.

Other serious side effects which need urgent medical attention:

- Fits (seizures), loss or reduction of consciousness, seeing or hearing things that are not there (hallucinations)
- Memory problems, reduced ability to perform mental tasks, being unable to concentrate
- Difficulty in speaking or slurred speech
- Muscle weakness, lack of co-ordination, muscle twitching or sudden jerks and shaking
- Difficulty in walking or unusual involuntary movements, such as unusual eye movements
- Blistering, peeling, bleeding, scaling or fluid filled patches on any part of your skin. This includes your lips, eyes, mouth, nose, genitals, hands or feet. You may also have flu-like symptoms and fever, joint aches and pains, swollen joints, headaches, chest pain and shortness of breath
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism)
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion)
- Rapid, uncontrollable movement of the eyes

Tell your doctor as soon as possible if you have any of the following side effects:

- Unusual behaviour including being very alert, and sometimes also aggressive, hyper-active and showing bad behaviour
- Water retention which may cause swollen arms or legs
- Bleeding a lot from a wound

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days

- Hair, including body or facial hair, grows more than normal
- Temporary hair loss
- Acne
- Diarrhoea
- Night sweats or joint pain
- Irregular periods or a lack/absence of menstrual periods
- Breast enlargement in men
- Loss of hearing
- Bed wetting
- Weight gain
- Headache
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet

Bone Disorders

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term antiepileptic medication, have a history of osteoporosis, or take steroids.

Tests

Blood and urine tests may show changes in the way the kidney is working. This includes an increase in the amounts of sugar, amino acids, uric acid and phosphates. Blood tests may show changes in the amount of blood cells or levels of liver enzymes.

Male Fertility

Taking Depakote can be a contributing factor in male infertility.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Epilim® 200mg and 500mg Gastro-resistant Tablets

sodium valproate

SANOFI

Is this leaflet hard to see or read? Phone 0845 372 7101 for help

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects

WARNING
Valproate can cause birth defects and problems with early development of the child if it is taken during pregnancy. If you are a female of childbearing age you should use an effective method of contraception throughout your treatment.
Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet. Tell your doctor at once if you become pregnant or think you might be pregnant.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Epilim is and what it is used for

What Epilim is
The name of your medicine is Epilim 200mg or 500mg Gastro-resistent Tablets (called Epilim in this leaflet). Epilim 200mg or 500mg Gastro-resistant Tablets are "enteric coated" this means that the tablets have a protective coating that allows it to reach the intestines (gut) without being dissolved in the stomach first. This helps stop it from causing a stomach upset.

What Epilim contains
Epilim contains sodium valproate. It belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down.

What Epilim is used for
Epilim is used to treat epilepsy (fits) in adults and children.

2. What you need to know before you take Epilim

Do not take Epilim and tell your doctor if:
- x You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of Epilim (see Section 6: Contents of the pack and other information)
  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- x You have liver problems or you or your family have a history of liver problems
- x You have a rare illness called porphyria
- x If you have a genetic problem caused by a mitochondrial disorder (e.g. Alpers-Huttenlocher syndrome)

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Epilim.

Warnings and precautions
A small number of people being treated with anti-epileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Talk to your doctor or pharmacist before taking Epilim if:
- ▲ You have diabetes. This medicine may affect the results of urine tests.
- ▲ You have kidney problems. Your doctor may give you a lower dose
- ▲ You have fits (epilepsy), brain disease or a metabolic condition affecting your brain
- ▲ You have a 'urea cycle disorder' where too much ammonia builds up in the body
- ▲ You have an illness called 'systemic lupus erythematosus (SLE)' - a disease of the immune system which affects skin, bones, joints and internal organs
- ▲ You know that there is a genetic problem caused by a mitochondrial disorder in your family.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Epilim.

Weight gain
Taking Epilim may make you put on weight. Talk to your doctor about how this will affect you.

Blood tests
Your doctor may wish to do blood tests before you start taking Epilim and during your treatment.

Other medicines and Epilim
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Epilim can affect the way some other medicines work. Also some medicines can affect the way Epilim works.

The following medicines can increase the chance of you getting side effects, when taken with Epilim:
- Some medicines used for pain and inflammation (salicylates) such as aspirin
- Some other medicines used to treat fits (epilepsy) – see page 2, section 3, "Patients taking other medicines for 'fits'". This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine and felbamate

Epilim may increase the effect of the following medicines:
- Medicines used for thinning the blood (such as warfarin)
- Zidovudine - used for HIV infection
- Temozolomide used to treat cancer
- Medicines for depression
- Monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid
- Medicines used to calm emotional and mental conditions such as diazepam and olanzapine

The following medicines can affect the way Epilim works:
- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine
- Cimetidine - used for stomach ulcers
- Carbapenem agents (antibiotics used to treat bacterial infections) such as imipenem, meropenem, rifampicin and erythromycin. The combination of Epilim and carbapenems should be avoided because it may decrease the effect of your medicine
- Colestyramine used to lower blood fat (cholesterol) levels

Taking Epilim with food and drink
Alcohol intake is not recommended during treatment.

Pregnancy and breast-feeding

Important advice for women

- Valproate can be harmful to unborn children when taken by a woman during pregnancy.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk , intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

FIRST PRESCRIPTION

If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND NOT TRYING FOR A BABY

If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY

If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should talk to your doctor well before you become pregnant so that you can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your doctor may decide to change the dose of valproate or switch you to another medicine before you start trying for a baby.

If you do become pregnant you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy is controlled and the risks to your baby are reduced
- Tell your doctor at once when you know or think you might be pregnant.

UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. If you are taking valproate and you think you are pregnant or might be pregnant contact your doctor at once. Do not stop taking your medicine until your doctor tells you to.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Tell your doctor at once if you know you are pregnant or think you might be pregnant.
- Do not stop taking valproate unless your doctor tells you to.

Make sure you read the patient booklet and sign the Acknowledgement of Risk form which should be given to you and discussed with you by your doctor or pharmacist.

Breast-feeding

Very little Epilim gets into the breast milk. However, talk to your doctor about whether you should breast-feed your baby. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

You may feel sleepy when taking Epilim. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

3. How to take Epilim

Always take Epilim exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Epilim treatment must be started and supervised by a doctor specialised in the treatment of epilepsy.

Taking this medicine

- Your doctor will decide how much Epilim to give you or your child depending on your or your child's body weight
- Take this medicine by mouth
- **Do not** crush or chew the tablets
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor

How to take this medicine

- The dose is normally split and given half in the morning and half in the evening.

How much to take

Adults (including the elderly)
- The starting dose is 600mg daily. Your doctor should gradually increase this dose by 200mg every 3 days depending on your condition
- The usual dose is between 1000mg and 2000mg (20-30mg per kilogram of body weight) each day
- This may be increased to 2500mg each day depending on your illness

Children over 20 kilograms
- The starting dose should be 400mg daily. Your doctor should increase this dose depending on your child's illness
- The usual dose is then between 20mg and 30mg for each kilogram of body weight each day
- This may be further increased to 35mg for each kilogram of body weight each day depending on your child's illness

Children under 20 kilograms
- The usual dose is 20mg for each kilogram of body weight each day
- Depending on the child's condition your child's doctor may decide to increase this dose

Patients with kidney problems
- Your doctor may decide to adjust your or your child's dose

Patients taking other medicines for 'fits' (epilepsy)
- You or your child may be taking other medicines for epilepsy at the same time as Epilim. If so, your doctor should gradually initiate treatment depending on you or your child's condition
- Your doctor may increase the dose of Epilim by 5 to 10mg for each kilogram of body weight each day depending on which other medicines you are taking

If you take more Epilim than you should
If you take more Epilim than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken.
The following effects may happen: feeling sick or being sick, pupils of the eye become smaller, dizziness, loss of consciousness, weak muscles and poor reflexes, breathing problems, headaches, fits (seizures), confusion, memory loss and unusual or inappropriate behaviour.

If you forget to take Epilim
If you forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Epilim
Keep taking until your doctor tells you to stop. Do not stop taking Epilim just because you feel better. If you stop your fits may come back.

Tests
Make sure you or your child keep your regular appointments for a check up. They are very important as your or your child's dose may need to be changed. Epilim can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly. If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Epilim.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Epilim can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:
- You have an allergic reaction. The signs may include: a rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.
- Liver problems and problems of the pancreas may show as a sudden illness which may happen in the first six months of treatment. This happens in a very small number of people taking Epilim. It includes feeling and being sick many times, being very tired, sleepy and weak, stomach pain including very bad upper stomach pain, jaundice (yellowing of the skin or whites of the eyes), loss of appetite, swelling (especially of the legs and feet but may include other parts of the body), worsening of your fits or a general feeling of being unwell. Your doctor may tell you to stop taking Epilim immediately if you have these symptoms
- You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'
- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome'
- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis'
- Bruising more easily and getting more infections than usual. This could be a blood problem called 'thrombocytopenia'. It can also be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots
- Blood clotting problems (bleeding for longer than normal), bruising or bleeding for no reason
- Changes in mood, loss of memory, lack of concentration and deep loss of consciousness (coma)
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism)
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion)

Tell your doctor as soon as possible if you have any of the following side effects:
- Changes in behaviour including being very alert, and sometimes also aggressive, hyper-active and unusual or inappropriate behaviour. This is more likely if other medicine to treat fits such as phenobarbital and topiramate are taken at the same time or if the Epilim starting dose is high or has been suddenly increased
- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and co-ordination, feeling lethargic or less alert
- Feeling shaky (tremor), sleepy or unsteady when walking or jerky muscle movements
- Feeling tired or confused with loss of consciousness sometimes accompanied by hallucinations or fits
- Blisters with the skin flaking away
- Rapid, uncontrollable movement of the eyes

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet:
- Feeling sick, stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the tablets with food

- Fainting
- Hearing loss
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine
- Acne
- Hair loss which is usually temporary. When it grows back it may be more curly than before
- Hair, including body or facial hair grows more than normal in women
- Skin rash caused by narrow or blocked blood vessels (vasculitis)
- Changes in women's periods and increased hair growth in women
- Breast enlargement in men
- Swelling of the feet and legs (oedema)
- Weight gain - as your appetite may be increased
- Kidney problems, bedwetting or increased need to pass urine
- Headache
- Aggression, agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity, and learning disorder
- Tingling or numbness in the hands and feet

Bone Disorders
There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term antiepileptic medication, have a history of osteoporosis, or take steroids.

Blood tests
Epilim can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Male Fertility
Taking Epilim can be a contributing factor in male infertility.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

United Kingdom
You can also report side effects directly via the Yellow Card Scheme at:
www.mhra.gov.uk/yellowcard

Malta
ADR Reporting, The Medicines Authority, Post-Licensing Directorate, 203 Level 3, Rue D'Argens,
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

By reporting side effects you can help provide more information on the safety of this medicine.

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5. How to store Epilim

Keep out of the sight and reach of children.

Do not take this medicine after the expiry date shown on the blister and carton after EXP. The expiry date refers to the
last day of that month.

Do not remove the tablets from the foil until just before you take them. Do not cut the blister strips. Store in a dry place below 30°C.

Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What Epilim contain
- Each 200mg gastro-resistant tablet contains 200mg of the active substance, sodium valproate
- Each 500mg gastro-resistant tablet contains 500mg of the active substance, sodium valproate
- The other ingredients are povidone (E1201), talc, calcium silicate (E552), magnesium stearate (E572), hypromellose (E464), citric acid monohydrate (E330), macrogol 6000, polyvinyl acetate phthalate, diethyl phthalate, stearic acid (E570), titanium dioxide (E171), amaranth aluminium lake (E123), indigo carmine lake (E132) and hyfroxypropyl cellulose (E463)

What Epilim looks like and contents of the pack
Epilim tablets are round and lilac coloured. The tablets are supplied in blister packs of 100

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sanofi
One Onslow Street
Guildford
Surrey
GU1 4YS
UK
Tel: 0845 372 7101
email: uk-medicalinformation@sanofi.com

Manufacturer
Sanofi-aventis S.A,
Carretera C-35 (La Batlloria-Hostalric), Km 63.09
17404 Riells i Viabrea (Girona)

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last revised in February 2015

There are two organisations that will also be happy to try and answer any general questions on epilepsy. They can be
contacted at:

Epilepsy Action, New Anstey House, Gate Way Drive, Yeadon, Leeds, LS19 7XY
Telephone: 0808 800 5050. Website:
www.epilepsy.org.uk

National Society for Epilepsy (NSE), Chesham Lane, Chalfont St Peter, Bucks, SL9 0RJ
Telephone: 01494 601400.
Website:www.epilepsynse.org.uk

170 x 315 mm
678907

[redacted]
02/05/2017 09:13 a.m.

To: [redacted]
cc:
bcc:

Subject: Re: New review of valproate use in pregnancy and women of childbearing age

Dear [redacted]
Thank you for the update.
I would be grateful if you could supply a copy of Sanofi's submission to the PRAC once it is available.
Kind regards
Susan
Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health | [redacted]

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

[redacted]

Dear Ms Kenyon, On March 9, 201... 02/05/2017 01:36:04 a.m.

From: [redacted]
To:
Cc:
Date: 02/05/2017 01:36 a.m.
Subject: New review of valproate use in pregnancy and women of childbearing age

Dear Ms Kenyon,

On March 9, 2017, the European Medicines Agency (EMA) has started a new Art 31 referral for valproate-containing medicines, carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), to review the use of these medicines in the treatment of women and girls who are pregnant or of childbearing age.

This review has been requested by the French Medicines Agency (ANSM) based on data from a French national pharmacoepidemiological study program covering all indications of valproate-containing products (which has been performed in addition to the European Drug Utilization Study (DUS) required by the PRAC as an outcome of the 2014 European referral), together with a national survey conducted in a sample of French pharmacies during the period from April to June 2016, and the advice of psychiatrists specifically consulted by the ANSM. The ANSM has asked the EMA to review the effectiveness of the Risk Minimization Measures (RMMs) for valproate-containing products and to consider whether further EU-wide action should be recommended to further minimize the risk in women who are pregnant or of childbearing age.
The PRAC list of questions to be addressed by Marketing Authorization Holders (6 questions) is published on the EMA website and attached for your information. Sanofi is contributing to this review and has submitted its answer to the list of questions on April 21, 2017.
The next step of the procedure is planned at next June PRAC meeting (to be held from June 5 to 9) where either a PRAC recommendation or an additional list of questions (List of Outstanding Issues) will be issued.
The outcome of this referral could lead to changes in the European SmPC, Patient Information Leaflet (PIL) and current RMMs for valproate-containing medicines. Once the outcome of the referral will be known and depending on that outcome, Sanofi might consider the alignment of its product labeling and RMMs in all countries, and might proceed with the corresponding regulatory

submissions in your country. This would have the objective of maintaining an identical level of information and awareness for both HCPs and patients in all countries worldwide.
As a reminder, the previous European Referral Art 31 ended in November 2014 (CMDh agreement) with the following outcome: *benefit-risk balance of valproate and related substances-containing medicinal products remains favorable subject to amendments to the product information, conditions to the marketing authorizations, including RMMs (guide for prescribers, patient booklet, acknowledgment of risk information form, DHPC) and request for a DUS* . Sanofi amended its Core Labeling to reflect these amendments and submitted related labeling variations in all countries where Sanofi markets valproate-containing medicines. The RMMs beyond routine were also submitted to Health Agencies to ensure a worldwide implementation.
Further to the 2014 referral, additional RMMs have been required by several National Competent Authorities in Europe and Sanofi decided to implement them in all countries where Sanofi markets valproate worldwide. These additional RMMs are: 1) an outer box warning statement regarding the risk in pregnancy, 2) a pregnancy pictogram to be associated to the outer box warning, and 3) a patient card.
In addition in France, based on newly available data from the national pharmacoepidemiological study program, the ANSM decided on March 30, 2017 to contraindicate valproate-containing medicines in the Bipolar Disorder indication in pregnant women and women of child-bearing age not using an effective contraception. This contra-indication is associated with a revision of the outer box pictogram and warning in France.

Sanofi remains available for any further information and will keep you updated as soon as the conclusions of the European referral procedure will be known.

Kind regards

[redacted]

SANOFI

[redacted] 02/05/2017 01:16 p.m.

To: [redacted]
cc:
bcc:

Subject: RE: New review of valproate use in pregnancy and women of childbearing age

Dear [redacted]
Many thanks for the confirmation.
Kind regards
Susan
Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health | (04) 819 6854 |

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

[redacted]

Dear Susan, Sanofi commits to pro... 02/05/2017 12:41:37 p.m.

From: [redacted]
To:
Cc:
Date: 02/05/2017 12:41 p.m.
Subject: RE: New review of valproate use in pregnancy and women of childbearing age

Dear Susan,

Sanofi commits to providing Medsafe with a copy of the PRAC submission when available.

Many thanks & kind regards

[redacted]

SANOFI

[redacted]

From: [redacted]
Sent: Tuesday, 2 May 2017 7:13 AM
To: [redacted]
Cc:
Subject: Re: New review of valproate use in pregnancy and women of childbearing age

Dear [redacted]

Thank you for the update.

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Kind regards

Susan

Susan Kenyon | Principal Technical Specialist - Pharmacovigilance | Clinical Risk Management | Medsafe | Ministry of Health [redacted]

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To: <
Cc: <
Date: 02/05/2017 01:36 a.m.
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As a reminder, the previous European Referral Art 31 ended in November 2014 (CMDh agreement) with the following outcome: *benefit-risk balance of valproate and related substances-containing medicinal products remains favorable subject to amendments to the product information, conditions to the marketing*

authorizations, including RMMs (guide for prescribers, patient booklet, acknowledgment of risk information form, DHPC) and request for a DUS . Sanofi amended its Core Labeling to reflect these amendments and submitted related labeling variations in all countries where Sanofi markets valproate-containing medicines. The RMMs beyond routine were also submitted to Health Agencies to ensure a worldwide implementation.
Further to the 2014 referral, additional RMMs have been required by several National Competent Authorities in Europe and Sanofi decided to implement them in all countries where Sanofi markets valproate worldwide. These additional RMMs are: 1) an outer box warning statement regarding the risk in pregnancy, 2) a pregnancy pictogram to be associated to the outer box warning, and 3) a patient card.
In addition in France, based on newly available data from the national pharmacoepidemiological study program, the ANSM decided on March 30, 2017 to contraindicate valproate-containing medicines in the Bipolar Disorder indication in pregnant women and women of child-bearing age not using an effective contraception. This contra-indication is associated with a revision of the outer box pictogram and warning in France.

Sanofi remains available for any further information and will keep you updated as soon as the conclusions of the European referral procedure will be known.

Kind regards

[redacted]

SANOFI

sanofi aventis

Because health matters

RECEIVED
03 MAR 2010

Regulatory Affairs Dept

26 February 2010

Attn. Ms Abby Cutfield
Advisor, Pharmacovigilance
Clinical Risk Management
MEDSAFE
PO Box 5013
Wellington
NEW ZEALAND

Dear Abby,

RE: **REVIEW OF THE EPILIM DATA SHEET REGARDING USE IN PREGNANCY**

Medsafe File No.'s: TT50-2501/1, TT50-2501/1a, TT50-2501/3, TT50-2501/4, TT50-2501/5, TT50-2501/7, TT50-2501/6

I refer to your letter dated the 14th of January 2010 regarding the recommendations made by the Medicines Adverse Reactions Committee (MARC) at its December 2009 meeting. Specifically, the MARC recommended that the Precautions section of the Epilim data sheets be updated to improve the clarity of the information regarding the use of sodium valproate in pregnancy.

Sanofi-aventis has reviewed the proposal and accepts to implement all suggested changes. Accordingly, enclosed please find the proposed Data Sheets for Epilim and Epilim IV (tracked and clean copies) for your review.

Following reception of your approval of the proposed changes a Changed Medicine Notification will be submitted to Hazel Tompson, as instructed in your letter.

Sanofi-aventis corporate headquarters intend to produce a booklet regarding Epilepsy and Pregnancy for global distribution. This booklet will cover, amongst other topics, the use of sodium valproate in pregnancy. Sanofi-aventis believes that a non-product specific booklet regarding Epilepsy and Pregnancy will be more useful for both doctors and patients. This booklet is expected to be available in the last quarter of 2010.

Should you require further information, please do not hesitate to contact me directly on [redacted]

Yours sincerely,

[redacted]

List of Attachments

Attachment 1: Epilim Data Sheet (highlighted and clean copies)
Attachment 2: Epilim IV Data Sheet (highlighted and clean copies)

sanofi-aventis australia pty ltd ABN 31 008 558 807
Talavera Corporate Centre, Building D, 12-24 Talavera Road, Macquarie Park, NSW 2113 - Tel: ++61 (0) 2 8666 2000 – Fax: ++61 (0) 2 8666 3055 -
www.sanofi-aventis.com.au

[redacted]

8 March 2010

[redacted]
Senior Regulatory Affairs Associate
Sanofi-Aventis Australia Pty Ltd
Locked Bag 2227
North Ryde Business Centre
NSW
AUSTRALIA 1670

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

TT50-2501/1, TT50-2501/3, TT50-2501/4, TT50-2501/5, TT50-2501/7
Epilim EC, Epilim Liquid, Epilim Crushable Tablet, Epilim IV, Epilim Syrup

Dear [redacted]

Re: Review of the Epilim data sheet regarding use in pregnancy

Thank you for your letter dated 26 February 2010 in response to the recommendation of the Medicines Adverse Reactions Committee to improve the clarity of the information provided in the Epilim data sheets regarding use in pregnancy.

I note that Sanofi-Aventis has accepted the wording suggested by Medsafe and intends to make the requested changes to the Epilim and Epilim IV data sheets.

I can confirm that the proposed updated data sheets, as you provided in your letter, are acceptable in terms of the wording in the *Use in Pregnancy* sections. Please proceed with submitting the Changed Medicine Notifications for these changes to Hazel Thomson at Medsafe.

Please keep Medsafe informed of the progress of the global booklet regarding epilepsy and pregnancy. Please forward Medsafe a copy of the booklet for review prior to its distribution in New Zealand.

Kind regards,

Abby Cutfield
Pharmacovigilance Advisor
Medsafe
[redacted]

[redacted]

From: [redacted]
Sent: Tuesday, 20 April 2010 2:29 PM
To: [redacted]
Subject: Re: FW: Review of gingival disorders associated with the use of sodium valproate

Dear [redacted]

Thank you for your e-mail.

I can confirm that Medsafe is satisfied with Sanofi-Aventis' intentions to update the Epilim data sheets in the immediate future with regard to the pregnancy warnings (as requested by the MARC) and the interaction with carbapenem antibiotics (as requested by Medsafe).

I can confirm that Medsafe has granted Sanofi-Aventis with an extension to complete the review of the risk of gingival disorders associated with the use of sodium valproate, and that a response is expected to be received by Medsafe by the end of June 2010.

Kind regards,
Abby

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

[redacted]

02/12/2014 11:54 a.m.

To: [redacted]
cc:
bcc:

Subject: Epilim

Dear [redacted]

Medsafe has noted the recommendations of the recent PRAC review of use of Epilim in pregnancy. Whilst the proposed updates to the SPC are consistent with the NZ data sheet we would like to discuss with you whether Sanofi is considering any changes to the NZ data sheet as a result.
I would also be grateful if you could provide me with any unpublished information that was relevant to the PRAC discussions.
I would be grateful if you could call me on the number below
Kind regards
Susan

Susan Kenyon
Principal Technical Specialist (Pharmacovigilance)
Clinical Risk Management
Medsafe
Ministry of Health
[redacted]

Department of Health
TE TARI ORA

133 Molesworth St
Wellington
New Zealand
P.O. Box 5013, Wellington
Phone (04) 496 2000
Fax (04) 496 2340

142/70/2501
2501/1
2501/2
2501/3
2501/4
2501/5

18 October, 1991

[redacted]
Group Product
Reckitt & Colman (NZ) Ltd
Private Bag
Avondale
AUCKLAND 7

Dear Ms Moser

Data Sheet for Epilim (sodium valproate) products

I have been asked to assess the data sheet for your Epilim medicines. The draft we have on our files are dated January 1989.

In June 1989 Dr Ronaldson wrote to Reckitt & Colman (NZ) requesting inclusion of the risk of spina bifida during pregnancy in the data sheet. This was shortly after your CMN submission to update the data sheet. There is no indication that your updates had been examined at that time.

In order to not repeat the assessment, I would greatly appreciate it if you could send me your latest data sheets on the medicines.

Yours sincerely

Khay Ooi

Khay Ooi
Scientist
Therapeutics Section

P.O. Box 1251, Auckland, N.Z. 21190. Fax (09) 884-648