

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-427**

**OTHER REVIEW(S)**

To: liver

PPTTS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 30, 1995 (Revision of Feb 21 draft)  
FROM: Maternal and Child Health Epidemiologist, HFD-733  
THROUGH: Acting Director,  
Division of Epidemiology and Surveillance HFD-730  
SUBJECT: Consult on teratogenicity of Vigabatrin.  
TO: Director Division of Neuropharmacologic Drugs HFD-120  
ATTENTION: Cynthia McCormick, Division of Neuropharmacologic Drugs HFD-120

This is in response to your consult request on this subject dated February 17, 1995 (attached).

Of the 72 pregnancies listed, 4 were interrupted with no indication of abnormality, and information is lacking on 2 other outcomes. This leaves 66 pregnancies with information on fetal outcome. It is not clear whether any of the 7 spontaneous abortions or the other 12 adverse pregnancy outcomes were retrospectively reported. Adverse outcomes are more likely to be retrospectively reported than normal outcomes. The 12 adverse pregnancy outcomes present 2 cases microcephaly, 1 of cerebral dysgenesis, and 1 dysmorphic syndrome. These 4 had concurrent exposure to carbamazepine or valproate. Prospective cohorts of the latter exposures do not show 4.5% (3 of 66) structural brain defects, but the excess could be easily achieved by bias from including retrospective reports. Conjoined twinning is a very unusual occurrence, but is not remarkable unless a second case is seen. Three cases of twins among 66 outcomes is moderately excessive, but again not remarkable, unless all 3 were monozygous.

The World Health Organization has 10 reports of spontaneous abortion/fetal death with vigabatrin. All of these reports have concurrent exposure with carbamazepine. These could overlap with 2 to 4 of the spontaneous abortions listed by the sponsor. The fetal deaths contrast with only 2 WHO birth defect reports: one "skeletal defects" (concurrent valproate), and the other an specified defect (concurrent carbamazepine).

As the applicant says, clearly the data are insufficient to say that vigabatrin has no more risks than other anti-epileptics, or has more risks. The applicant is fully aware of the need for additional data. I suggest that the following should be implemented in so far as feasible in collecting this data.

1. Clearly distinguish between retrospectively reported and prospectively reported cases.
2. Provide information on birth weight-for-dates.
3. Provide dosages and where possible levels for all antiepileptic agents involved.
4. Clearly specify what is known about any fetal deaths or interrupted pregnancies.
5. Determine whether any further twins are monozygous, or at least whether they are like sexed.
6. Describe all minor dysmorphic features.
7. Follow up cases for neurofunctional development.
8. If this is done on a postmarketing basis, clearly specify how and when reporting will be made available to FDA and the public.

*Franz Rosa*

Franz Rosa, M. D., M. P. H.

Clearance Acting Chief Epidemiology Branch HFD-733

*K. Kelly*

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HFD-733 Chron, vigabatrom, Rosa , *Baresh*  
HFD-120 Potts  
HFD-730  
HFD-700  
HFD-735 Baresh

### Request for Consultation:

Vigabatrin is a new antiepileptic drug. The NDA for this product is currently under review in the Division of Neuropharmacological Drug Products. The compound is an enzyme-activated inhibitor of GABA transaminase.

In animal studies a number of safety findings have been reported. The most troublesome of these is the finding of intramyelinic edema in the brains of mice, rats, dogs and monkeys. The finding of intramyelinic edema has not been evaluated in the immature nervous system with the goal of determining if there is any deleterious effect of this drug on the ability to lay down myelin. The drug has been given to infants outside of the US and there is some in utero exposure as will be discussed further. The sponsor at present is only seeking labeling in adults.

In animal models of reproductive safety, cleft palate was reported in New Zealand White rabbits. There have been reports of adverse pregnancy outcomes in humans in association with the use of vigabatrin during pregnancy ranging from spontaneous abortion to multiple congenital anomalies. Many of the pregnancies reported to date have had normal outcomes (approximately 50%), however the incidence of congenital abnormalities associated with vigabatrin does appear to exceed many of the reported malformation rates among drug treated mothers with epilepsy as seen below in the table adapted from Sponsor's Table A "Malformation Rates in Live Births of Mothers with Epilepsy Related to whether or not Antiepileptic Drug Treatment was Given".

<u>AUTHORS</u>	<u>DRUG TREATED MOTHERS</u>		<u>UNTREATED MOTHERS</u>	
	<u>WITH EPILEPSY</u>		<u>WITH EPILEPSY</u>	
	<u>PREGNANCIES</u>	<u>MALFORMATION RATE</u>	<u>PREGNANCIES</u>	<u>MALFORMATION RATE</u>
Monson 1973	205	5.3%	101	2.3%
Annegers 1974	141	7.1%	56	1.8%
Nakane 1980	3703	7.1%	825	4.5%
Dansky 1982	114	15.9%	50	6.5%
Lindhout 1992	170	9.9%	14	7.0%
Koch 1982	89	10.0%	20	7.0%

There have been 72 pregnancies reported to this NDA. Of these, 10 resulted in early termination (at least 7 spontaneously), 4 had unknown outcomes, and 9 (12.5%) had either obvious congenital malformations or had abnormal development on followup. For many of the pregnancies there is insufficient information to determine outcome. There have been reports of severely abnormal pregnancy outcomes including, a child with multiple congenital abnormalities (intraventricular agenesis of the cardiac septum, pulmonary artery atresia, microcephaly and spina bifida), a child with microcephaly dorsolumbar meningocele, conjoined twins, and diaphragmatic hernia with death in 24 hours. The outcomes of the pregnancies associated with vigabatrin are summarized in the table on the following page which includes time of exposure and concomitant AED use.

**Table: Pregnancy Outcomes in Vigabatrin-exposed Mothers  
(NDA + Safety Update)**

<i>Pt ID</i>	<i>Dose VGB</i>	<i>Trimesters Exposed</i>	<i>Other AEDs</i>	<i>Comments</i>
21204	3g	1,2,3	CBZ	38/40 week ND male
—	unk	unk	unk	Bilateral cleft palate
93012948	unk	unk	CBZ,PB	Cardiac anomaly, Spina bifida, Microcephaly
101268	3g	3	VPA	Cerebral dysgenesis-seizures
—	2g	1,2,3	CBZ	Club feet-mild
21208	3g	1,2,3	CBZ	Congenital hip dysplasia
93-92-003	2g	1,2,3	CBZ	Died at 24 hrs/diaphragmatic hernia
93-92-008	unk	1,2,3	V P A , P R M , Propranolol	Died: intracerebral hemorrhage
21208	3g	1,2,3	CBZ	Difficulty feeding;SGA; microcephaly;undescended testiclestrabismus, congenitalhip dysplasia
—	3g	1,2,3	CBZ, CLZ, PB	Elective CS (no information about infant)
0753160	4g	1,2,3	CBZ	FT
—	unk	unk	unk	FT (little information)
—	unk	1,2,3	CBZ	FTN
1355038	unk	unk	unk	FTND
308055	unk	1	unk	FTND
—	1g	1,2,3	CBZ	FTND
—	1g	2,3	CBZ	FTND
-25 yrs	3g	1,2,3	VPA	FTND female
—	4.5g	1st only	PHT, LTG	FTND female
615964	1g	1,2,3	CBZ,CLB, PB	FTND female
64-87-00106	1g	1st only	CBZ, PB	FTND female
7717738	unk	1st only	unk	FTND female
909785	3g	1,2,3	PB	FTND female
91-033	1g	1,2,3	CBZ	FTND female
94-103	3g	1,2,3	VPA	FTND female
—	1g	1,2,3	unk	FTND female
—	unk	1st only	CBZ	FTND female
UK07	1g	1st only	CBZ, PHT	FTND female
UK09	2g	1st only	CBZ	FTND female
UK11	3g	1,2,3	VPA	FTND female
UK12	1g	1st only	PHT	FTND female
UK13	1.5g	1st only	CBZ	FTND female
—Age 20	1g	1	CBZ, PB	FTND male
30430410	3g	1st only	CBZ, PHT	FTND male
56-92-001	2.5g	1st only	none	FTND male
781002	unk	1,2,3	unk	FTND male
—	1-2g	1,2,3	CBZ,VPA,CLZ	FTND male
91-062	1.5g	1,2,3	CBZ	FTND male
959378	3g	1,2,3	PHT	FTND male
96-92-00214	2g	1,2,3	CBZ	FTND male
—	3g	1,2,3	none	FTND male
—	2.5g	1,2,3	CBZ, CLB	FTND male
—	unk	1st only	PRM, PB	FTND male
—	1g	1,2,3	CLB	FTND male
—	1g	1st only	CBZ, PHT	FTND male

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UK06	4g	1,2,3	CBZ, CLB	FTND male
0909785	3g	1,2,3	PB	FTND-strabismus
25807	3g	1,2,3	PB, CBZ, VPA	Hyperkinetic/ delayed speech
93-89-001	2.5g	1,2,3	CBZ	Hypospadias , clinodactyly, dysmorphism syndrome,
93-92-002	2g	1,2,3	unk	Neonatal seizures (no further information)
93-92-005	5g	1,2,3	OCBZ	No information
	unk	1,2,3	unk	No information
	3g	>1,2,3	PHT	No information
	1.5g	1,2,3	unk	No information
9400-1377	unk	unk	VPA	Normal
	3g	1,2,3	PB, CLP	Normal male (C-section)
93-92-004	unk	unk	unk	Premature (no further information)
93-92-001	unk	1,2,3	CBZ	Premature; maternal diabetes
93-92-002	5g	1,2,3	OCBZ	Second pregnancy, No information
303301	3g	1st only	PB	Spontaneous abortion
93-92-007	unk	1st only	CBZ, VPA	Spontaneous abortion
	1g	1st only	CBZ, LTG	Spontaneous abortion
	1.5g	1st only	CBZ, VPA	Spontaneous abortion
UK08	4g	1st only	CBZ, PHT	Spontaneous abortion
UK16	3-2g	1st only	CBZ	Spontaneous abortion
	2g	1st only	CBZ	Spontaneous abortion
	unk	unk	unk	Spontaneous abortion
92-037	unk	unk	unk	Therapeutic abortion
	3g	1	unk	Therapeutic abortion
93-92-006	2g	1,2,3	CBZ, PHT, PR	Therapeutic abortion
64-92-00243	.5g	1st only	M	
8650915	1g	1,2,3	unk	Twin pregnancy
			CBZ, PB	Twins-conjoint at head
			CBZ	Twins-premature

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While the known malformation rate calculated from the information gleaned from various sources was 12.5% (this does not include spontaneous abortions), it must be pointed out that for many of the pregnancies there is little or no information provided, so that this rate may be falsely low. Nevertheless as it stands it is still within the range reported for malformations in the sources quoted above.

Additional reports received through the IND 17.213 (Vigabatrin) have included the following reports:

Pt ID	Dose	VGB	Trimesters Exposed	Other AEDs	Comments
94007330	unk	unk	unk		Delayed speech at 3 years old
95000301	unk	unk	unk		Shuddering when handled
95000320	3g	1,2,3	none		VSD
94007123	unk	unk	VPA/cbz		Premature, Musculoskeletal probs

Questions:

- 1-As this information stands, albeit incomplete, can you say anything about the teratogenic potential of this new drug?
- 2-Is the incidence of multiple births more than expected?
- 3-Could you suggest any further evaluation which the sponsor could initiate, if this drug were to be marketed, to better define its teratogenicity vs contributions from other drugs vs.

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