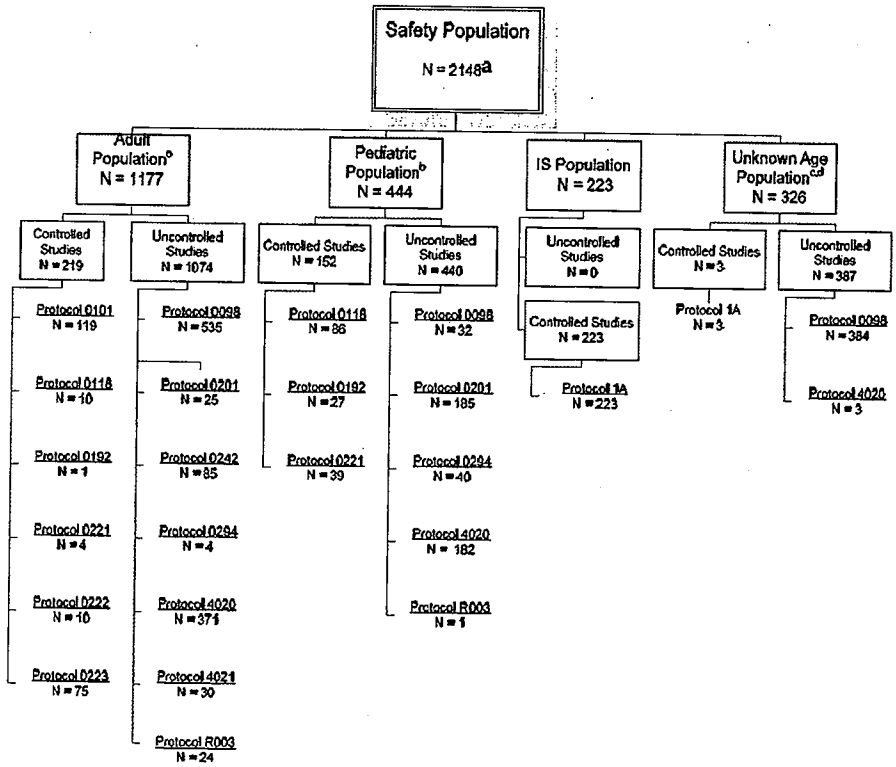

[a] Overall safety population (n=2148) is comprised of 1177 adult subjects; 444 pediatric subjects; 223 infants; 326 subjects of unknown age minus 3 infants included in the IS population; minus 19 subjects included in both the adult and pediatric subpopulations (2148=1177+444+223+326-19-3).
[b] 19 subjects are included in both the adult and pediatric subpopulations.
[c] Excludes 3 subjects of unknown age counted in the IS subpopulation.
[d] Excludes 64 subjects in 0098 since age was determined from patient's enrollment in prior study.

Integrated Data

Ovation explained the source of the denominators they used in different safety data AE analyses. Ovation limited their Integrated Data analyses to epilepsy trials (no data included from clinical pharmacology trials or trials for indications other than epilepsy). Ovation presented three separate totals of subjects exposed to vigabatrin for different analyses and explains that the different totals result from the way safety data were presented in previous submissions. Ovation explains that for the purpose of analyzing AEs they use a total of 4,077 subjects exposed to vigabatrin, for the analyses of SAEs they use a total of 4,739 subjects, and for the analyses of discontinuations due to AEs and deaths they use a total of 4,855 subjects. Ovation explains that the cumulative totals differ for the different analyses because they relied on the previous sponsor's analyses that integrated only the US and primary non-US studies for AE analyses but integrated US, primary non US, and secondary non US studies for SAEs, discontinuations and deaths. The difference in exposure for the SAE analyses compared to the analyses of

discontinuations and deaths is due to the fact that Ovation presented the SAEs from studies 0098 and 4021 separately.

In their description of the integrated data, Ovation provided tables that included numbers of subjects exposed to vigabatrin for the regulatory submissions (5/97-NDA amendment, 1/98-Final Safety Update, NDA Amendment + Final Safety Update, Current submission, and the total across all submissions). As an example, I provide one such table below:

Table 4. Integrated Safety Population for Adverse Events (N=4077)

Submission Date	Reporting Period	N	Identified as
December 2007	Integrated Data (Current + Prior)	4077	Combined
	Currently Reported Data		
December 2007	16 March 1997 – 30 June 2007	2148	Period 2
	Prior Reported Data		
20 January 1998 Safety Update + 29 May 1997 Amendment	2 prior reporting periods combined: 16 March 1994 – 15 March 1997	2662 (2605[b] + 57)	Period 0 + 1
20 January 1998	1 January 1996 – 15 March 1997 Safety Population Infantile Spasms Studies (primary non-US)	1667[a] + 57	Period 1
29 May 1997	16 March 1994 – 31 December 1995 NDA Amendment (US, non-US primary studies)	1208	Period 0

[a] Infantile Spasms subjects excluded and addressed as a special population in the 20 January 1998 Safety Update.

[b] 1208 subjects from the 1997 NDA Amendment, 1667 subjects from the 20 January 1998 Safety Update, minus 733 subjects who participated in more than one study (Integrated Summary of All Adverse Events, Safety Update, 20 January 1998).

The differences in the exposure totals listed above when compared to the exposure totals from **previous submissions is due to the fact that Ovation's Integrated Data analyses are restricted to** epilepsy trials. For example, in Table 4 above Ovation identifies 1,208 subjects exposed to vigabatrin in US and primary non US studies in the NDA Amendment. In the Division review of the NDA Amendment, the previous sponsor reported that 1,726 subjects were exposed to vigabatrin in US and primary non US studies. The reason for this discrepancy is that Ovation did not include safety data for subjects from clinical pharmacology studies or studies for indications other than epilepsy (Response to Reviewer questions, 2/11/08).

In Amendment Tables 5 and 6 (not shown), Ovation reports that for the SAE, discontinuation for AE and death analyses, 1,942 subjects were exposed during studies reported in the NDA Amendment submission. The reason for this apparent discrepancy is that for these analyses, Ovation also included subjects in the Secondary (epilepsy) studies database (Response to Reviewer questions, 2/11/08).

7.2.1.2 Demographics

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

According the Amendment review, the sponsor did not provide a separate demographic profile for US studies in the NDA or the NDA Amendment. In the NDA Amendment, the sponsor provided table B-27 that summarized demographic factors for subjects enrolled in the non-US primary studies. I summarize that information in the table below.

Summary of Demographics for All Subjects Enrolled in Non-US Primary Studies						
	Clinical Pharmacology		Epilepsy		Other indications	
Demographic factor	Epilepsy patients N=25 % (n)	Non epilepsy patients N=154 % (n)	Controlled N=396 % (n)	Uncontrolled N=461 % (n)	Total N=254 % (n)	Total N=1290 % (n)
Sex						
Male	52% (13)	83% (128)	52% (205)	50% (228)	51% (130)	55% (704)
Female	48% (12)	12% (18)	48% (191)	41% (188)	47% (120)	41% (529)
Unknown	0	5% (8)	0	10% (45)	2% (4)	4% (57)
Age (years)						
Mean ±SD	31.8±9.3	32.8±19.8	31.8±10.4	24.2±15	40.4±23.5	30.9±17.4
Range	16, 47	18, 97	10, 64	0, 70	0, 87	0, 97
<2	0	0	0	2% (7)	13% (34)	3% (41)
2-<12	0	0	1% (5)	25% (113)	4% (9)	10% (127)
12-<16	0	0	2% (6)	5% (22)	1% (3)	2% (31)
16-<40	76% (19)	77% (118)	75% (297)	54% (248)	24% (62)	58% (744)
40-<65	24% (6)	7% (10)	22% (86)	14% (66)	41% (103)	21% (271)
≥65	0	10% (15)	0	1% (3)	15% (39)	4% (57)
Unknown	0	7% (11)	<1% (2)	<1% (2)	2% (4)	2% (19)
Race						
Caucasian	100% (25)	51% (79)	64% (255)	36% (168)	0	41% (527)
Black	0	0	0	0	0	0
Other	0	0	<1% (1)	<1% (1)	0	<1% (2)
Unknown	0	49% (75)	35% (140)	63% (292)	100% (254)	59% (761)

Safety Update, Cutoff Date 3/15/97

According to the Safety Update review, the demographics of the population exposed in the 14 completed trials were similar to the demographics of the population described in the NDA amendment. Except for the clinical pharmacology study and the infantile spasm trials, roughly equal numbers of males and females were exposed, most subjects were between the ages of 16 and 40, and most were Caucasian.

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation provided Table 8 summarizing demographic factors for the subjects enrolled in the Safety Update trials in the current submission. I provide data from Table 8 below.

Demographics Overall Safety Population, 12/28/07 Submission						
	Controlled		Uncontrolled	Long Term		Total
	US N=566	Non-US N=28	Non-US N=611	US N=1169	Non-US N=44	N=2148
Sex	N=564	N=28	N=611	N=1158	N=44	N=2135
Male	49% (276)	43% (12)	51% (312)	51% (590)	46% (20)	50% (1074)
Female	51% (288)	57% (16)	49% (299)	49% (568)	54% (24)	50% (1061)
Age, years	N=563	N=28	N=608	N=815	N=44	N=1822
Mean (SD)	16.3 (17.6)	11.2 (3.3)	28.7 (15.8)	29.1 (14.9)	11.4 (3.3)	25.3 (17.1)
Range	0.1-66	5.0-16	7.7-74.7	3-78	4-16	0.1-78
Race	N=566	N=28	N=611	N=1169	N=44	N=2148
Caucasian	82% (465)	96% (27)	9% (53)	89% (1039)	100% (44)	65% (1386)
Black	10% (58)	4% (1)	0	7% (84)	0	6% (122)
Other	8% (43)	0	<1% (1)	3% (35)	0	3% (72)
Unknown	0	0	91% (557)	1% (11)	0	26% (568)

Integrated Data

Ovation did not provide a summary of demographic data for the Integrated population.

7.2.1.3 Extent of exposure (duration/dose)

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Duration
The presentations in the NDA and NDA Amendment suggest that 679 subjects were exposed to vigabatrin for at least 6 months and 286 subjects were exposed to vigabatrin for at least 1 year in the US and non-US primary studies. The following table summarized the exposure by duration data for the US and primary non-US study populations.

Exposure by Duration, US and non-US Primary studies through 12/31/95, NDA Amendment

	Primary US		Primary Non US					
VGB Duration	Controlled Epilepsy	Open label Epilepsy	Clin Pharm Epilepsy	Clin Pharm Other	Controlled Epilepsy	Open label Epilepsy	Other	Total
≥2weeks	220	412	13	2	335	425	208	983
≥1month	217	407	13	0	330	414	155	912
≥3months	197	391	0	0	167	355	85	607
≥6months	0	307	0	0	89	229	54	372
≥1year	0	157	0	0	20	76	33	129
≥2years	0	40	0	0	0	19	4	23
≥4years	0	31	0	0	0	0	0	0
≥6years	0	26	0	0	0	0	0	0

Unknown	1	0	N/A	N/A	N/A	N/A	N/A	N/A
Total	**221**	**414**	**25**	**153**	**335**	**430**	**246**	**1189**

Source: Amendment review 10/28/97, attachment p.20 and attachment table B-19

Dose

Although the data were not presented in a manner that would allow an exact determination of exposure by dose, there appears to have been roughly 1,000 subjects in the US and non-US primary trials exposed to a maximum vigabatrin dose of at least 2.5g/day. The following table summarizes the exposure by maximum dose data for the US (controlled, open label) and primary non-US studies as presented in the NDA and NDA Amendment.

Exposure by Dose, US and non-US Primary studies through 12/31/95, NDA Amendment

	Primary US		Primary Non US					
VGB Dose (g/day)	Controlled Epilepsy	Open label Epilepsy	Clin Pharm Epilepsy	Clin Pharm Other	Controlled Epilepsy	Open label Epilepsy	Other	Total
0.5-<1.5	44	2	0	59	3	47	19	128
1.5-<2.5	0	13	0	21	126	116	115	378
2.5-<3.5	134	257	13	26	161	195	66	461
3.5-<4.5	0	80	12	47	45	47	31	182
4.5-<5.5	0	12	0	0	0	5	3	8
5.5-<6.5	44	48	0	0	0	11	9	20
>=6.5	0	1	0	0	0	9	3	12
Total	**222**	**414**	**25**	**153**	**335**	**430**	**246**	**1189**

Source: Amendment review 10/28/97, attachment p.21 and attachment table B-23

Safety Update (Cutoff Date 3/15/97)

The Final Safety Review did not summarize exposure by dose or duration.

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Duration

Ovation provided table 9 (p.39) documenting that 1,268 subjects from the Overall population had exposure to vigabatrin for greater than 6 months and 1,058 had exposure greater than 1 year. This table also documents that 599 subjects had missing data (573 from long term US studies) that did not allow determination of the duration of exposure. I provide duration of exposure data from Ovation's table 9 below.

Duration of Exposure, Overall Safety Population, 12/28/07 Submission						
	Controlled		Uncontrolled	Long Term		Total
Duration	US N=566	Non-US N=28	Non-US N=611	US N=1169	Non-US N=44	N=2148

1-14 days	6	0	3	8	0	16
>14-30 days	21	0	5	18	2	40
>30-60 days	56	0	8	10	1	47
>60-90 days	50	3	8	19	1	48
>90days-6months	170	21	23	64	36	130
>6 months-1 year	58	4	41	82	4	210
>1-2 years	144	0	72	139	0	305
>2-3 years	42	0	56	208	0	294
>3-5 years	13	0	136	48	0	220
>5-10 years	0	0	196	0	0	196
> 10 years	0	0	43	0	0	43
Missing	6	0	20	573	0	599

Note: Percentages are with respect to the number of subjects exposed for each study type.
Note: For subjects that participated in multiple studies, exposure duration are represented in each study separately **and then represented in the "Total" column for the patients total exposure duration.**

Integrated data

In response to a question from the Division, Ovation reported in the 5/1/08 submission that 3,476 epilepsy subjects were exposed for at least 6 months, and 2,758 were exposed for at least 1 year (Source 5/1/08 submission, p.140).

Dose and Duration

Overall Safety Population

In response to a request by the Division dated 3/14/08, Ovation provided a table summarizing exposure by dose and duration for the Overall population. I provide that information below.

	Vigabatrin Dose (g/day)									
Time	**0***	**>0 to<1**	**>1 to<2**	**>2 to<3**	**>3 to<4**	**>4 to<5**	**>5 to<6**	**>6 to<7**	**>=7**	**Unknown**
<=1week	188	381	386	302	43	20	14	5	4	42
1 wk to 1 mo	9	467	465	153	46	47	27	12	4	32
>1 to 3 mos	2	104	187	110	85	51	35	23	11	14
>3 to 6 mos	2	42	90	56	136	31	15	17	3	7
>6 to 9 mos		12	43	29	50	16	8	2		4
>9 to 12 mos	1	13	26	12	12	7	3	6		2
>12 to 18 mos	1	20	34	16	8	14	8	4	1	1
>18 to 24 mos	1	8	11	4	5	2	2	6		3
>24 to 36 mos			7	7	5	2		2		1
>36 to 48 mos			1	3						
>48 to 60 mos				1	1					
>60 to 72 mos				1	3					
>72 to 84 mos					1					
>84 mos					6					
Total pt days	2232	40438	79253	51955	83624	23475	11638	13474	1529	6927
Total pt years	6.11	110.71	216.98	142.25	228.95	64.27	31.86	36.89	4.19	18.97

*0 refers to time off drug, not Placebo

1-14 days	6	0	3	8	0	16
>14-30 days	21	0	5	18	2	40
>30-60 days	56	0	8	10	1	47
>60-90 days	50	3	8	19	1	48
>90days-6months	170	21	23	64	36	130
>6 months-1 year	58	4	41	82	4	210
>1-2 years	144	0	72	139	0	305
>2-3 years	42	0	56	208	0	294
>3-5 years	13	0	136	48	0	220
>5-10 years	0	0	196	0	0	196
> 10 years	0	0	43	0	0	43
Missing	6	0	20	573	0	599

Note: Percentages are with respect to the number of subjects exposed for each study type.
Note: For subjects that participated in multiple studies, exposure duration are represented in each study separately **and then represented in the "Total" column for the patients total exposure duration.**

Integrated data

In response to a question from the Division, Ovation reported in the 5/1/08 submission that 3,476 epilepsy subjects were exposed for at least 6 months, and 2,758 were exposed for at least 1 year (Source 5/1/08 submission, p.140).

Dose and Duration

Overall Safety Population

In response to a request by the Division dated 3/14/08, Ovation provided a table summarizing exposure by dose and duration for the Overall population. I provide that information below.

	Vigabatrin Dose (g/day)									
Time	**0***	**>0 to<1**	**>1 to<2**	**>2 to<3**	**>3 to<4**	**>4 to<5**	**>5 to<6**	**>6 to<7**	**>=7**	**Unknown**
<=1week	188	381	386	302	43	20	14	5	4	42
1 wk to 1 mo	9	467	465	153	46	47	27	12	4	32
>1 to 3 mos	2	104	187	110	85	51	35	23	11	14
>3 to 6 mos	2	42	90	56	136	31	15	17	3	7
>6 to 9 mos		12	43	29	50	16	8	2		4
>9 to 12 mos	1	13	26	12	12	7	3	6		2
>12 to 18 mos	1	20	34	16	8	14	8	4	1	1
>18 to 24 mos	1	8	11	4	5	2	2	6		3
>24 to 36 mos			7	7	5	2		2		1
>36 to 48 mos			1	3						
>48 to 60 mos				1	1					
>60 to 72 mos				1	3					
>72 to 84 mos					1					
>84 mos					6					
Total pt days	2232	40438	79253	51955	83624	23475	11638	13474	1529	6927
Total pt years	6.11	110.71	216.98	142.25	228.95	64.27	31.86	36.89	4.19	18.97

*0 refers to time off drug, not Placebo

The table illustrates that the majority of exposure in terms of duration for the Overall population occurred at >1 g/day to <4g /day (70%, 588.18PY/836.1PY).

Integrated Data
The Division requested a table displaying dose and duration information for the Integrated population. In a response dated 3/14/08, Ovation provided a table summarizing exposure by dose and duration for the Integrated population. I provide that information below.

	Vigabatrin Dose (g/day)									
Time	**0***	**>0 to<1**	**>1 to<2**	**>2 to<3**	**>3 to<4**	**>4 to<5**	**>5 to<6**	**>6 to<7**	**>=7**	**Unknown**
<=1week	373	738	975	749	190	75	40	25	7	143
1 wk to 1 mo	60	642	2432	1296	297	175	103	21	2	105
>1 to 3 mos	17	186	676	1280	1119	498	195	82	8	54
>3 to 6 mos	5	72	250	412	541	280	118	53	9	42
>6 to 9 mos	1	22	117	169	273	133	59	33	6	39
>9 to 12 mos	3	15	62	146	231	105	34	28	5	42
>12 to 18 mos	5	22	58	105	250	101	32	39	2	101
>18 to 24 mos	1	5	23	40	133	68	6	31	3	138
>24 to 36 mos	1	4	16	46	99	35	10	19	2	87
>36 to 48 mos			3	12	41	16	7	18	1	
>48 to 60 mos				5	21	4		4		1
>60 to 72 mos			1	1	16	4				
>72 to 84 mos					8	1				
>84 mos				1	12	8				
Total pt days	7873	57485	218515	384511	744180	321729	88842	113649	10526	240384
Total pt years	21.6	157.4	598.3	1052.7	2037.5	880.9	243.2	311.2	28.8	658.1

*0 refers to time off drug, not Placebo

The table above illustrates that 86% of person time exposure was to vigabatrin doses ranging from 1g/day to less than 5g/day. Less than 14% of person time exposure to vigabatrin was at doses >=5g/day.

In response to a question from the Division, Ovation reported in the 5/1/08 submission that 1,112 epilepsy subjects were exposed to a vigabatrin dose between 3 to <4g/day for at least 6 months, and 587 subjects were exposed to a vigabatrin dose between 3 to <4g/day for at least 1 year (Source 5/1/08 submission, p.140).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

In the original NDA review, the Division reviewer documented that the sponsor submitted safety data for subjects from non US studies that did not have available case report forms and this was one of the reasons for not approving the NDA. In response to this identified deficiency, the

sponsor collected and reviewed available CRFs from non US study sites. Some CRFs were located and others were not. In instances where some but not all CRFs were located for a given study, the data for patients with CRFs were grouped into a cohort called Secondary data (n=968). Another cohort was created to include data for those patients for whom CRFs were not located (non-CRF data, n=925). In addition to "Secondary Data" and data from non-CRF supported studies, the sponsor submitted data from compassionate use programs.

Current Submission

Ovation did not identify any secondary data sources in their current submission.

7.2.2.1 Other studies

Ovation did not identify any data from other studies in their current submission.

7.2.2.2 Post marketing experience

Exposure
Ovation gathered post marketing exposure estimate data from Periodic Safety Update Reports written by Aventis. Ovation provided 2 tables with exposure information. Table 1 (12/28/07 submission, Postmarketing section, p.6) summarized exposure in patient months by region for the years 1989-1994. This table provided sales data that were converted to person time (patient months) estimates using the assumed daily dose of 2g/day. The estimated person time exposure for this interval was 166,377 person years (1,996,533 patient months). Table 2 provided estimates of the number of patients exposed for each year from 1992 through 2004. These estimates were created using sales data and were based on the assumptions of an average daily dose of 2g/day and an average duration of treatment of 6 months. I converted these patient estimates to person time estimates by multiplying the number of patients by 6 months (the average estimate of use) and then dividing by 12months (to convert to years). For the period of 1995-2004 (not covered in table 1), I estimated 616,906 person years of use. Summing the data from tables 1 and 2, I estimated a total of roughly 783,000 person years of use from 1989-2004.

In their 5/16/08 submission, Ovation responded to a Division request for estimates of use for 2005-2007. Ovation reported that for 2005, the estimated number of patients exposed to vigabatrin was 59,742. Based on the assumption of 6 months of use per patient as above, the estimated vigabatrin use for 2005 is 29,871 person years. For 1/06-6/06 Ovation estimated 14,794 person years of vigabatrin use and for 7/06-7/07 Ovation estimated 28,219 person years of use. Adding the person year estimates for 2005-6/07 (72,884 PYs) to the exposure estimate for 1989-2004 (783,000 PYs), yields an estimated person time exposure for 1989-6/07 of roughly 856,000 patient years exposure.

The exposure information from Ovation demonstrates that vigabatrin use peaked in 1998 and declined yearly since (with the exception of 2003). The first publication of vigabatrin related visual field defect cases occurred in 1997. The table below includes information from Ovation's

Table 2 included in the post marketing section of their current submission and data from their response to Division questions (5/16/08).

Estimated Number of Patients Exposed from Marketed Use of Vigabatrin 1992 through 2004

Worldwide Patient Exposure / Year						
1992	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**
50,546	87,638	108,762	126,989	137,193	153,152	162,958
1999	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
151,992	119,024	98,577	84,672	114,611	84,648	59,742
1/06-6/07*						
86,026						

Exposure was calculated based on the assumption that each patient received 2 grams (4 tablets daily) for 6 months (183 days).
*Includes 18 months of data
Source Data: PSUR No. 13, 14, 15 (Appendix 3); Submission 8/16/08, p14.

Reports
Current submission
Ovation identified 1791 reports for the period 3/15/97-6/30/07 from the following sources: spontaneous reports (n=1466), medical literature (n=206), regulatory agencies (n=24), and unknown (n=95).

I provide demographic and indication information for the reports in the following table.

Table 3. Demographic and Baseline Characteristics of Patients Described in Vigabatrin Postmarketing Adverse Event Reports

Variable	Vigabatrin Reports[1] (N=1791) n (%)
Gender	
Male	747 (41.7)
Female	822 (45.9
Unknown	222 (12.4)
Age Groupings	
< 2 Yrs	92 (5.1)
2 to <12 Yrs	177 (9.9)
12 to <16 Yrs	68 (3.8)
16 to <40 Yrs	524 (29.3)
40 to <65 Yrs	366 (20.4)
>= 65 Yrs	46 (2.6)
Unknown	518 (28.9)
Race	
Asian	1 (0.1)
Caucasian	1 (0.1)
Other	1 (0.1)
Unknown	1788 (99.8)
Reported Indication for VGB Use	

Infantile spasms	53 (3.0)
Partial seizures[2]	134 (7.5)
Generalized seizures, and seizures NOS[3]	950 (53.0)
Other reported indications [4]	20 (1.1)
Unknown	634 (35.4)

NOS = not otherwise specified.
1 Includes events reported between 15 March 1997 and 30 June 2007
2 Partial seizures include the following indication terms: Complex partial seizures, Frontal lobe epilepsy, Partial seizures, Simple partial seizures, Temporal lobe epilepsy.
3 Generalized seizures include the following indication terms: Convulsion, Epilepsy, Grand mal convulsion, Petit mal epilepsy, Status epilepticus.
4 Other (non-seizures) include the following indication terms: Accidental exposure, Cerebral palsy, Congenital toxoplasmosis, Drug exposure during pregnancy, Electroencephalogram abnormal, Encephalopathy, Muscle spasms, Post herpetic neuralgia, Post-traumatic epilepsy, Sturge-Weber syndrome, Tuberous sclerosis.

Source NDA Amendment 12/28/07, Post Marketing Reports Section, p.8

Ovation reported that the top 5 countries with spontaneous adverse event reports were France (n=313), Great Britain (n=272), Australia (n=107), Canada (n=97), and Denmark (n=91). (Source NDA Amendment 12/28/07, Post Marketing Reports Section, p.7)

7.2.2.3 Literature

As part of the 12/28/07 amendment submission, Ovation provided a review of the medical literature. Ovation divided their presentation of vigabatrin related medical literature into publications discussing complex partial seizures and publications discussing infantile spasms. Ovation hired NERAC Inc. to search the medical literature. The searches spanned from the inception of the individual literature databases to June 30, 2007. NERAC Inc. searched the following databases: BIOSIS Previews (1972-Present), CAB Abstracts (1968-Present), Conference Papers Index (1973-Present), Embase (1974-Present), International Pharmaceutical Abstracts (1970-Present), Life Sciences Collection (1978-Present), MEDLINE (1966-Present), PsychINFO (1983-Present). NERAC used the following search terms: vigabatrin, infantile spasms, West syndrome, Tuberous sclerosis, and vigabatrin and prednisone or ACTH. Ovation discussed only the publications subsequent to 3/97 since earlier publications were discussed in the NDA.

CPS results
Ovation reported that the literature search identified 46 publications discussing the use of vigabatrin in CPS or other seizure disorders. The 46 publications were comprised of 13 journal articles, 6 case reports, 17 review articles, and 10 other publications.

Ovation identified 3 double blind placebo controlled trials. The publication by Spanaki et al did not present adverse event data. The publications by Bruni et al and Dean et al did provide AE data. Bruni et al identified the following events that occurred at least twice a frequently in vigabatrin subjects compared to placebo subjects: vision abnormal, diplopia, amnesia, ataxia, vertigo, speech disorder, aggressive reaction, and weight increased. Dean et al identified the following AEs occurring at least twice as frequently among vigabatrin subjects compared to placebo: nystagmus, agitation, amnesia, confusion, depression, abnormal coordination, diarrhea,

parasthesia, hyporeflexia, asthenia, diplopia, abnormal gait, abnormal thinking, and impaired concentration.

Ovation identified 10 publications reporting results from open label studies with vigabatrin. Seven of these publications dealt with ophthalmologic findings. The remaining publications reported AEs similar to those reported in the Amendment.

Of the 6 case reports, 3 were described ophthalmologic changes and one described MRI findings. Garcia Pastor et al described a 69 year old female that developed acute encephalopathy, psychotic state, and generalized myoclonic status after 4 months on vigabatrin. The patient's condition improved 24 hours after stopping vigabatrin. A report by Sorri et al described physical exam, neurological exam and ophthalmologic findings in 2 individual exposed to vigabatrin in utero. The first child's mother was treated with carbamazepine and vigabatrin through week 22 of pregnancy. At birth, the child required supplemental oxygen and a feeding catheter. At age 7, the child was described at normally developed, with retrognathis, large ears, and irregular tooth placement, and with normal neurological and ophthalmologic exams. The second child's mother was treated with carbamazepine and valproate and vigabatrin was added at 16 weeks following an episode of status epilepticus. The child was examined at age 6 and the investigators noted that the child had a seizure at age 4 and was diagnosed as mild mental retardation at age 5. The reporters noted multiple minor and major malformations (not described) but a normal ophthalmologic exam.

Among the group of 10 publications that Ovation described as "other", 2 were retrospective reviews assessing ophthalmologic findings. Two studies (Landmark et al and Ulmanova et al) looked at use of vigabatrin in Norway and the Czech Republic and documented that use was low in these countries. Two studies examined psychiatric AEs in AED users. Trimble et al found similar risks for psychosis and affective disorders among vigabatrin treated (n=50) and topiramate treated (n=34) patients. Weintraub et al found no psychiatric AEs reported for 13 patients treated with vigabatrin in their study cohort of 1394 patients treated with newer AEDs. Handoko et al conducted a case control study to examine the risk for aplastic anemia. The investigators found increased risk of aplastic anemia with valproate, carbamazepine, and phenytoin. The investigators noted that one patients that developed aplastic anemia was taking vigabatrin and phenytoin. Arif et al conducted a study to examine risk of rash among users of AEDs and reported no cases of rash among 47 vigabatrin treated subjects. Prasad et al conducted a chart review of 73 patients treated with vigabatrin and documented that 11% (n=8) developed irritability/aggression and 2.7% (n=2) developed worsening of myoclonic seizures. Iorio et al reviewed spontaneous reports for AEDs used in Italy and found that vigabatrin had the highest rate of hearing and vision reports.

Ovation listed 17 review articles that were identified in the medical literature search. The majority of these articles discussed issues arising across the class of AEDs (ex. psychiatric symptoms, weight change, etc.). On review article by Cohen et al examined the potential for IME among patients treated with vigabatrin. A review article by Ferrie et al commented on phsychotic and behavioral reactions with vigabatrin.

Infantile Spasms
Ovation reported that the literature search identified 40 publications discussing the use of vigabatrin in IS. The 40 publications were comprised of 21 journal articles, 6 case reports, 4 review articles, and 9 other publications.

The 21 journal articles were publications of 6 open label controlled trials and 15 open label uncontrolled trials. The publication by Gaily et al did not report AE data. Lux et al reported similar AE risks for 52 IS patients treated with vigabatrin and 55 patients treated with prednisolone or tetracosactide. In a follow up of subjects from that study, Lux et al reported that 2 prednisolone or tetracosactide patients died compared to 3 vigabatrin patients. The deaths were felt to be consistent with the course of IS. Vigevano et al reported that in a randomized open label cross over study of vigabatrin and ACTH, somnolence (n=2) and hypotonia (n=2), and irritability (n=1) was observed with vigabatrin and hyperexcitability, irritability and increased appetite with ACTH. In another study by Vigavano et al, the investigators reported lower AE risks with vigabatrin compared to ACTH. Hammoudi et al published results of a study looking at visual field in IS patients treated with vigabatrin. In the publications describing open label studies, a number of AEs were reported in vigabatrin treated subjects including drowsiness, somnolence, sleep disturbances, insomnia, irritability, nervousness, hyperactivity, behavioral changes, increased seizure frequency, weight gain, and edema. Villeneuve et al noted in their open label study of 70 children with IS that 2 infants died, one was a sudden death and the other was due to congenital nephritic syndrome.

Among the cited case reports, Haas Lude et al described a 6 year old female with Alexander disease and hydrocephalus who presented with uncontrolled seizures and was treated with vigabatrin. The patient developed apathy, somnolence, and sluggishness. Vigabatrin was stopped and the symptoms resolved over 2 days. Pearl published two case series of MRI changes in children treated with vigabatrin.

Among the other reports cited by Ovation, adverse events mentioned in vigabatrin treated patients included irritability, somnolence, decreased sleep, and sedation.

The four review articles identified by the search included the article by Cohen et al mentioned above examining IME in patients treated with vigabatrin, two articles about treatment of infantile spasms, and one article about vigabatrin in treating pediatric epilepsy.

The complete list of references identified by NERAC Inc. on behalf of Ovation is provided in an appendix to this review.

7.2.3 Adequacy of Overall Clinical Experience

The exposure, in terms of number of subjects, exceeded the minimum ICH recommendations for medications products intended for long term treatment. The ICH Guidance recommends that 1,500 subjects exposed with 300-600 subjects exposed for 6 months, and 100 exposed for 1 year (at relevant doses, with reasonable exposure to the highest proposed dose). In the Integrated database, which includes only the subjects exposed to vigabatrin during epilepsy trials, Ovation

reports that 4,077 subjects have been exposed to vigabatrin and have sufficient information to assess AEs. Ovation reported that 3,456 subjects were exposed for >6months, 2,753 subjects were exposed for >1year and 403 subjects were exposed for >5 years (Source 3/14/08 Submission, Table 2.2, p.3).

Ovation's proposed labeling states that the usual effective dose of vigabatrin is 3g/day. The labeling also states that doses up to 6g/day were studies but were not statistically superior in efficacy to 3g/day and were associated with higher adverse event risks. As noted above, Ovation reported that 1,112 epilepsy subjects were exposed to a vigabatrin dose between 3 to <4g/day for at least 6 months, and 587 subjects were exposed to a vigabatrin dose between 3 to <4g/day for at least 1 year.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The cardiac in vitro and animal testing, which included examination of electrical stimulation threshold or the ventricular fibrillation threshold in perfused rabbit heart preparations, long term toxicity study in dogs that included ECGs, studies of vigabatrin's effect on the hERG channel current, and follow up tests in isolated rabbit Purkinje fibers appeared adequate. Additional non clinical studies since the NDA submission designed to examine specific safety topics included visual field defect toxicity studies, and juvenile rat toxicity study looking at developmental toxicity in neonatal and juvenile development.

7.2.5 Adequacy of Routine Clinical Testing

The approach used to collect adverse event data in the development program studies appeared appropriate, with AEs recorded at each visit. One noted limitation related to AE capture was the use of a separate database (GADERS) to collect SAE data. Using this approach meant that SAE information was not recorded in the CRFs in several studies and it is not completely clear if investigators were able to review the information included in the GADERS database for accuracy. The use of this separate SAE database led the sponsor to overlook several SAEs in vigabatrin subjects. Ovation did eventually identify these events when asked by the Division.

The routine lab data testing in the vigabatrin development program appeared appropriate. One limitation of the lab data testing was that despite identifying vigabatrin related anemia, the sponsor made no attempt to include additional hematological testing in subsequent studies that would allow for further evaluation and classification of the anemia.

The ECG recording in clinical trial subjects was inadequate with little available pre and post exposure ECG data available for vigabatrin subjects. In addition, timing of ECG recording in relation to dose was not specified and there was no pre-specified interval measurement methodology. The available ECG data does not allow for a reliable assessment of the effect of vigabatrin on cardiac repolarization in humans.

Vital sign testing in the vigabatrin clinical trials was generally adequate. One notable deficiency for vital signs was the lack of height and weight data in children to allow assessment of development.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup
Ovation explains that vigabatrin is rapidly and completely absorbed, is not metabolized to a significant extent, does not induce cytochrome P450 enzymes systems in animals and is not protein bound. OCP reports that vigabatrin induces CYP2C9 and CYP2C19 in vitro. Vigabatrin is eliminated unchanged through renal excretion. A decrease in phenytoin levels of 20-30% occurs with vigabatrin. Studies of vigabatrin and carbamazepine found no effect, increases, or decreases in carbamazepine concentrations. Other antiepileptic drugs reportedly have minimal effect on vigabatrin concentrations.

As noted in Dr. Leber's Division Director's 11/18/97 memo, OCBP concluded that the sponsor's approach to studying interaction between vigabatrin and other AEDs was acceptable (Source Division Director Vigabatrin Approvable Action Memo, 11/18/97, pp.12-13).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The most important safety issues with vigabatrin are the permanent visual field defects and MRI/IME findings. Dr. Farkas and Dr. Sheridan will address these topics in their reviews. In terms of the remaining general safety, there did not appear to be any major areas neglected in the application. Additional information regarding anemia, potential for liver injury, long term edema data, and implications of long term weight gain would be informative.

7.2.8 Assessment of Quality and Completeness of Data
Division reviewers have highlighted a number of deficiencies in the sponsors' presentations of adverse events over the course of the vigabatrin development program. These deficiencies have included lack of supporting information (narratives, CRFs) in applications, use of sources other than CRFs to capture data, including data from studies with no prespecified protocol, and the use of separate databases to capture serious adverse events. When these deficiencies have been identified, the sponsor has attempted to address them and the result has been generally acceptable.

There are several issues particular to this application that raise concerns about the quality and completeness of the data. The duration of the development program means that it is difficult to collect additional data about issues that are identified during the review. When questions arise about a particular case, the sponsor had difficulty amassing additional information to address the specific questions. The switching of sponsors over time also raises concerns. The current sponsor, Ovation, did not conduct any of the clinical trials included in the submission. When the Ovation obtained the rights to vigabatrin, data was transferred from Aventis to Ovation. An example of a difficulty arising from the switch is related to Ovation's uncertainty about classification of AEs. The Division asked Ovation why 2 rash SAEs were coded as serious given that the narratives did not provide any details that would support such a classification. Ovation

was only able to reply that they presented the events as SAEs to be consistent with how previous sponsor coded them. Ovation did not appear capable of addressing why the previous sponsor took that action, suggesting some loss of information in the transfer of data.

The approach to recording SAE data in some trials resulted in omissions in Ovation's safety presentation. The use of a separate data base to capture SAEs meant that 21 SAEs were not identified in the current submission, but instead were only subsequently discovered. Although Ovation attempted to convince the Division that all events were ultimately discovered and reported, it is not known if the effort was successful.

Another concern is related to the lack of data for subjects. For example, in the current submission, Ovation identified 599 subjects in the current submission with missing data that did not allow determination of the duration of exposure. Another example of lacking data is related to information presented in narratives. Many of the narratives provide woefully inadequate information for assessing what actually occurred to the subject.

The approach to presentation of lab data meant that not all subject labs were included in the lab data sets used for analyses. For example, for patients with SAEs during the study, if labs were captured during hospitalization, they could have been recorded with narratives but not in the lab data set. This was seen with the decreased platelet count event in patient 0242/1543003 and with the liver injury death in subject 0201/1621007. This approach could have limited the ability to identify extreme lab outliers.

7.2.9 Additional Submissions, Including Safety Update

In accordance with an agreement with the Division, Ovation did not provide a safety update for the adult CPS amendment submission. Ovation provided additional information in responses to Division questions submitted 2/11/08, 3/14/08, 4/15/08, 4/23/08, 5/1/08, 5/2/08, 5/7/08, 5/16/08, 5/23/08, 5/27/08, 6/2/08, and 6/6/08.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.3.1 Visual Field defects
See Dr. Farkas' review.

7.3.2 IME/MRI abnormalities
See Dr. Sheridan's review.

7.3.3 Anemia/Declines in Hemoglobin, Hematocrit
Lab data suggest that vigabatrin subjects experienced declines in hemoglobin and hematocrit that were not seen in subjects that received placebo. Vigabatrin subjects experienced mean decreases in hemoglobin and hematocrit from baseline and had higher risks for low hemoglobin and hematocrit result outliers. Analyses also suggested that these declines were dose related. Despite these laboratory findings, vigabatrin subjects did not appear to experience high frequencies of

concerning clinical events. Ovation reported that 3 vigabatrin subjects (0.06%, 3/4737) from the Integrated database experienced anemia SAEs, and 3 vigabatrin subjects (0.06%, 3/4855) from the Integrated database discontinued for anemia AEs. A search of the development program identified only 2 vigabatrin subjects that experienced unexplained declines in hemoglobin below 8g/dL and or hematocrit below 24%. In addition, there appeared to be few post marketing reports of anemia adverse events. The sponsors did not collect sufficient information to classify the observed anemia events.

Ovation would not include in the vigabatrin label information about anemia/decreases in hemoglobin and hematocrit. I have proposed labeling language discussing these events.

7.3.4 Weight gain
Weight data support that vigabatrin use is associated with weight gain. Data from controlled trials demonstrated that vigabatrin treated subjects had a higher mean increase in weight from baseline than did placebo treated subjects. In addition, vigabatrin subjects had a higher risk of gaining >=7% of baseline body weight. One analysis suggested that weight increase risk was greater among female vigabatrin subjects but there did not appear to be evidence suggesting differential weight increase risk by age. In the Integrated database, 10.2% (415/4077) of vigabatrin subjects had a weight increased AE. Ovation did not provide information about weight gain in their labeling proposal for vigabatrin. I have proposed labeling language for weight gain with vigabatrin.

7.3.5 Edema
Vigabatrin use was associated with development of edema. In the Integrated Database, Ovation identified 3% (124/4077) patients with AE of edema peripheral, 0.4% (16/4077) with edema, 0.1% (5/4077) with generalized edema, 0.1% (5/4077) with localized edema, 0.1% (4/4077) with facial edema, <0.1% (3/4077) with pitting edema <0.1% (3/4077) with gravitational edema. None of these events were SAEs, and only 5 edema peripheral events and 2 edema events led to discontinuation. In analyses of pooled controlled trial data, the risk of edema was higher among vigabatrin subjects compared to placebo subjects. Dose response analyses of controlled trials data suggested an increasing risk of edema peripheral and generalized edema with increasing vigabatrin dose but not other edema related adverse events.

In a separate analysis, 50 of 215 vigabatrin subjects with an edema related AE also had a weight gain AE (only 23 of these occurred within a month of the edema related AE). The edema AEs did not appear to be related to cardiac, renal, or hepatic AEs and did not appear to be associated with increased creatinine, low serum albumin, or proteinuria.

Ovation did not propose labeling language for edema adverse events. I have proposed labeling language for edema with vigabatrin.

7.3.6 Depression/Suicidality
Evidence supports an increased risk for depression with vigabatrin and insufficient evidence to support an increased risk of suicidal behavior.

A sponsor submitted expert review of psychiatric events with vigabatrin found an increased risk for depression among vigabatrin subjects and more serious outcomes (hospitalizations, discontinuations) among vigabatrin subjects.

In the Integrated database, 8.2% (334/4077) of subjects reported depression AEs, 1.0% (40/4077) reported depressed mood AEs, 0.6% (23/4077) reported suicidal ideation AEs 0.3% (13/4077) reported suicide attempt AEs, 0.1% (4/4077) reported depression suicidal AEs, and 0.07% (3/4077) reported major depression AEs and 1 subject committed suicide. In addition, there were 21 Depression SAEs (0.44%) 12 Suicidal ideation (0.25%) SAEs, 10 Suicide attempt (0.21%) SAEs, 2 (0.04%) Depression suicidal SAEs and 1 (0.02%) major depression SAE.

Data from 12 pooled controlled studies demonstrate slightly increased risks for depression AEs for vigabatrin and placebo subjects, and show an increased risk for depression and suicide related SAEs among vigabatrin subjects, although the number of SAEs was relatively small. In addition, data from these trials suggest an increased risk for depression AEs leading to discontinuation among vigabatrin subjects compared to the subjects randomized to other treatments.

There did not appear to be a clear dose response for depression related AEs in a pool of 5 randomized placebo controlled trials that included more than one dose of vigabatrin.

Ovation proposes including information about depression in a Warnings and Precautions statement titled "Neuropsychiatric Adverse events". This labeling statement covers a variety of AEs including psychiatric symptoms, somnolence, fatigue, and sleep disorders. Ovation would provide the risk for depression AEs among vigabatrin subjects in the Integrated database but would not provide comparative data from controlled trials.

I have proposed labeling language for depression and suicidality with vigabatrin that is similar to the class labeling being considered for all AEDs.

7.3.7 Peripheral Neuropathy
In the NDA review, Dr. McCormick noted that treatment emergent risks for parathesia and hyporeflexia adverse events were 3 times higher among vigabatrin subjects compared to placebo subjects. Dr. McCormick commented that neurological symptoms were not correlated with careful examinations and that affected subjects were not tested to determine if the process was axonal or demyelinative. Dr. McCormick suggested that the sponsor perform additional analyses to evaluate peripheral neuropathy AEs. In addition, Dr. McCormick suggested that patients with hyporeflexia and sensory loss be evaluated for "NCV and EMG changes", and study data be reviewed to determine if nerve biopsies had been performed (Source NDA Review, 3/5/95).

Dr. James Sherry reviewed the sponsor's response to the Division's request for additional information about peripheral neuropathy. The sponsor submitted a report evaluating peripheral neuropathy events that was written by their expert consultant. Dr. Sherry noted that the sponsor's consultant reviewed the peripheral neuropathy events "on the basis of their association with demyelination/IME rather than as a separate process." Dr. Sherry felt that the consultant's conclusion that none of the cases of peripheral neuropathy were demyelinating was not

substantiated. Dr. Sherry found that symptoms and signs of peripheral neuropathy occurred more frequently among vigabatrin subjects compared to placebo subjects in the US studies 024 and 025. Dr. Sherry requested that peripheral neuropathy be mentioned in the vigabatrin label and requested additional information about the course, onset, duration of exposure, and resolution of these events (Source, Clinical Review, 11/5/97).

In the current submission, Ovation summarized the previous submissions related to peripheral neuropathy, particularly the consultant report noted above, but provided no new information. Ovation noted that the reviewed studies were not designed to systematically evaluate peripheral neuropathy and did not include nerve conduction studies, quantitative sensory testing or skin or nerve biopsy.

In addition to summarizing the expert review, Ovation provided a review of post marketing reports of neurological events. Ovation commented that few postmarketing reports described events related to peripheral neuropathy.

In their proposed labeling, Ovation includes a Warnings and Precautions statement regarding peripheral neuropathy. Ovation's statement only provides absolute risks for peripheral neuropathy AEs among vigabatrin treated subjects from the Integrated database but includes no comparative data. I provide edits to the Ovation peripheral neuropathy labeling language.

7.3.8 Liver Injury

There have been cases of liver injury resulting in death or transplant in patients treated with vigabatrin but it is not clear if vigabatrin is causally related to these cases. In the development program studies that were part of the vigabatrin safety database, one study subject died from multiorgan failure (including hepatic failure) following an episode of status epilepticus. This event was likely related to the patient's underlying medical condition and not vigabatrin. A patient with metastatic cancer developed elevated transaminases and died. A third liver failure case resulting in death involved a study subject that had been taking vigabatrin for six years prior to the event and the liver injury was temporally related to treatment with clarithromycin. A subject in a Japanese study that was not part of the vigabatrin safety database died from hepatic failure but there were insufficient details about this event to allow a determination about whether vigabatrin was causally involved.

From post marketing reports, there were four hepatic related deaths and one liver transplant. In none of the cases was a likely alternative explanation documented but all were taking multiple medications at the time of the event. Excluding cases with exposure to vigabatrin for more than 1 year prior to developing liver injury leaves 3 cases of death/transplant. The reporting rate with of hepatic failure resulting in death or transplant with vigabatrin exceeds the general population background risk that we have relied on in the past, but liver injury risk may be elevated among patients with seizure disorders that are treated with medications that are known hepatotoxins.

Examination of available laboratory data did not identify any "Hy's law" (Transaminase 3x ULN with total bilirubin >2.0mg/dL) liver injury cases in the development program. From a pool of data from controlled trials there did not appear to be an increased risk of high transaminase

outlier results for vigabatrin subjects compared to placebo. These laboratory results must be intepreted in light of vigabatrin's ability to decrease transaminases.

I do not believe that available data are sufficient to allow the conclusion that vigabatrin causes liver injury but the data do merit close followup. I agree that a warning statement for hepatic injury is not required at this time. If vigabatrin is approved, Ovation should closely follow all post marketing reports of hepatic injury, collect complete follow up data on each case, and provide expedited reporting to FDA of any such cases.

7.3.9 CNS Effects
Vigabatrin was associated with an increased risk for a number of CNS AEs including somnolence, sedation, coordination abnormalities and confusional state. The occurrence of these events could impair a patient's ability to perform tasks such as driving or operating machinery. I include a labeling statement about the risk for these events.

7.3.10 Effects on Serum Transaminases
Vigabatrin causes reductions in serum transaminases (ALT>AST), presumably through its effect as a transaminase inhibitor. Vigabatrin treated subjects experienced mean declines in ALT and AST that were not observed among placebo subjects. In one analysis, 94% of subjects had a 60-100% maximum decrease in their ALT compared to baseline and 4% had an ALT result of 0. The magnitude of the declines appeared to be dose related. This effect could impair the ability to monitor for liver toxicity.

Recommendations
Any ongoing or planed vigabatrin clinical trials should incorporate monitoring of hemoglobin, hematocrit, serum iron, transferrin, ferritin, reticulocyte count, red cell morphology, red cell indices, haptoglobin, urine hemoglobin, and erythropoietin.

Any ongoing or planned vigabatrin clinical trials should incorporate hematologic testing during post-treatment washout in order to assess rate of recovery from reduction of hemoglobin and hematocrit.

Ovation should conduct a thorough QT study in humans. This could be conducted as a phase IV commitment.

If approved for pediatric indications, Ovation should collect data that address the effect of vigabatrin on growth and development.

Ovation should closely follow up any spontaneous reports of liver injury. Follow up should include complete description of the case, outcome information, lab test results, biopsy results, and post mortem test results. In addition, Ovation should submit any serious liver injury cases as 15-day reports.

Ovation should incorporate the labeling language that will be requested by the Division.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Prior submissions used separate pools of data to explore vigabatrin related adverse event risks. In the NDA, the comparative analyses were generally based on data from two controlled US epilepsy trials (024, 025). These studies were pooled because of their similar designs. The NDA also included data from non US studies, but these data were considered of lower value because the sponsor neither submitted with the NDA nor had available for audit/review the Case Report Forms (CRFs) for most of the non US studies that contributed safety data. In addition, the NDA lacked complete dose and duration of exposure data for non US studies subjects, and did not include narrative summaries of serious adverse events and discontinuations for these subjects. In the NDA Amendment the sponsor collected and reviewed available CRFs from non US study sites. Some CRFs were located and others were not. Using the available data, the sponsor assembled the safety data for resubmission. The sponsor created three separate cohorts of non-US studies safety data. The first cohort was comprised of data from non-US studies for which CRFs were available for all subjects, where data was designated to be captured by a prospectively written protocol and where data was contemporaneously captured in the CRF. These data were termed the non-US studies primary safety data. In instances where some but not all CRFs were located for a given study the data for patients with CRFs were grouped into the second cohort called Secondary data. A third cohort included data for those patients for whom CRFs were not located (non-CRF data). The NDA amendment focused mainly on data pooled from the primary non US studies and included additional information from the secondary data sources.

For the Current submission, Ovation presents results of analyses from pooled data for several different cohorts. The main focus of the Amendment submission safety presentation is the Overall cohort, which includes data from 15 studies (epilepsy, IS, and safety studies looking at VFDs) for the time period of 3/16/97 through 6/30/07. In addition, Ovation divided the data from the studies in the Overall cohort into the following subgroups: adult partial epilepsy studies, pediatric (non-IS) studies, and infantile spasms studies. Lastly, Ovation presented data for an Integrated cohort. The Integrated cohort includes data from all epilepsy studies in the development program, dating back to the original NDA submission. Ovation presented these data using 3 columns. The "Prior" column of the table includes information from US, primary non-US, and secondary studies (for SAEs only) through the 1998 Safety Update (3/1/07 submission, p.194). The "Current" column of the table includes information from the studies in the current submission except for studies 0098 and 4021, which were reported separately. The "Combined" column adds the data from the Prior and Current columns. This analysis allows for comparisons of risk across time.

During the course of the present review, the Division requested additional analyses from pooled controlled trial data that would allow comparisons of adverse event risk to assess causality. Ovation pooled data from 12 phase II/III epilepsy controlled trials that used a double blind, parallel group, dose, placebo or active control design. The choice of studies for pooling appeared appropriate although there were differences among the studies in terms of the durations (range 5 days to 52 weeks) and numbers of subjects enrolled (range 18- 457).

In response to a Division request for a dose response analysis, Ovation analyzed pooled data from 5 fixed-dose, randomized, placebo-controlled CPS trials.

Ovation did not provide pooled analyses of lab or vital sign data and the results for the current submission studies and the results cited above come from the study reports of individual studies.

7.4.1.2 Combining data

For the adverse event analyses using pooled data, the adverse event counts from the selected studies were summed and the numbers of subjects or the person time from each of the selected studies were summed. To calculate the pooled adverse event risk, the total number of adverse events was divided by the total number of subjects or the total person time. For the Integrated data analyses, Ovation had to re-code verbatim preferred terms to MedDRA prior to summing the numerator events, because prior submissions used a WHOART coding dictionary.

For the dose response AE analysis, Ovation summed the adverse events for the numerator of the risk calculation and summed person time exposure for the different dose groups for the denominator. Ovation then assigned adverse events to the dose category at which the event occurred.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Ovation did not provide dose response analyses in their NDA amendment submission. The Division requested dose response analyses using data from 12 pooled randomized controlled trials. Most clinical studies in the vigabatrin development program used titration designs which complicate interpretation of dose response analyses. One of the difficulties with titration designs is that subjects in these studies are exposed to a range of doses. For that reason subjects could be assigned to multiple dose groups so that calculating risks for a given dose becomes complicated and misclassifying events in terms of dose can occur. The Division requested analyses that determined the amount of person time at each dose and then assigned adverse events to the dose taken at the time of the event. AE rates across the dose groups were then compared to look for dose response.

7.4.2.2 Explorations for time dependency for adverse findings

Ovation submitted no time dependency analyses.

7.4.2.3 Explorations for drug-demographic interactions

Ovation submitted analyses that compared adverse event risks stratified by sex and age. These analyses are of limited usefulness because there are no comparator (non vigabatrin treated) data to allow one to assess if any observed differences in AE risks are due to drug-demographic interactions, or merely represent differences in adverse event risk that occur in the background.

7.4.2.4 Explorations for drug-disease interactions

Ovation submitted no drug-disease interaction analyses.

7.4.2.5 Explorations for drug-drug interactions

Ovation submitted no drug-drug interaction analyses for the 15 trials in the current submission. In their Clinical Summary, Ovation notes that clinical and pharmacokinetic studies show a vigabatrin phenytoin interaction. In one study, when vigabatrin was added in 8 patients who had been taking phenytoin for a month, the phentoin plasma levels decreased by 23%. Ovation states that this interaction may be due to induction of cytochrome P450 2C in some patients.

7.4.3 Causality Determination

Evidence for causality for specific adverse events is presented in section 7.3.

10 APPENDICES

Summary of completed studies included in the 12/28/07 submission that were not previously submitted

5 Adult epilepsy studies

0098- open label, flexible dose long term study as add on therapy in patients with partial seizure. This study enrolled subjects that previously participated in vigabatrin clinical trials and allowed them to continue vigabatrin treatment. Some data from this study were reported in the last safety update but the actual dataset used for that safety update was not available. Other data problems include missing age data for 384 subjects and use of different data fields for the SAE database resulting in inconsistent subject number capture and date of birth (12/28/07 submission, p. 19).

0101- A randomized double blind placebo controlled study of vigabatrin as add on to carbamazepine or phenytoin in adult patients with complex partial seizures. The study included a 4 week titration phase followed by a 24 week maintenance phase and then an open label phase. For the placebo controlled phase, 119 subjects were assigned to vigabatrin and 58 to placebo.

0222- A randomized double blind study of vigabatrin versus gabapentin in complex partial seizures. The study included an 8 week baseline phase followed by a 5 week titration phase where vigabatrin or gabapentin was added to the subjects' treatment regimen, and an 8 week withdrawal phase where baseline AEDs were withdrawn. Nineteen subjects were enrolled in this study (vigabatrin n=10, gabapentin n=9).

0223- A double blind study where subjects with complex partial seizures were randomized to one of four doses of vigabatrin. The study included an 8 week baseline phase where subjects were maintained on their usual AEDs, a 6 week titration phase (vigabatrin doses 1, 3, 4, and 6g/day), an 8 week phase where the baseline medications were withdrawn, an 8 week maintenance phase, and an open label phase. Seventeen subjects were randomized to 1g/day, 18 to 3g/day, 19 to 4g/day, and 21 to 6g/day.

0242- An open label long term maintenance study of vigabatrin in patients with complex partial seizures (enrolled subjects from studies 0222 and 0223). This study included 85 subjects.

5 pediatric complex partial seizure studies

0118- A randomized double blind placebo controlled add-on study in pediatric subjects with complex partial seizures. The study included a 10 week baseline phase (single blind placebo), a 6 week titration phase where vigabatrin subjects were titrated to their randomly assigned target dose of 20mg/kg/day, 60mg/kg/day, or 100mg/kg/day, and an 8 week maintenance phase. The study randomized 96 subjects to vigabatrin and 34 to placebo.

0192- A randomized double blind placebo controlled add-on study in pediatric subjects with complex partial seizures. This study included a 6 week baseline phase, a 10 week titration phase where vigabatrin patients were titrated to tolerability/response, and a 7 week maintenance phase. The study randomized 55 patients (28 vigabatrin, 27 placebo).

0201- An open label long term follow up study that enrolled subjects from 0118 and 0221. Subjects completing this study rolled over into 0098. This study included 210 subjects (185 children, 25 adults).

0221- A randomized double blind placebo controlled add-on study in pediatric patients with complex partial seizures. This study included a 6 week baseline phase, a 10 week titration phase where vigabatrin patients were titrated to tolerability/response, and a 7 week maintenance phase. This study randomized 88 subjects (43 vigabatrin, 45 placebo).

0294- An open label 24 week study that enrolled subjects from study 0192. Forty-four subjects enrolled in this study **but data are available for only 43 subjects (one subject's record is missing 12/28/07 submission, p.23).**

4 Studies Assessing Visual Field Defects

4020- An open label study of the prevalence, incidence and clinical course of VFD in patients with partial seizures. The study enrolled subjects with current, previous, and no vigabatrin exposure. The study enrolled 735 subjects (562 with vigabatrin exposure).

4021- An open label study of the clinical course of VFD in patients with partial seizures. The study enrolled 30 subjects.

4103- An observational cohort studying reversibility/progression and predictive factors of visual field loss with vigabatrin. This study enrolled 23 subjects.

R003 A prospective cohort study designed to detect early VFD, and to assess the frequency and clinical course of early VFD associated with first time vigabatrin treatment. This study enrolled 25 of a planned 200 subjects.

Infantile spasm study

1A- A randomized, single-blind parallel group study of vigabatrin in subjects younger than 2 years with new onset IS. This study included a 14-21 day single blind phase where subjects were randomized to low dose (18-36mg/kg/day) or high dose (100-148mg/kg/day) vigabatrin (7 day titration followed by maintenance of 7-14 days). This study also included a long term follow up phase (up to 3 years). The study enrolled 223 subjects but one subject was excluded from the safety analysis for lack of reliable dosing data.

Labeling Review

Pending the outcome of the planned advisory committee meeting, the following language should be considered for a black box warning.

Boxed Warning

Suicidal Behavior and Ideation and Antiepileptic Drugs
Antiepileptic drugs increase the risk of suicidal thoughts and behavior in patients taking the drugs for any indication. In a meta-analysis of placebo-controlled studies, antiepileptic drugs approximately doubled the risk of suicidal behavior and ideation compared to placebo. Anyone considering the use of vigabatrin or any other antiepileptic drug must balance this risk with the clinical need. Patients who take antiepileptic drugs should be monitored closely for suicidal thinking or actions, thoughts about self-harm, or any notable changes in behavior that could indicate the emergence or worsening of depression or suicidal thoughts or behavior.

Families and caregivers should be advised that close observation and communication with the prescriber are important.

Warnings and Precautions

Suicidal Behavior and Ideation
Antiepileptic drugs increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Pooled analyses of 199 placebo-controlled clinical trials of 11 different antiepileptic drugs showed that patients receiving one of the antiepileptic drugs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.6) of suicidal thinking or behavior compared to patients receiving placebo. The estimated incidence of suicidal behavior or ideation among 27,863 antiepileptic drug-treated patients was 0.37% compared to 0.24% among 16,029 placebo-treated patients. There were suicides in the trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior was observed as early as one week after starting drug treatment and continued to at least 24 weeks. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be reliably assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs and did not vary substantially by age in the clinical trials analyzed.

The relative risk for suicidal thoughts or behavior was higher in patients in clinical trials for epilepsy compared to those in clinical trials for psychiatric or other conditions. The absolute risk differences, however, were comparable in patients with epilepsy and psychiatric conditions.

The following table shows absolute and relative risk by indication.

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.5	3.6	2.5
Psychiatric	5.2	8.3	1.6	3.1
Other	0.8	2.0	2.3	1.1
Total	2.2	4.3	2.0	2.1

Anyone considering prescribing vigabatrin or any other antiepileptic drug must balance this risk with the clinical need. Patients treated with any antiepileptic drug for any indication should be monitored appropriately and observed closely for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Patients, their caregivers, and families should be informed that antiepileptic drugs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with vigabatrin and should counsel them in its appropriate use. A patient Medication Guide is available for vigabatrin. The prescriber or healthcare professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking vigabatrin.

Suicidal Thinking and Behavior - Patients, their caregivers, and families should be informed that antiepileptic drugs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or

thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Warnings and Precautions

Peripheral Neuropathy
During randomized controlled trials, vigabatrin treated study subjects experienced an increased risk compared to placebo treated subjects for adverse events suggestive of peripheral neuropathy including parathesia, diminished reflexes, and diminished vibratory sense. In the overall epilepsy development program, among 4,077 vigabatrin-treated patients, adverse events related to peripheral nerves included paresthesia (2.7%), hypoesthesia (2.2%), neuropathy peripheral (0.4%), reflexes abnormal (0.2%), areflexia (0.2%), sensory loss (0.2%), peripheral sensory neuropathy (0.1%), neuropathy (0.1%) and polyneuropathy (0.02%).

[Note to Sponsor: There is a clear increase in the incidence of symptoms and signs consistent with peripheral neuropathy e.g.,paresthesia, stocking glove distribution, diminished vibratory sense and reflexes,etc.] with vigabatrin. Please develop a proposed case definition for peripheral neuropathy which should be discussed with us before additional work is done. Once we have agreed on a case definition, please submit comprehensive information about all cases in your database, including nerve conduction studies, if available. Please also provide incidence estimates from your controlled trials, as well as from open and post-marketing experience. Examine the effects of dose, duration, and vigabatrin discontinuation on the symptoms and signs of peripheral neuropathy.]

Peripheral Edema
Vigabatrin treatment is associated with an increased risk of developing peripheral edema. Pooled data from controlled trials demonstrated increases in risk among vigabatrin treated study subjects compared to placebo treated study subjects for edema peripheral (vigabatrin 4.3/100PY, 19/446PY; placebo 3/100PY, 3/101PY), edema (vigabatrin 1.1/100PY, 5/446PY; placebo 0/101PY) and generalized edema (vigabatrin 0.7/100PY, 3/446PY; placebo 0/101PY). In these studies, one vigabatrin (0.2/100PY, 1/446PY) and no placebo subjects (0/101PY) discontinued for an edema related AE. There was no apparent association between peripheral edema and cardiovascular adverse events such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

Vigabatrin should be used with caution in patients with existing peripheral edema and in patients with a history of congestive heart failure.

Weight Gain
Vigabatrin may cause weight gain. Data pooled from randomized controlled trials found that 17% (77/443) of vigabatrin study subjects gained >=7% of baseline body weight compared to 8% (22/275) of placebo treated subjects. In epilepsy trials, 0.6% (31/4855) discontinued for weight gain. The long term effects of vigabatrin related weight gain are not known.

Decreases in Hemoglobin and Hematocrit
In controlled trials, vigabatrin was associated with declines in hemoglobin and hematocrit. Data pooled from 2 epilepsy studies found a mean decline in hemoglobin among vigabatrin treated study subjects of -0.29g/dL and a mean increase in hemoglobin among placebo treated study subjects of 0.53g/dL. In those same studies, there was a mean decline in hematocrit among vigabatrin treated study subjects of -0.46% and a mean increase in hematocrit among placebo treated study subjects of 0.02%. The declines in hemoglobin and hematocrit among vigabatrin treated study subjects appeared dose related. It is not known whether these changes are readily reversible with discontinuation of vigabatrin.

Despite these laboratory findings, only 3 vigabatrin treated study subjects (0.06%, 3/4855) from epilepsy trials discontinued for anemia and 2 vigabatrin treated subjects experienced unexplained declines in hemoglobin below 8g/dL and or hematocrit below 24%.

CNS Adverse Events
Vigabatrin was associated with an increased risk for a number of CNS adverse events including somnolence, sedation, coordination abnormalities and confusional state. The occurrence of these **events could impair a patient's ability to perform tasks such as driving or operating machinery.**

Decreases in ALT and AST
In North American controlled studies, vigabatrin decreased alanine transaminase (ALT) and, to a lesser extent, aspartate transaminase (AST) plasma activity. This represents a chemical interference with the assays, not an effect of vigabatrin on the liver. The magnitude of ALT suppressions in over 90% of vigabatrin treated patients ranged from 60 to 100% while the magnitude of AST suppressions in over 90% of vigabatrin treated patients ranged from 0 to 60%. In patients with maximum ALT decreases of 80 to 100%, a greater percentage occurred in patients with higher vigabatrin doses (95.1%; 39/41 at 6 g) than in patients with lower vigabatrin doses (11.1%; 5/45 at 1 g). Dose trends were not as evident in vigabatrin treated patients with AST suppression. The time to onset of the first abnormal value in vigabatrin treated patients occurred most frequently during the first three weeks for ALT and between 4 to 8 weeks for AST, after starting vigabatrin therapy. The majority of vigabatrin treated patients reached their maximum decrease in ALT and AST values 4 to 8 weeks after starting vigabatrin therapy. Therefore, the suppression of ALT and AST activity by vigabatrin may preclude the use of these markers, especially ALT, to detect early hepatic injury.

Increases in Amino Acids in Urine
Sabril may increase the amount of amino acids in the urine, possibly leading to a false positive test for certain rare genetic metabolic diseases (e.g., alpha aminoadipic aciduria).

Table 5: Studies Included in Pooled Mortality Analysis				
		Total Number of Patients		
Study Number	**Design / Duration of Double-Blind Treatment**	**Vigabatrin**	**Active Comparator**	**Placebo**
71754-3-C-024	Double-blind, placebo controlled, parallel group, multicenter study / 18 weeks	92	0	90
71754-3-C-025	Double-blind, placebo controlled, parallel group, multicenter study / 18 weeks	129	0	45
097-WUK04	Double-blind, placebo controlled, parallel group, single center study / 2 weeks	22[a]	0	23
71754-3-C-021	Multicenter, double-blind, placebo-controlled, parallel group trial / 36 weeks	58	0	53
71754-3-W-007	Multicenter, randomized, double-blind, active-controlled, parallel group trial / 52 weeks	228	229 (CBZ)	0
71754-3-W-012	Multicenter, randomized, double-blind, active-controlled, parallel group trial / 40 weeks	110	113 (VPA)	0
0101	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial / 28-32 weeks	119	0	58
0222	Multicenter, randomized, double-blind, double-dummy, parallel group trial / 21 weeks	9	9 (GBP)	0
0118	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial / 14-17 weeks	94	0	32
0221	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial / 17-20 weeks	43	0	45
0192	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial / 17-20 weeks	28	0	27
71754-3-W-019	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial / 5 days	20	0	20

a In this study the 2 week double-blind phase was followed by a 4-month phase in which all patients received vigabatrin. For the double-blind phase alone, the correct numbers are 22 vigabatrin and 23 placebo. When the 4-month phase is included, the number on vigabatrin is 22+23=45, which is consistent with Table B-1 from the 1997 Amendment.

Sources: Table of All Studies (Table 8.1) from original NDA; Table of All non-US Studies (Table B-1)and V2 p 89 from 1997 Amendment; Table of All Clinical Studies for Final Safety Update (Table 9-1) from 1998 Safety Update; Tabular Listing of Clinical Studies (5.2) from 2007 submission.

Post Marketing Liver Failure Deaths Reported In the 5/97 NDA Amendment

Patient 31730707, a 39 year old male died of hepatic failure. This patient who was being treated with vigabatrin (3.5g/day for 6 years) presented with fever and was treated with clarithromycin, aspirin, and noraminopyridine. Less than 30 days later he developed hepatic failure and died.

Patient VGZ-9500-1102, an 18 year old male treated with only vigabatrin (5g/day for 4 years) died of hepatic failure. A liver biopsy showed massive acute hepatitis and serologies were reportedly non-diagnostic.

Patient VGZ-9400-3033, a 10 year old female treated with vigabatrin (1.5g/day for 1 year) died of hepatic failure. She presented with "febrile enteritis" and subsequently developed abnormalities of transaminases and indicators of liver synthetic function. An autopsy reported "subacute hepatic dystrophy, extensive parenchymal necrosis, and intrahepatic cholestasis." Viral serologies were reportedly negative. Concomitant medications were carbamazepine and clonazepam.

Patient VGZ-9400-1440, a 34 year old female treated with vigabatrin (2g/day for 26 months) carbamazepine, and phenytoin, died of hepatic failure. The patient developed elevated transaminases. The patient's physician stopped the carbamazepine with slight improvement, but her transaminases increased again and she was hospitalized. Vigabatrin was stopped and her phenytoin dose reduced. Her liver function continued to deteriorate. A liver biopsy showed subacute hepatitis. She developed hepato-renal syndrome and died.

Patient VGZ-9300-3075, a 37 year old male treated with vigabatrin (1g/day for 4 days) phenytoin, and carbamazepine, died of hepatic failure. The patient developed status epilepticus that was treated with paraldehyde and diazepam. The next morning he was hypotensive and vomited blood. He developed altered mental status and left sided hemiparesis. He subsequently experienced a cardiac arrest and was resuscitated. He subsequently developed liver failure, renal failure, and died.

Patient VGZ-9203-130, a 10 year old male treated with vigabatrin (1g/day for 17 days) and carbamazepine, died of hepatic failure. The patient experienced a generalized tonic-clonic seizure and prolonged unconsciousness and was admitted to a hospital. Admission labs included abnormal LFTs. The patient died and a liver biopsy immediately following death demonstrated massive hepatic necrosis. The patent did not have serology testing.

Summaries of Clinical Details for the 16 Clinical Trial Deaths Reported in the Current Submission

0098/11920014 Cause of death: seizure
This 48 year old female with a history of complex partial seizures and partial generalized seizures who was treated with vigabatrin for 28 months (dose 5.5g/day at the time of the event) was found dead by her daughter. The reported cause of death was natural death as a result of seizure disorder. There was no documented preceding illness or injury. The narrative mentioned that she was seen by neighbors earlier that day as she walked her dog and was "frothing at the mouth" and complaining of arm and shoulder pain. Concomitant medications included gabapentin and premarin.

0098/12110008 Cause of death: grand mal seizure, sudden death
This 38 year old male subject with a history of seizures, Osler Weber Rendu syndrome with pulmonary arterio-venous malformation, and anxiety attacks died six hours after experiencing a grand mal seizure. The narrative mentioned that an autopsy was performed but that the results were not available. Concomitant medications were dilantin, ativan, and herbal vitamins.

0098/13040004 Cause of death: seizure
This 35 year old male subject with a history of seizures, asthma (no episodes since age 12), environmental allergies, and upper respiratory congestion died and seizure was listed as the case of death. No details were provided about the subject's death. The narrative noted that subject had been seizure free for 1 year and lowered his own vigabatrin dose against medical advice.

R003/0405010 Cause of death: seizure
This 58-year-old white male presented with a 55-year history of secondary generalized seizures consequent to a head injury sustained at the age of three. His medical history included chest pain and cardiac arrhythmia (summer of 2000), severe psoriasis, constipation, mild depression, and decreased hearing along with different nervous system disorders (poor memory, somnolence and bilateral hand tremors). He began vigabatrin therapy on December 19, 2001 and discontinued study medication on December 15, 2002, due to an acquired visual field defect. He had a fatal seizure that was not considered related to study medication but resulted in his death on May 21, 2003.

0098/12340002 Cause of death: myocardial infarction
This 52 year old male subject with a history of seizures, learning disability, memory deficits, s/p left temporal lobectomy for seizures was found dead in bed. No autopsy was performed and the death certificate listed myocardial infarction as the cause of death. The subject had no history of heart disease. The narrative listed only tegretol as a concomitant medication.

0098/13030106 Cause of death: myocardial infarction
This 63 year old male with a history of seizures, coronary artery disease, myocardial infarctions, congestive heart failure, ischemic cardiomyopathy, angina pectoris, hypertension, and cataracts died and the narrative reported that the cause of death was a massive myocardial infarction at home. The narrative provided no information about the evidence supporting this diagnosis. Concomitant medications at the time of death were lamictal and tegretol.

0098/13040002 Cause of death: myocardial infarction
This 53 year old male with a history of seizures, cardiomegaly, chronic edema, pulmonary hypertension, possible sleep apnea, paroxysmal nocturnal dyspnea, hand tremors, IQ 77, cerebellar atrophy, and obesity died and the reported cause of death was myocardial infarction. The narrative provided no information about the evidence supporting this diagnosis. The only listed concomitant medication was dilantin.

4020/0034014 Cause of death: cardiac arrest while sleeping
This 56 year old female subject with a history of seizures and closed head injury died and the reported cause of death was cardiac arrest while sleeping. An autopsy was not performed and the narrative provided no information about the evidence supporting this diagnosis. Concomitant medications included tegretol and paroxetine.

1A/911 Cause of death: sudden death
This was a sudden death occurring in a 7-1/2-month-old, 6.4 kg, African American female child with symptomatic **Aicardi's Syndrome, sickle cell trait, and a history of** clonic and tonic-clonic seizures. She initiated vigabatrin therapy on March 21, 1997. The subject had been receiving phenobarbital at baseline but this was abruptly discontinued due to change in caregiver. The subject was seen by the pediatrician for a well-baby checkup and age-appropriate immunizations on the day prior to death. The physician reported that she was more alert, interactive, and **"much better" seizure-wise compared to baseline. At the** time of death she had been on vigabatrin therapy for 74 days and was receiving a vigabatrin dose of 195 mg/kg for 3 consecutive weeks. On June 3, 1997 at 1:30 pm, the **infant's caregiver put her down for a nap. When the caregiver attempted to wake the infant at 3:30pm, the infant** was not breathing. The infant was taken to a local hospital and given vigorous cardiopulmonary resuscitation but could not be revived. The child had no intercurrent illness and did not receive pertussis immunization. An autopsy was performed; however, repeated attempts to obtain the report were unsuccessful. The sponsor believes this death would be considered a SUDEP (Sudden Unexplained Death in Epilepsy) (*Aicardi's syndrome is an X-linked disorder that includes agenesis of the corpus callosum, cystic intracerebral anomalies, infantile spasms, mental retardation, lacunar chorioretinopathy, and vertebral body abnormalities).*

0098/12040015 Cause of death: pneumonia, respiratory arrest
This 30 year old female with a history of seizures, profound mental retardation, cerebral palsy, and respiratory arrest was in hospice (reason not explicitly noted but narrative suggested a debilitated state) and died with pneumonia listed as the cause of death.

0098/12300010 Cause of death: pneumonia, pulmonary carcinoma, multiple organ failure
This 46 year old male subject with a history of seizures, mild mental retardation, and tobacco abuse was diagnosed with lung cancer during a vigabatrin clinical trial. The narrative reported that the subject developed pneumonia, multi organ failure and died.

1A/461 Cause of death: pneumonia
This subject had been off vigabatrin for three weeks at the time of onset of the adverse event. This subject was a 10-3/4 month 5 kg old female with infantile spasms and Miller-Dieker Syndrome, a genetic disorder associated with lissencephaly, microcephaly, severe mental deficiency, seizures, and frequent infections. She had begun vigabatrin therapy on August 8, 1997. Due to lack of efficacy, vigabatrin was tapered and discontinued with the last dose given on November 13, 1997. At this time, she started clonazepam, 0.5 mg bid. Lamictal® therapy was started for seizure control on November 20, 1997. She was hospitalized on [redacted] with a diagnosis of upper lobe **pneumonia. "Do Not Resuscitate" orders were written at least 24 hours prior to her death.** Supplemental oxygen was discontinued the evening of [redacted] as agreed upon by her parents and the attending physician. She continued to receive feedings per a gastrostomy tube, antibiotics, and acetaminophen for comfort measures until she died on [redacted] No autopsy was performed. b(6)

1A/559 Cause of death: pulmonary hemorrhage secondary to pulmonary angiomatosis
This death occurred in a 3-month-old, 4.2 kg female with a history of severe encephalopathy of unknown etiology with onset of IS at 5 weeks of age. The infant also had a history of another unclassified seizure type. Vigabatrin treatment was initiated in June 12, 1997 and the dose was increased to a maximum dose of 750 mg without obvious improvement. The infant was also receiving an unspecified dose of chloral hydrate in addition to vigabatrin. She was initially treated with vitamin B6, but the spasms continued. Once on vigabatrin, her spasms decreased from 3 per day to 1-2 per day; however, startle seizures increased and she had development of a new seizure type during which she stared and was unresponsive. She was also diagnosed with cortical blindness. Metabolic studies and an MRI were normal. The infant was in hospice care and had developed increasing spasm activity the weekend prior to her death. At midnight on the day before her death, she began to bleed from the mouth and expired 2 hours later. At the time of death she was receiving a dose of 148.8 mg/kg vigabatrin and had been on this dose for 3-1/2 weeks. Autopsy findings showed the infant died from a pulmonary hemorrhage secondary to pulmonary angiomatosis. Plexuses of large abnormal muscularized vessels with focal subintimal fibrosis were present next to the right and left bronchi of the lungs, which raises the possibility of arteriovenous shunting. Left ventricular hypertrophy in the heart is additional evidence that there was an abnormal hemodynamic state.

0098/12370012 Cause of death: carcinoma
This 54 year old male with a history of seizures was diagnosed with pancreatic cancer during a vigabatrin trial. The narrative provided descriptions of the imaging and laboratory evidence supporting this diagnosis. The subject died and pancreatic cancer was listed as the cause of death.

0242/1540001 Cause of death: adenocarcinoma
This 60 year old male with a history of complex partial seizures died after approximately 22 months of vigabatrin therapy. The patient was diagnosed with adenocarcinoma of the "windpipe" and was treated with chemotherapy and radiation. Approximately three months later, he expired. No autopsy was completed. This event was considered severe in intensity and the investigator felt the causality to be not related to study drug but to the concurrent illness of adenocarcinoma. There were no concomitant AEDs at the time of the event.

0201/1621007 Cause of Death: hepatic necrosis with multisystem organ failure
This 17 year-old female had received vigabatrin 1g QD for approximately 20 months prior to hospitalization for elective intracranial monitoring prior to a possible lobectomy for intractable epilepsy. During treatment with vigabatrin, AST and ALT values decreased, but were still within normal limits, with the exception of a low ALT at the study visit prior to hospitalization.

The subject was admitted on [redacted] and had surgery the following day. Her dose of vigabatrin had been reduced to 500 mg BID for this procedure and the final dose was on the day of surgery. The evening after surgery, she was found seizing with generalized tonic clonic seizures that progressed to status epilepticus. The seizures lasted approximately 50 minutes. She was treated with phosphenytoin, phenobarbital, IV fluids and was intubated. Upon examination the patient was afebrile, hypotensive and unresponsive; broad spectrum antibiotics (including ceftazadine, clindamycin, gentamycin) were initiated as well as hemodynamic support with levophed and dopamine. Her clinical course continued to decompensate with liver enzymes escalating rapidly until her death 4 days after last vigabatin dose. Post-mortem report described the cause of death as extensive hepatic necrosis with multisystem organ failure. The investigator assessed this case as "definitely" drug related when completing the CRF, however, it was assessed as "possibly" related on the SAE Reporting Form. Concomitant medications included carbamazepine 400 mg BID (duration unknown) and Prozac (dose / duration unknown). Post mortem examination revealed extensive hepatocellular necrosis with prominent steatosis evident in the remaining viable parenchyma. Examination of the brain showed right hippocampal sclerosis, malrotation of the left hippocampus (findings consistent with old injury or a developmental abnormality), and diffuse acute ischemic injury in the cortex and brainstem. The acute ischemic injury was felt to be a consequence, not a cause, of her clinical course.

b(6)

Liver Enzymes:	AST (U/L)	ALT (U/L)	GGT (U/L)	AlkPhos (U/L)
Clinical Study:				
[redacted]	15	12	n/a	68
	13	8	n/a	276
	9	4 (low)	n/a	231
Hospital:				
[redacted]	67	41	103	125
	245	86	140	150
	4700	4609	149	183
Normal values:	(0-31)	(7-56)	(0-65)	(39-117)

b(6)

Summaries of Clinical Details for the Select Serious Adverse Events Reported in the Current Submission

Rash

Subject 0101/1325-0002 This 56-year old Caucasian male with a history of non-refractory complex partial seizures since age 10, experienced a mild rash on his arms lasting 23 days, when he had been taking vigabatrin for 32 days. The rash resolved without sequelae, there was no change in study medication and the subject completed the study. The subject was also treated with carbamazepine at the time of the event. The investigator noted in the CRF that the alternative etiology was poison ivy. When asked why this event was considered an SAE, Ovation responded that the previous sponsor had flagged the event as an SAE and that they took a conservative approach to be consistent with how the previous sponsor classified the event (Submission dated 3/14/08).

Subject 0101/1335-0004 This 40-year old black female with a history of complex partial seizures since age 37, experienced moderate agitation, moderate amnesia, and a mild skin rash all lasting 173 days and mild increased appetite lasting 127 days, while randomized to vigabatrin. The subject was on study medication for 35 days prior to the onset of agitation, 81 days prior to the onset of rash, 35 days prior to the onset of amnesia, and 81 days prior to the onset of increased appetite. All of the events resolved without sequelae; however, the subject discontinued from the study due to these events. Theo-Dur was the only concurrent medication taken. In the CRF, the rash was characterized as mild and located on the subject's hands. As with the previous event, Ovation categorized this event as an SAE because the previous sponsor had flagged the event as an SAE. (Submission dated 3/14/08).

Subject 0101/1359-0007 This 21 year old Caucasian female with a history of complex partial seizures developed a rash on vigabatrin. The narrative did not characterize the rash. At the time of the event she was taking vigabatrin 1g BID. She discontinued from the trial for the rash. The rash resolved. Concomitant medications at the time of the event were carbamazepine, ibuprofen, and naproxen. Ovation noted that the CRF captured 2 events of rash in this subject but that the sequence of these events was not clear. The investigator diagnosed one rash as atopic dermatitis and described the rash as dry and scaly and moderate in intensity. Ovation was unable to characterize the second rash and provided no explanation for why rash was an SAE for this subject.

Subject 0118/1272-0002 This 12 year old Caucasian female with complex partial seizures experienced confusional state, disorientation, hallucination, headache, rash, and tremor while taking vigabatrin. Twenty-one days after receiving her first vigabatrin dose, she was hospitalized for the events listed above. She was treated with acetaminophen, morphine, naloxone, diphenhydramine, and pyridoxine. The events were reportedly resolved 4 days after stopping vigabatrin. Concomitant medications at the time of the event were phenytoin and acetaminophen.

Rash maculopapular

Subject 0101/1359-0001 This 32-year old Caucasian female with a history of complex partial seizures since age 30 reported a severe migraine headache lasting for 4 hours and a moderate macropapular rash lasting for 38 days while on vigabatrin. The subject was on study medication for 38 days prior to the migraine and 64 days prior to the rash event. Study medication was unchanged and the events resolved without sequelae. The subject did not discontinue from the study due to these events. Concurrent medications included aspirin, ibuprofen, sertraline hydrochloride, hydrocortisone cream, Ortho-Novum, Elocon cream and Temovate.

Subject 0201/1386-0002 This 14-year old female Caucasian with a history of complex partial seizures was hospitalized for increased seizure frequency. The subject was also noted to have a bilateral extremity erythematous rash with crusts and excoriation that was described as moderate intensity. The subject was discontinued from the study. The narrative provides no diagnosis for the rash and does not indicate how the rash was treated. The rash was decreased when the subject was discharged from the hospital.

Leucocytoclastic vaculitis

Subject 0223/1480-0005 This 57 year old Caucasian female with a history of simple partial seizures, complex partial seizures and partial generalized seizures experienced leukocytoclastic vasculitis and shortness of breath while

on vigabatrin. Subject was on vigabatrin for 23 days prior to the events. On [redacted] the subject noted a rash (described as bilateral petechia of the lower extremities) on the back of her legs (more severe on the left leg) which worsened the next day. Subject also complained of shortness of breath and wheezing. She took two of her husband's nitroglycerin tablets to relieve the shortness of breath. The outcome of the events was not provided but the subject was hospitalized due to the events. The physical and neurological exams were unremarkable. Lab and x-ray results were not provided. A dermatologist diagnosed leukocytoclastic vasculitis as 'commonly seen' in drug-type reactions. The intensity of the reaction was considered moderate, with a duration of four days. The event resolved. Vigabatrin was discontinued on 28Feb1996 due to the events. Medical history included renal failure, arthritis, left hip fracture 1995, hysterectomy due to carcinoma and fibroids with chemotherapy treatment, carpal tunnel syndrome of the right hand and release, poor memory and drug allergy to Feldene. Concomitant medications included Dilantin, Tegretol, Tylenol, Aleve, Didronel, aspirin, Premarin, Nitrostat and calcium carbonate. b(6)

Stevens Johnson Syndrome

Subject 0201/1398-0009 This 12 year old Caucasian male with a history of complex partial seizures was hospitalized for Stevens-Johnson Syndrome on [redacted] after 3 months of treatment with vigabatrin in this study. The patient received his first dose of vigabatrin on 14Jan1997 in this study and his last dose on 22Apr1997. The event was considered by the investigator to be severe in intensity, and not related to study drug, but rather to a concurrent drug. Concomitant anti-epileptic medications included Tegretol and Lamictal. The patient discontinued study medication and the event was still under treatment at the conclusion of the study. Use of these medications was discontinued on 22Apr1997. Phosphenytoin was administered on 22Apr1997 through 26Apr1997. Other concomitant medications at the time of the event included Ritalin (discontinued on 22Apr1997), ibuprofen and Sulfacetamide Ophthalmologic (15Apr1997 to 19Apr1997). b(6)

Approximately 3 months after discontinuation of vigabatrin treatment, the patient was hospitalized for conjunctivitis and stomatitis (onset date of 22Jul1997) and erythema (onset date of 25Jul1997). The investigator assessed the events to be moderate in intensity and not related to study drug, and the events resolved on 29Jul1997. Concomitant anti-epileptic medications at the time of the events were Depakote and IV Depacon. Depakote 500 mg TID was taken by the patient from 25Apr1997 through 25Jul1997, and then re-initiated on 29Jul1997. Depacon 500 mg TID was administered on 25Jul1997 only. Other concomitant medications administered at the time of the events were: Ibuprofen; Benadryl (alcohol free)/Maalox 50/50 (25Jul1997 to 29Jul1997); Tylenol (25Jul1997 to 26Jul1997); acetaminophen (26Jul1997 to 29Jul1997); Lacrilube (26Jul1997 to 29Jul1997); Artificial Tears (26Jul1997 to 29Jul1997); Indocin (26Jul1997 to 10Aug1997); Sustasol (28Jul1997 to 29Jul1997); and Nubain (28Jul1997).

Prior to this current study, the patient participated in Study 0221 and received vigabatrin for 117 days.

Acute Renal Failure

Subject 0242/1504-0003 This 25 year old Caucasian male with a history of refractory epilepsy since childhood experienced acute renal failure secondary to dehydration and altered mental status changes while on vigabatrin. Subject was on vigabatrin for one year and five months prior to the events. Subject experienced two generalized seizures on 30Jan1998. On 01Feb1998 subject had flu-like symptoms. On [redacted] he became less coherent with alteration in mental status and was hospitalized. Admission labs revealed a creatinine of 8.6 and BUN of 70. The subject had a creatinine of 1.1 in [redacted]. A renal consultant felt that the renal failure was most likely secondary to dehydration, and that the renal failure was acute tubular necrosis, secondary to decreased volume. The subject was rehydrated with large amounts of fluid and the creatinine steadily declined over the course of hospitalization. Discharge creatinine level was 1.7. Renal ultrasound and urine eosinophils were negative. Also on admission subject was noted to be extremely slow to respond to questions, although responded appropriately and was oriented. Subject was unable to perform calculations or digit span; had prominent asterixis and twitches of the eye brows, corners of the mouth and lips. Admission EEG showed generalized delta waves and multi-focal spikes. There was no EEG correlation for the myoclonic jerking. Vigabatrin was stopped and the subject showed gradual improvement of mental status. An EEG on [redacted] showed marked improvement. Carbamazepine therapy was continued. Discharge status was good; subject was able to function independently. Hospital discharge diagnosis was acute renal failure and vigabatrin toxicity. The subject was withdrawn from the study and the events resolved on b(6)

08Feb 1998. Medical history included migraines. Concomitant medications included Tegretol, aspirin and nortriptyline.

Subject 0201/1400-0003 This 13 year old Caucasian male, 145 pounds, with a history of complex partial seizures experienced aggression, anorexia, coma, diarrhea, disseminated intravascular coagulation, encephalitis, hypoxia, lethargy, pyrexia, renal failure and abnormal visual evoked potentials, abnormal optic nerve in right eye, optic neuropathy and two episodes of visual field defect while on vigabatrin. Prior to this current study, subject participated in another vigabatrin study. For this study, subject received first dose of vigabatrin on 08Nov1996 and last dose of vigabatrin on 07Sept1998. On [redacted], the subject was hospitalized in the pediatric intensive care unit for meningeal encephalitis with decreased oxygen saturation, increased creatinine, decreased platelets, lethargy, decreased mental status, decreased oral intake, diarrhea, fever and combativeness. The encephalitis was treated with ceftriaxone 2 gm BID for 6 days and acyclovir 650 mg BID for 8 days. On [redacted] the subject was in a coma. While hospitalized, the subject had transient increases in blood pressure that were treated with nifedipine. The subject had unknown number of episodes of multiple loose stools of unknown etiology. Stool enteric pathogen studies were negative. The subject developed a new onset acute renal failure while hospitalized (baseline creatinine 0.8). On admission, BUN was 56 and creatinine was 2.8, which was initially thought to be secondary to dehydration/prerenal azotemia. Despite vigorous fluid rehydration, the subject urine output remained low. Urine analysis on admission revealed moderate blood. Specific gravity was 1.045 and WBCs were 8 to 10 with some cellular casts. The subject was noted to have proteinuria, which resolved. Lumbar puncture on admission revealed WBCs 209 with 74% PMNs (polymorphonuclear leukocytes), glucose 55 and protein 47. b(6)

There was a history of the subject's intake of some hamburger meat, which in conjunction with other data raises suspicions for hemolytic uremic syndrome. The subject's renal status slowly improved and on the day of discharge, the BUN was 29 and creatinine 1.5. The subject also developed disseminated intravascular coagulation (DIC) while hospitalized. The subject was given fresh frozen plasma and had an allergic reaction with chills and hives. The allergic reaction was treated with diphenhydramine. The subject remained on vigabatrin while hospitalized and received valproic acid 1750 mg/day. The start/stop date, severity, action taken/outcome were not provided for aggression/anorexia/coma/lethargy/pyrexia. The events of diarrhea/DIC/encephalitis/hypoxia were severe in intensity, unlikely related to study drug, and resolved on [redacted] The subject was discharged on [redacted] The principle discharge diagnosis was meningeal encephalitis and the secondary discharge diagnoses were acute renal failure and DIC. Medical history was not provided. The investigator assessed all of the events as not related to vigabatrin, but rather due to concurrent illnesses. Concomitant medications included Topamax, Lamictal 75 mg QHS, Depakote 500 mg BID, Depakote 750 mg QHS, acetaminophen 650 mg PRN and Tofranil 25 mg QHS. b(6)

Hypersensitivity

Subject 0101/1358-0001 This 27 year old Caucasian female with a history of simple partial seizures, complex partial seizures and partial generalized seizures experienced depression, headache and hypersensitivity while on vigabatrin. Subject was on study medication for 21 days prior to onset of event of hypersensitivity. The investigator assessed the event of hypersensitivity as possibly related to study medication and moderate in intensity. The subject was discontinued due to the event and the event resolved. Study medication was reintroduced at the same dosage (1 **gram BID) and the event did not reappear. Medical history included tonsillectomy 1975, lungs "underdeveloped" as a premature infant, tubal ligation 1989, occasional yeast infections, cyst removal left knee 1983, bipolar – non** active, suicide attempt ten years ago.

Tongue edema

Subject 0101/1342-0006 This 34 year old Caucasian female with a history of complex partial seizures experienced tongue edema while on vigabatrin. The subject was on vigabatrin since 27Sep1995. The narrative supplied by Ovation did not mention tongue edema. In response to a request from the Division, Ovation reported that the subject experienced tongue edema that was moderate in intensity and that lasted approximately 1 week (2/20/96-2/27/96). The investigatory noted a possible alternative etiology of infection. Ovation reported that vigabatrin was continued and that the event resolved (Source 3/14/08 submission).

Adverse Events Occurring Between 0.1 % and 1 % of Vigabatrin- Treated Subjects (Overall Safety Population)

Nervous System Disorders Cognitive disorder, Dyskinesia, Complex partial seizures, Dyscalculia, Grand mal convulsion, Hypotonia, Nervous system disorder, Speech disorder, Aphasia, Drooling, Hemiparesis, Migraine, Partial seizures, Carpal tunnel syndrome, Depressed level of consciousness, Movement disorder, Postictal state, Simple partial seizures, Febrile convulsion, Hemianopia homonymous, Hypertonia, Mental impairment, Myoclonus, Neuropathy peripheral, Clumsiness, Epilepsy Reflexes abnormal, Extensor plantar response, Facial paresis, Hypokinesia, Infantile spasms, Sinus headache, Asterixis, Clonus, Neurological symptom, Sensory disturbance, Burning sensation, Cerebellar syndrome, Dysgeusia, Dysgraphia, Epileptic aura, Facial palsy, Hemiplegia transient, Hypersomnia, Hyporeflexia, Intention tremor, Myoclonic epilepsy, Psychomotor skills impaired, Restless legs syndrome, Syncope

Infections and Infestations Infection, Rhinitis, Candidiasis, Varicella, Tooth infection, Croup infectious, Fungal infection, Vaginal mycosis, Hordeolum, Respiratory syncytial virus infection, Respiratory tract infection, Roseola, Localized infection, Streptococcal infection, Bronchiolitis, Dental caries, Impetigo, Otitis media chronic, Postoperative infection, Tonsillitis, Viral upper respiratory tract infection, Conjunctivitis infective, Cystitis, Eye infection, Gastrointestinal infection, Otitis externa, Tooth abscess, Vaginal infection, Lobar pneumonia, Candida nappy rash, Herpes simplex, Infected insect bite, Tinea infection, Viral rash, Genital candidiasis, Prostate infection

Psychiatric Disorders Affect lability, Nervousness, Disorientation, Sleep disorder, Hallucination, Bradyphrenia, Crying, Depressed mood, Libido decreased, Anger, Cognitive deterioration, Dysphemia, Mood altered, Nightmare, Stress, Attention deficit/hyperactivity disorder, Dissociation, Panic attack, Personality change, Restlessness, Self injurious behavior, Conversion disorder, Hallucination auditory, Initial insomnia, Mental status changes, Middle insomnia, Psychotic disorder, Thinking abnormal, Depersonalisation, Distractibility,Hostility, Mental disorder, Paranoia

General Disorders and Administration Site Conditions Pain, Gait disturbance, Feeling abnormal, Adverse drug reaction, Influenza like illness, Malaise, Drug interaction, Swelling, Chills, Cyst, Oedema, Death, Feeling drunk, Feeling hot, General symptom, Sluggishness, Thirst

Gastrointestinal Disorders Abdominal pain, Stomach discomfort, Flatulence, Gastrooesophageal reflux disease, Gastrointestinal disorder, Abdominal distension, Toothache, Dry mouth, Mouth ulceration, Salivary hypersecretion, Abdominal discomfort, Gingival hyperplasia, Gingival hypertrophy, Gingivitis, Teething, Tooth disorder, Dysphagia, Gingival bleeding, Haematochezia, Rectal haemorrhage, Faecaloma, Frequent bowel movements, Gastritis, Gingival pain, Gingival swelling, Halitosis, Stomatitis, Tooth discolouration, Tooth loss

Injury, Poisoning and Procedural Complications Contusion, Foot fracture, Head injury, Thermal burn, Joint sprain, Drug toxicity, Excoriation, Back injury, Hand fracture, Joint injury, Road traffic accident, Ankle fracture, Laceration, Limb injury, Mouth injury, Post procedural pain, Facial bones fracture, Fracture, Joint dislocation, Lower limb fracture, Muscle strain, Rib fracture, Wrist fracture, Clavicle fracture, Face injury, Incision site complication, Ligament injury, Polytraumatism, Arthropod bite, Arthropod sting, Concussion, Post procedural complication, Animal bite, Burns second degree, Eye injury, Femur fracture, Shunt occlusion, Sunburn, Upper limb fracture, Wound

Eye Disorders Conjunctivitis, Strabismus, Visual acuity reduced, Eye pain, Blepharitis, Hypermetropia, Astigmatism, Eye irritation, Myopia, Blepharospasm, Ocular hyperaemia, Optic nerve disorder, Retinal disorder, Amblyopia, Conjunctival haemorrhage, Corneal disorder, Corneal opacity,Dry eye, Eye discharge, Eye haemorrhage, Eyelid ptosis, Keratitis, Optic disc disorder, Scotoma, Vitreous detachment, Vitreous floaters

Investigations Blood alkaline phosphatase increased, Body temperature increased, Retinogram abnormal, Anticonvulsant drug level increased, Anticonvulsant drug level decreased, Cardiac murmur, Platelet count decreased, Tandem gait test abnormal, Blood pressure increased, Gamma-glutamyltransferase increased,

Blood creatinine increased, Blood glucose increased, Alanine aminotransferase increased, Anticonvulsant drug level below therapeutic, Blood potassium decreased, Blood potassium increased, Heart rate increased, Nuclear magnetic resonance imaging abnormal, Visual evoked potentials abnormal, White blood cell count decreased

Skin and Subcutaneous Tissue Disorders Eczema, Dermatitis contact, Dry skin, Urticaria, Rash macular, Skin lesion, Hyperhidrosis, Pruritus, Rash popular, Dermatitis diaper, Ingrowing nail, Rash erythematous, Rash maculo-papular, Dermatitis, Erythema, Dermal cyst, Ecchymosis, Hypotrichosis, Increased tendency to bruise, Photosensitivity reaction, Night sweats Purpura, Rash generalized,Rash pruritic, Rosacea, Swelling face

Respiratory, Thoracic and Mediastinal Disorders Dyspnoea, Rhinorrhoea, Epistaxis, Sinus congestion, Asthma, Upper respiratory tract congestion, Wheezing, Respiratory disorder, Aspiration, Pneumonia aspiration, Bronchospasm, Respiratory tract congestion, Dysphonia, Sinus disorder, Respiratory distress, Apnoea, Productive cough, Respiratory arrest, Rhinitis allergic, Sleep apnoea syndrome

Musculoskeletal and Connective Tissue Disorders Muscle spasms, Myalgia, Muscular weakness, Neck pain, Musculoskeletal pain, Arthritis, Muscle twitching, Bursitis, Joint swelling, Musculoskeletal discomfort, Musculoskeletal stiffness, Shoulder pain, Chest wall pain, Osteoarthritis, Osteoporosis, Scoliosis, Tendonitis, Arthropathy, Exostosis, Flank pain, Limb discomfort, Pain in jaw

Metabolism and Nutrition Disorders Anorexia, Feeding disorder, Dehydration, Fluid retention, Hypercholesterolaemia, Hypoglycaemia, Hypokalaemia

Reproductive System and Breast Disorders Amenorrhoea, Menstruation irregular, Breast mass, Erectile dysfunction, Breast pain, Menstrual disorder, Endometriosis, Metrorrhagia, Ovarian cyst, Prostatitis, Benign prostatic hyperplasia, Menorrhagia

Ear and Labyrinth Disorders Tinnitus, Ear pain, Ear disorder, Vertigo, Hypoacusis, Hearing impaired, Middle ear effusion, Tympanic membrane disorder

Renal and Urinary Disorders Urinary incontinence, Proteinuria, Dysuria, Enuresis, Urinary retention, Haematuria, Pollakiuria, Nephrolithiasis, Incontinence, Renal pain

Blood and Lymphatic System Disorders Anaemia, Lymphadenopathy, Neutropenia, Iron deficiency anaemia, Leukopenia, Vascular Disorders, Hypertension, Hot flush, Orthostatic hypotension

Surgical and Medical Procedures Brain lobectomy, Cataract operation, Tooth extraction

Immune System Disorders Hypersensitivity, Seasonal allergy, Drug hypersensitivity

Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps) Skin papilloma, Uterine leiomyoma,

Cardiac Disorders Palpitations, Tachycardia, Bradycardia

Congenital, Familial and Genetic Disorders Cleft palate, Tuberous sclerosis

Endocrine Disorders Cushingoid

Pregnancy, Puerperium and Perinatal Conditions Pregnancy

Adverse Events Occurring in <0.1% of Vigabatrin-Treated Subjects (Overall Safety Population)

Nervous System Disorders Areflexia, Atonic seizures, Coma, Dizziness postural, Encephalitis, Essential tremor, Facial nerve disorder, Gait spastic, Hydrocephalus, Hyperkinesia, Hyperreflexia, Neuralgia, Sensory loss, Stupor, Temporal lobe epilepsy, Tunnel vision, Ageusia, Athetosis, Aura, Brain oedema, Cerebrosclerosis, Cerebrovascular accident, Dizziness exertional, Drop attacks, Dysaesthesia, Dysphasia, Dystonia, Encephalitis toxic, Encephalopathy, Head discomfort, Hemianopia heteronymous, Horner's syndrome, Intracranial pressure increased, Meralgia paraesthetica, Monoplegia, Muscle spasticity,Neuropathic pain, Neuropathy, Neurotoxicity, Paraesthesia oral, Paresis, Parosmia, Partial seizures with secondary generalization, Peripheral sensory neuropathy, Peroneal nerve palsy, Petit mal epilepsy, Polyneuropathy, Poor quality sleep, Post-traumatic headache, Postictal headache, Pyramidal tract syndrome, Quadriparesis,Radicular pain, Sciatica, Speech disorder developmental, Subdural hygroma, Syncope vasovagal, Tongue paralysis

Infections and Infestations Bronchitis acute, Cellulitis, Chronic sinusitis, Enterobiasis, Erythema infectiosum, Febrile infection, Fungal skin infection, Gingival infection, Herpes zoster, Infected sebaceous cyst, Kidney infection, Laryngitis, Mycetoma mycotic, Onychomycosis, Oral candidiasis, Pneumonia respiratory syncytial viral, Pneumonia viral, Respiratory tract infection viral, Skin infection, Staphylococcal infection, Tinea pedis, Viral pharyngitis, Abscess oral, Acute sinusitis, Adenovirus infection, Appendicitis, Bacteraemia, Bacterial infection, Breast abscess, Bronchitis viral, Bronchopneumonia, Cervicitis, Clostridium colitis, Conjunctivitis viral, Corneal infection, Diverticulitis, Ear lobe infection, Endocarditis, Folliculitis, Fungal rash, Gastroenteritis rotavirus, Genital infection fungal, Genitourinary chlamydia infection, Hand-foot-and-mouth disease, Herpes virus infection, Infectious mononucleosis, Infusion site infection, Kawasaki's disease, Laryngotracheitis, Lice infestation, Lower respiratory tract infection, Mastitis, Meningitis, Nail infection, Osteomyelitis, Parametritis, Pelvic inflammatory disease, Pharyngotonsillitis, Pneumococcal bacteraemia, Pneumonia streptococcal, Purulent discharge, Rash pustular, Sepsis, Tinea cruris, Tracheitis, Urinary tract infection pseudomonal, Vaginal candidiasis

Psychiatric Disorders Abnormal dreams, Apathy, Decreased activity, Delusion, Dysphoria, Eating disorder, Euphoric mood, Flat affect, Hallucination visual, Indifference, Logorrhoea, Major depression, Obsessive-compulsive disorder, Suicidal ideation, Acute stress disorder, Adjustment disorder, Affective disorder, Antisocial behaviour, Belligerence, Communication disorder, Daydreaming, Delirium, Delusional disorder persecutory type, Delusional disorder unspecified type, Depression suicidal, Depressive symptom, Disturbance in sexual arousal, Early morning awakening, Emotional disorder, Excitability, Factitious disorder, Hallucinations mixed, Hypervigilance, Inappropriate affect, Listless, Mania, Orgasm abnormal, Panic disorder, Personality disorder, Posturing, Pressure of speech, Reading disorder, Self esteem decreased, Social avoidant behaviour, Suicide attempt, Tearfulness, Tension, Tic

General Disorders and Administration Site Conditions Difficulty in walking, Face oedema, Facial pain, Feeling jittery, Gravitational oedema, Infusion site reaction, Local swelling, Localised oedema, Nodule, Secretion discharge, Abasia, Catheter related complication, Chest discomfort, Developmental delay, Discomfort, Drug intolerance, Feeling cold, Hangover, Hunger, Inflammation, Infusion site swelling, Mass, Non-cardiac chest pain, Pitting oedema, Polyp, Submandibular mass, Temperature intolerance, Tenderness, Ulcer

Gastrointestinal Disorders Abdominal pain lower, Eructation, Faecal incontinence, Gastric ulcer, Haemorrhoids, Hypoaesthesia oral, Inguinal hernia, Irritable bowel syndrome, Lip ulceration, Pancreatic mass, Tongue disorder, Tooth fracture, Tooth impacted, Abdominal distention, Abnormal faeces, Anal fissure, Anorectal disorder, Aphthous stomatitis, Cheilitis, Colitis, Colonic polyp, Defaecation urgency, Enamel anomaly, Food poisoning, Gastrointestinal haemorrhage, Gastrointestinal motility disorder, Gastrointestinal pain, Gingival disorder, Glossodynia, Hiatus hernia, Ileus paralytic, Inflammatory bowel disease, Lip pain, Oesophagitis, Oesophagitis ulcerative, Oral pain, Parotid gland enlargement, Periodontal disease, Proctitis, Pruritus ani, Rectocele, Reflux gastritis, Reflux oesophagitis, Retching, Salivary gland enlargement, Sensitivity of teeth, Swollen tongue, Tongue coated, Tongue oedema

Injury, Poisoning and Procedural Complications Accident, Accidental overdose, Fibula fracture, Heat exhaustion, Neck injury, Overdose, Periorbital haematoma, Stress fracture, Alcohol poisoning, Anaesthetic complication, Brain contusion, Cephalhaematoma, Cervical vertebral fracture, Corneal abrasion, Delayed recovery from anaesthesia, Ear injury, Epicondylitis, Feeding tube complication, Femoral neck fracture, Foreign body in eye, Headache postoperative, Hip fracture, Incorrect dose administered, Limb crushing injury, Medication error, Meniscus lesion, Near drowning, Poisoning, Postmastectomy lymphoedema syndrome, Postoperative fever, Scratch, Snake bite, Soft tissue injury, Spinal compression fracture, Subdural haematoma, Subdural haemorrhage, Surgical procedure repeated, Thoracic vertebra injury, Tongue injury, Tooth injury, Traumatic brain injury, Ulna fracture, Vaccination complication, Ventriculoperitoneal shunt malfunction, Wound complication

Eye Disorders Altered visual depth perception, Asthenopia, Blindness cortical, Cataract, Cataract nuclear, Chalazion, Eye movement disorder, Eye swelling, Eyelid disorder, Eyelid oedema, Maculopathy, Photopsia, Pupillary disorder, Retinal detachment, Vitreous disorder, Arcus lipoides, Blindness, Blindness transient, Cataract cortical, Cataract subcapsular, Chorioretinal disorder, Conjunctival cyst, Conjunctival follicles, Conjunctival hyperaemia, Conjunctivitis allergic, Erythema of eyelid, Exophthalmos, Extraocular muscle paresis, Eye inflammation, Eye pruritus, Eyelid cyst, Eyelid margin crusting, Heterophoria, Lacrimation increased, Macular degeneration, Optic atrophy, Optic neuropathy, Orbital cyst, Oscillopsia, Periorbital disorder, Photophobia, Pinguecula, Presbyopia, Punctate keratitis, Pupils unequal, Refraction disorder, Retinal naevus, Vitreous degeneration, Xerophthalmia

Investigations Blood amylase increased, Blood creatine increased, Blood glucose decreased, Blood sodium decreased, Blood urine present, Liver function test abnormal, Neutrophil count decreased, Ophthalmological examination abnormal, Positive rombergism, Tuberculin test positive, Urine analysis abnormal, White blood cells urine positive, Ammonia increased, Anticonvulsant drug level above therapeutic, Antinuclear antibody positive, Arthroscopy, Biopsy breast, Biopsy kidney, Blood albumin abnormal, Blood albumin decreased, Blood cholesterol increased, Blood corticotrophin abnormal, Blood growth hormone decreased, Blood insulin increased, Blood magnesium decreased, Bone density decreased, Colour vision tests abnormal, Corneal reflex decreased, Cystoscopy, Diagnostic procedure, Drug level increased, Electroencephalogram, Faecal occult blood, Glycosylated haemoglobin, Haematocrit decreased, Haemoglobin abnormal, Haemoglobin decreased, Heart sounds abnormal, Hepatic enzyme increased, Laboratory test abnormal, Liver palpable subcostal, Low density lipoprotein increased, Lymph node palpable, Neurological examination abnormal, Optic nerve cup/disc ratio increased, Pedal pulse absent, Pedal pulse decreased, Protein total decreased, Pupillary light reflex tests abnormal, Red blood cell count decreased, Red blood cell count increased, Respiratory rate increased, Thyroid function test abnormal, Thyroxine decreased, Vibration test abnormal, Visual tracking test abnormal, White blood cell count increased

Skin and Subcutaneous Tissue Disorders Dermatitis acneiform, Dermatitis allergic, Hirsutism,Hypohidrosis, Nail disorder, Periorbital oedema, Petechiae, Scar, Seborrhoea, Skin disorder, Skin hypopigmentation, Skin irritation, Anhidrosis, Blister, Cafe au lait spots, Dandruff, Dermatitis atopic, Fat atrophy, Hair disorder, Hair growth abnormal, Hyperkeratosis, Leukocytoclastic vasculitis, Neurodermatitis, Oily skin, Onychorrhexis, Pruritus allergic, Pruritus generalized, Rash follicular, Skin discolouration, Skin exfoliation, Skin odour abnormal, Skin tightness, Skin ulcer, Stevens-johnson syndrome, Urticaria localized

Respiratory, Thoracic and Mediastinal Disorders Hiccups, Hypoxia, Nasal septum deviation, Obstructive airways disorder, Paranasal sinus hypersecretion, Pharyngeal erythema, Pulmonary congestion, Throat irritation, Tonsillar disorder, Apnoeic attack, Choking, Crackles lung, Dyspnoea exacerbated, Grunting, Increased upper airway secretion, Laryngeal stenosis, Lower respiratory tract inflammation, Nasal discomfort, Pleural effusion, Pleurisy, Pleuritic pain, Pneumomediastinum, Pneumonitis, Postnasal drip, Pulmonary embolism, Pulmonary haemorrhage, Pulmonary oedema, Respiratory failure, Rhinitis seasonal, Rhonchi, Sputum discoloured, Stridor, Throat tightness, Tonsillar hypertrophy, Upper respiratory tract inflammation

Musculoskeletal and Connective Tissue Disorders Groin pain, Joint stiffness, Muscle atrophy, Osteopenia, Sensation of heaviness, Spinal osteoarthritis, Back disorder, Bone pain, Costochondritis, Hip deformity, Intervertebral disc disorder, Intervertebral disc protrusion, Kyphoscoliosis, Kyphosis, Lumbar spinal stenosis,

Muscle contracture, Muscle swelling, Musculoskeletal chest pain, Spinal deformity, Tendon disorder, Toe deformity, Trismus,

Metabolism and Nutrition Disorders Diet refusal, Hyperglycaemia, Oral intake reduced, Weight fluctuation, Acidosis hyperchloraemic, Diabetes mellitus non-insulin-dependent, Feeding problem in newborn, Gout, Hyperlipidaemia, Hypernatraemia, Hypomagnesaemia, Metabolic acidosis, Metabolic disorder, Obesity, Vitamin b12 deficiency

Reproductive System and Breast Disorders Breast discharge, Reproductive tract disorder, Breast swelling, Breast tenderness, Dyspareunia, Ejaculation disorder, Genital erythema, Genital pain female, Genital rash, Menometrorrhagia, Ovarian cyst ruptured, Pelvic pain, Perineal pain, Polycystic ovaries, Testicular pain, Vaginal discharge, Vaginal disorder, Vulva cyst

Ear and Labyrinth Disorders Deafness, Deafness unilateral, Tympanic membrane perforation, Cerumen impaction, Deafness bilateral, Ear haemorrhage, Hyperacusis, Tympanic membrane hyperaemia

Renal and Urinary Disorders Glomerulonephritis focal, Micturition frequency decreased, Renal failure acute, Bladder disorder, Glycosuria, Ketonuria, Kidney enlargement, Leukocyturia, Micturition disorder, Micturition urgency, Polyuria, Renal cyst, Stress incontinence, Urethral disorder, Urinary hesitation, Urinary tract disorder

Blood and Lymphatic System Disorders Lymphadenitis, Disseminated intravascular coagulation, Leukocytosis, Lymph node pain, Monocytosis, Nephrogenic anaemia, Thrombocythaemia

Vascular Disorders Circulatory collapse, Flushing, Hypotension, Pallor, Aortic stenosis, Deep vein thrombosis, Infarction, Varicose vein

Surgical and Medical Procedures Brain operation, Colon polypectomy, Fundoplication, Hospitalisation, Suture insertion, Brain tumour operation, Breast lump removal, Coronary artery bypass, Drug delivery device implantation, Endodontic procedure, Eye operation, Gastrointestinal tube insertion, Haemorrhoid operation, Mole excision, Osteotomy, Shoulder arthroplasty, Surgery Toe operation, Tooth repair, Tubal ligation, Tumor excision, Uterine operation, Vagal nerve stimulator implantation, Wisdom teeth removal

Immune System Disorders Immunisation reaction, Allergy to arthropod bite, Food allergy, Milk allergy

Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps) Benign breast neoplasm, Adenocarcinoma, Angiosarcoma, Astrocytoma, Basal cell carcinoma, Benign uterine neoplasm, Breast cancer, Fibroadenoma of breast, Glioma, Meningioma, Neoplasm, Neuroblastoma, Rhabdomyoma, Sebaceous adenoma

Cardiac Disorders Angina pectoris, Angina unstable, Atrioventricular block second degree, Cardiac failure congestive, Cardio-respiratory arrest, Cardiomegaly, Cyanosis, Myocardial infarction, Ventricular extrasystoles, Ventricular tachycardia, Wolff-parkinson-white syndrome

Congenital, Familial and Genetic Disorders Colour blindness, Congenital eye naevus, Talipes, Arteriovenous malformation, Bronchial cyst, Cryptorchism, Dermoid cyst, Epidermal naevus, Facial dysmorphism, Hip dysplasia, Phakomatosis, Porphyria non-acute, Retinitis pigmentosa, Skull malformation
Endocrine Disorders Hypothyroidism, Diabetes insipidus, Goitre, Growth hormone deficiency, Hypothalamo-pituitary disorders, Precocious puberty

Social Circumstances Corrective lens user, Educational problem, Alcohol use, Illiteracy, Sexual assault victim

Hepatobiliary Disorders Cholecystitis, Hepatomegaly, Cholelithiasis, Hepatic cyst, Hepatic failure, Hepatic necrosis

Pregnancy, Puerperium and Perinatal Conditions Abortion spontaneous, Normal delivery

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/s/

Jerry Boehm
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Sally Yasuda
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BIOPHARMACEUTICS

FEB 9 1999

Review and Evaluation of Clinical Data

NDA (Serial Number)	**20-427**
Sponsor:	**Hoechst Marion Roussel**
Drug:	**vigabatrin**
Proposed Indication:	**seizures**
Material Submitted:	**Correspondence**
Correspondence Date:	**12/4/98**
Date Received / Agency:	
Date Review Completed	**2/5/99**
Reviewer:	**Armando Oliva, MD**

1. Introduction

On 10/27/98, the Agency issued a non-approvable letter based on the occurrence of severe, asymptomatic, stereotypical visual field deficits in patients on long-term vigabatrin therapy. In the letter, we described that basic information about the defects remain unknown, such as:

- True incidence
- Anatomic location
- The relation to dose and/or duration of therapy
- Natural course
- Sensitivity of any method of surveillance
- Potential reversibility

The letter did not provide detailed information regarding the nature and amount of safety data that would be necessary to support approval; however, we did suggest that a long term safety study in a large number of patients, followed prospectively for a sufficient duration and monitored appropriately would be required.

The sponsor has now submitted a briefing packet in advance of a scheduled meeting with the Division on 2/9/99 during which time we will discuss their planned response to the non-approvable letter. They have the following two questions:

1. What additional data are required to support approval as an adjunctive therapy in the treatment of complex partial seizures in adults and/or the pediatric population?
2. What additional data are required to support approval for the treatment of infantile spasms.

As background material, they provide a summary of previous or ongoing studies, and an outline of the proposed clinical plan for investigation of the visual field defects, a comprehensive summary of all available information regarding the use

of vigabatrin in infantile spasms, and an independent assessment of the utility of vigabatrin for infantile spasms, including risk/benefits, provided by Dr. Shields (chief of pediatric neurology at UCLA).

2. Characterization of Visual Field Loss

This report contains data up through 11/18/98. The sponsor identified 222 patients on long-term vigabatrin therapy from 9 open label studies conducted in Finland (2), Japan (4), US, UK, and Germany (1 each). They also identified 101 patients who never took vigabatrin from the US, UK and Germany studies as reference controls.

These patients demonstrated an even distribution of males and females (56% females, 44% males). Results of one-way ANOVA on age, duration of vigabatrin treatment, cumulative vigabatrin dose, duration of epilepsy, and weight were significant, indicating that the studies were heterogeneous for these variables.

The average patient was 36 years old. Finnish and UK patients tended to be younger than their Japanese and US counterparts. The average treatment duration was 4.4 years and ranged from less than one month to 10.2 years. The average duration of epilepsy was 19.6 years and varied widely from 9.2 years in Finland to 22.5 years in the UK. As a consequence, any analysis using combined data must be viewed with caution for any background variable which interacts with the risk of vigabatrin attributed VFD.

Of the 222 identified vigabatrin patients, 208 has usable visual fields. Of these, 56 (27%) had vigabatrin-attributed visual field defect (Table 1).[1] These prevalence estimates were similar across countries and studies (chi square, p=0.26). In contrast, zero of the 101 patients not exposed to vigabatrin had VFD with the pattern observed with vigabatrin (upper 95% CI of 3%).

Table 1: Prevalence of Vigabatrin-Attributed VFD's

Country	Vigabatrin		Control	
	VGB VFD	Total (N=208)	VGB VFD	Total (N=101)
Finland	12 (35%)	34		
Japan	26 (26%)	99		
US	7 (25%)	28		
US			0	11
UK	9 (35%)	26		
			0	5
Germany /S2	2 (10%)	21		
Germany /S2			0	28
Germany 4017			0	42
Germany Pilot			0	15
Total	**56 (27%)**	**208**	**0**	**101**

VGB VFD – visual field defect of the type attributed to vigabatrin

[1] A VFD was attributed to vigabatrin if it could not be attributed to another cause.

The VFD's were graded on a four point scale, 7 Grade 1 (13%), 19 Grade 2 (34%), 17 Grade 3 (30%), and 13 grade 4 (23%).[2]

An association was found for male gender and VFD with a crude relative risk of 2.9 (CI 1.5-5.4). Thirty-eight percent (38%) of the males and 18% of the females had VFD. This pattern was consistent within all cohorts.

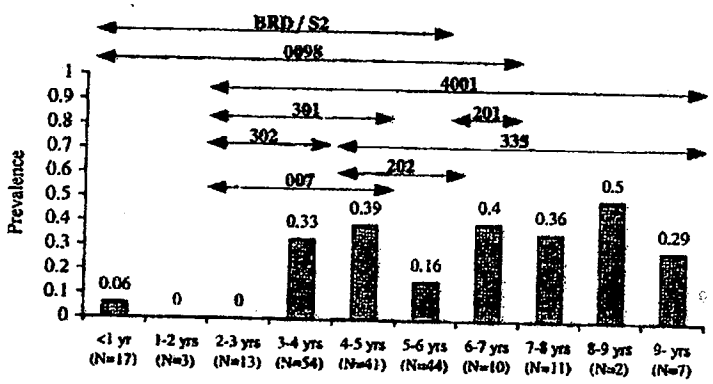
No association was found between VFD and age, weight, BMI, and duration of epilepsy.

Patients without VFD had a lower mean cumulative vigabatrin dose (4.2 kg vs. 4.7 kg) and a longer mean duration of epilepsy (19.9 years vs. 19 years) than patients with VFD. The mean duration of therapy was similar between subjects with and without VFD (4.8 years vs. 4.3 years). Since both of these were calculated to the time of diagnosis, the true time to onset of VFD is unknown and the true incidence remains unknown.

In a subset of 52 patients with known smoking status, there was a four fold increased risk of VFD in smokers or ex-smokers compared to never smokers. This will be investigated in future studies.

The sponsor plotted the prevalence of VFD with respect to duration of therapy, and there appeared to be an increase in prevalence after 3 years of treatment.

Figure 1: Prevalence of Vigabatrin-Attributed VFD By Study



N = number of subjects tested during the respective time intervals

The sponsor also modeled a hazard function to provide an indication of the risk of any patient developing VFD at any duration of vigabatrin. They suggest that the risk within the first 6 months and after 3-4 years is likely to be negligible.

[2] Details on how the grading was performed are not provided.

3. Proposed Investigational Plan

As a result of these findings, the sponsor proposes four studies designed to investigate:

- The time to new occurrence of VFD after the start of vigabatrin therapy
- The reversibility of VFD relative to vigabatrin therapy
- The long-term effects on the visual fields of children previously treated for infantile spasms.

They have submitted very brief (2 page) descriptions of each study. The outline of these studies are described below.

1. A one year follow-up study to investigate the clinical course of visual field defects
2. A 3 year follow-up study to investigate the clinical course of VFD
3. Prospective cohort of new vigabatrin users to elucidate the time to onset of VF defects and reversibility after early treatment withdrawal
4. Follow-up study to investigate long-term effects on visual fields in children

3.1 One Year Follow Up Study

The objective of this study is to assess the reversibility and progression of the VFD's between two visual field examinations at least one year apart. Secondary objectives will be to explore the impact of daily living in association with severity of VFD's and to explore or test predictive factors of vigabatrin associated VFD's. The study is expected to run 1 year.

This will be a multicenter, multinational follow-up study using a cohort of previous or current vigabatrin users with a well documented and reliable first visual field examination performed prior to 4/98. They plan to enroll 170 patients.

The outcome variable will be static perimetry and additional kinetic perimetry. They will analyze the expert's judgement of a significant change of the visual field in comparison with the first visual examination. The algorithm for any change in the visual field will be developed prior to case validation.

3.2 Three Year Follow Up Study

The primary objective is to assess the clinical course of visual field constrictions associated with the use of VGB. Secondary objectives are to assess the prevalence of VGB attributed visual field constrictions and to explore predictive factors of the severity of the visual field constriction pattern reported in association with VGB use. The study is expected to run three years. Data will be collected at 6 month intervals.

This will be a single center trial (Finland) using 21 current or previous VGB patients.

The outcome variable will be the perimetric testing of visual fields. The primary analysis will assess the change of type and severity of visual field defects.

3.3 Prospective Study

3.3.1 Title

Open, multicenter study of the prevalence, incidence, and clinical course of visual field defects (VFD's) in adults and children with refractory partial epilepsy treated with antiepileptic drugs (AED's).

3.3.2 Objectives

The objectives are to assess the prevalence, incidence, and clinical course of VFD's by perimetric testing (Humphrey and Goldmann) in patients with refractory partial epilepsy. Patients will include those who are currently treated with vigabatrin or other AED's and those never exposed to vigabatrin.

3.3.3 Study Design

The design is open, parallele, multicenter, multinational, cross-sectional (baseline evaluation) and longitudinal. Patients will be assessed every six months for 3 years.

3.3.4 Entry Criteria

Patients ≥8 years old of either sex with refractory epilepsy will be enrolled. It will consist of three groups:

- Patient on VGB ≥ 6 months and who have received any AED (including vigabatrin) ≥ 1 year
- Patients previously treated with VGB for ≥ 6 months who discontinued vigabatrin ≥ 6 months before entering the trial.
- Patients currently treated with other AED's ≥1 year and who have never received vigabatrin. Following a baseline perimetric evaluation, this cohort will serve as a reference group, and the patients will be candidates for the initiation of add-on vigabatrin treatment.

3.3.5 Sample Size

The total sample size is calculated to be 1060 in 60 centers.
The sample size was calculated based on the desired accuracy of the prevalence estimate for VFD's, the cumulative incidence of VFD's observed in patients taking VGB (27%),

The patient population will be stratified by age (8-12, and >12) and by current treatment on entry to the study.

The sample size assumes an assessed withdrawal rate of 15%. The breakdown is as follows:

Table 2: Planned Sample Size

Subgroup	N	
Adults on VGB	280	
Adults previously on VGB	210	Total Adults = 700
Adults never on VGB	210	
Children on VGB	140	

Subgroup	N	
Children previously on VGB	110	Total Children = 360
Children never on VGB	110	
Adults and Children never on VGB who become new VGB users	320	Adults = 210 Children = 110

3.3.6 Outcome Measure

- Clinical ophthalmologic examination every 6 months for up to 3 years.
- Perimetric testing (Humphrey and Goldmann) every 6 months for up to 3 years

3.3.7 Analysis Plan

- 95% confidence intervals will be used for prevalence rate in each stratum
- at baseline, following clinical examination, an interim analysis will be performed for at least 70% of the patients within each stratum. This will indicate a preliminary VFD prevalence rate, as required by French authorities.
- At 1, 2, and 3 years, a multiple logistic regression analysis will be used to identify the predictive factors for VFD's.
- The dependent variable will be the presence of VFD's and the factors will be age, sex, duration of current antiepilepsy treatment, duration of previous antiepilepsy treatment, severity and frequency of disease.
- A stepwise procedure will be used to select variables for the multiple logistic regressions analysis. Stepping will be stopped when there is no further candidate variable entering the model at the 5% significance level.
- A multiple logistic regression will be used, with the treatment group as the response variable and all independent variables for which the significance level would be <0.20 in a univariate analysis.
- VFD incidence will be determined in the prospective cohort study of new vigabatrin users at 1, 2, and 3 years after treatment initiation.

3.4 Follow Up Study in Children

The primary objective is to assess the type, severity, and prevalence of visual field abnormalities at least 5 years after vigabatrin use for infantile spasms. Secondary objectives are to explore predictive factors of vigabatrin-associated visual field loss.

The design is a cross-sectional multicenter follow-up study. About 40 children previously treated with vigabatrin for infantile spasm at least 5 years ago will be enrolled.

The outcome variable will be visual field examinations using multiple VEP's and static perimetry, depending on the children's age, will be performed. The primary analysis will evaluate the presence of visual field defects not explained by known causes.

4. Infantile Spasms

In a meeting with the sponsor on 3/25/97, we requested data on the use of vigabatrin in infants with infantile spasms. The sponsor provides in this submission a summary of these data.

4.1 Controlled Studies

Three controlled studies in infantile spasms are described. Only one was blinded (71754-3-W-019), referred from now on as study 19. The other two were open label, partial crossover in design and used either hydrocortisone or ACTH as controls (097WFR03, referred from now on as study 3, and the Vigevano study). Studies 19 and 3 were both sponsored by Hoechst Marion Roussel (HMR), and the third study was an independent study conducted by Dr. Vigevano in Italy, the CRF's of which were not made available to the sponsor. The primary outcome measure in all three studies was the cessation of clinical spasms according to the primary caregiver. Although this is not the gold standard (*i.e.*, video EEG telemetry), it was chosen due to the ease of collection and the fact that this is what would be used in clinical practice.

4.1.1 Study 19

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter study comparing vigabatrin vs. placebo. There were three phases of treatment. The first phase was a 2-3 day observation period. The second phase was a 5 day period of vigabatrin treatment or placebo (initial dose 50 mg/kg/d, with titration up to 150 mg/kg/d permitted). The third phase was an open 6 month follow-up period.

Males and females between 1 and 18 months with newly diagnosed and previously untreated infantile spasms were enrolled. Spasms could be associated with partial seizures.

The primary efficacy variable was the percent change in daily infantile spasms frequency, assessed during a predefined 2 hour window, from baseline to end of double blind period. Secondary measures included the average percent change in daily spasm frequency, average percent change in the frequency of clusters, proportion of patients showing disappearance of hypsarrhythmia, investigator's overall assessment of efficacy, and assessment of psychomotor development.

The study enrolled 20 in each treatment arm. Baseline demographics were similar.

The study failed on the primary outcome measure. There was no statistically significant difference in the reduction of infantile spasms during the pre-defined 2 hour window (baseline and final 2 days, 41.5% PBO vs. 54.4% VGB, p=0.562). However, it won on several secondary measures: the overall frequency reduction in a 24 hour period (baseline and final two days, 17% PBO vs. 68.9% VGB, p=0.030), and in the proportion of patients experiencing cessation of spasms on the final day (15% PBO, vs. 35% VGB, p=0.036), and the investigator's overall

assessment of marked to moderate improvement (15% PBO, 80% VGB, p<0.0001)

There were no acute safety concerns.

4.1.2 Study 3

This was an open, randomized, partial crossover, multicenter trial using vigabatrin 150 mg/kg/d and hydrocortisone (HC) 15 mg/kg/d. Phase one used VGB or HC for 4 weeks; phase 2 was a cross-over to the other treatment if the patient failed to respond to initial treatment.

Males and females between the ages of 1 month and 2 years with tuberous sclerosis and infantile spasms were treated.

The primary efficacy measure was the proportion of infants with total disappearance of infantile spasms, based on seizure counting by caregiver. Secondary measures included the frequency of other seizures, EEG pattern variations, global efficacy assessment by physician, and assessment of psychomotor development.

Eleven patients received VGB initially, and 12 received HC. Baseline demographic characteristics were similar between the two groups.

During the first phase of treatment, 100% of the vigabatrin patients achieved complete cessation of spasms at one month, and 36% (4/11) achieved a similar response with hydrocortisone (p=0.001). After the crossover, the 7 HC non-responders in phase one all responded to vigabatrin in phase two (100%). There were no HC treated patients in phase 2.

There were no safety concerns. VGB was generally better tolerated than HC.

4.1.3 Vigevano Study

This was an open label, randomized, partial crossover single center study comparing VGB 100 mg/kg/d vs. ACTH depot 0.1 mL/d. Titration up to VGB 150 mg/kg/d was permitted if necessary. Phase 1 used VGB or ACTH for 20 days; phase 2 treated the non-responders with the alternate therapy for 20 days.

Males and females between 4 and 9 months with newly diagnosed infantile spasms were treated.

The primary efficacy measure was the cessation of infantile spasms.[3] The secondary efficacy measure was the EEG.

Twenty-three (23) patients received VGB in phase 1 and 19 received ACTH. Baseline demographic characteristics were similar between the two groups.

[3] There were no details how this was determined.

ACTH was better than VGB in the initial phase of treatment (74% vs. 48%). In phase 2, ACTH still beat VGB (92% - 11/12, vs. 40% - 2/5).

VGB appeared to be better tolerated than ACTH.

4.2 Uncontrolled Studies

In open label studies for infantile spasms, vigabatrin was used as follows:

- Prospectively as initial therapy in newly diagnosed patients with infantile spasms under an independent IND (protocol 1-A)
- Prospectively as add-on therapy in refractory infants in a study sponsored by HMR (097-332.5)
- As initial monotherapy for which retrospective analyses of efficacy and safety data from 59 European centers were conducted (protocol 71754/3/E/01)
- Prospectively or retrospectively as initial therapy or add-on therapy in other studies conducted independently, for which only published efficacy and safety data are available (multiple literature reports)

The efficacy and safety data for each of these four datasets are described below.

4.2.1 Protocol 1-A

This was conducted under an independent IND by Drs. Elterman and Shields. The study is ongoing. Interim results are available. The study is a randomized, open label comparison of low dose (18-36 mg/kg/d) vs. high dose (up to 150 mg/kg/d) in newly diagnosed infants with infantile spasms.

As of 6/30/97, there were 29 high dose treated patients and 33 in the low dose. At two weeks, 15% of the low dose and 28% of the high dose were free from infantile spasm using clinical and EEG criteria. Patients with tuberous sclerosis seemed to do better (50%).

There was one death, a 7.5 month old female child died suddenly at day 74 of treatment after taking a nap. Ophthalmologic examinations were done but not analyzed.

4.2.2 Protocol 097-332.5

This study was submitted in the NDA. This was an open label, uncontrolled study in 45 infants and children (2 months – 13 years of age, most <2) with uncontrolled infantile spasms. Doses up to 150 mg/kg/d for up to 23 months were used. Two discontinued early and were not included in the efficacy analysis. At the end of the evaluation phase (mean duration of therapy, 3.8 months), 20/43 (47%) of the patients were seizure free. Thirty-three (33) with adequate responses entered a long-term phase. Decreased spasm frequency was maintained in 22 patients, spasms recurred in 5 patients and efficacy was inconsistent in the remaining 6 patients.

In addition to the two early discontinuations, there were two others who temporarily discontinued due to hypotonia and weight increase. Most commonly reported AE's were hypotonia, insomnia, somnolence.

4.2.3 Protocol 717/54/3/E/01

This was a multinational, multicenter, retrospective analysis of data collected in 59 European centers on 250 patients treated with vigabatrin for initial therapy of infantile spasms. An independent panel determined that 192 patients actually had classical infantile spasms. These were evaluated for efficacy. The doses used ranged from 20 to 400 mg/kg/d and the duration of therapy was 0.2 to 28.6 months. Complete disappearance of spasms was reported in 131/192 (68%) of patients. Those with tuberous sclerosis had the highest response rates (98%, or 27/28).

There were 42 AE's reported. The majority were mild to moderate in intensity. The most common events were somnolence, and hyperkinesia. Four patients died but only 2 were receiving vigabatrin at the time of death. One VGB death was that of a 17 month old who died of bronchopneumonia after 358 days of therapy. The other was a 33 month old who died of sudden infant death syndrome following 129 days of vigabatrin therapy. There were two adverse drop outs (myoclonus and irritability).

4.2.4 Published Literature Reports

There sponsor describes 17 published reports describing the use of vigabatrin in infantile spasms. Limited conclusions can be made on the basis of these uncontrolled published reports. The sponsor notes that the highest response rates were found when vigabatrin was initiated as monotherapy early after the onset of the disorder.

A total of 50 AE's were reported among the 285 infants and children documented in these reports. Most were mild and transient. Agitation, hyperexcitability, irritability, drowsiness, weight gain, and hypertonia or hypotonia were the most common events seen and occurred more often at the higher VGB doses.

Ten published case reports describe the use of vigabatrin in 11 infants with infantile spasms. One AE was reported: progressive deterioration of cerebral lesions associated with tuberous sclerosis was noted.

4.3 Dr. Shield's Letter

Dr. Shield's, Chief of Pediatric Neurology at UCLA, provided a letter describing interim results of a study of VGB in patients with new onset infantile spasms. As of 10/19/98, they had enrolled 173 patients, and 140 had been entered into the database. Seventy-three (73) were randomized to low dose and 67 to high dose therapy. He doesn't describe the exact dose(s) used.

At the 2 week point, 16% of the low dose and 31% of the high dose patients had become seizure free. The chi square is 3.52, just below the required statistic for a p=0.05 (3.84). They have yet to perform an analysis of efficacy at 1 or 2 months.

He has found that those with tuberous sclerosis respond remarkably well (9/10 at one month so far) and development is improved. He describes that of a typical case, a 3 year old who is close to her development—a finding which he would not otherwise expect to see given his 20+ years of clinical experience.

He attributes the lack of a significant result at 2 weeks to the fact that so many TS patients responded at the low dose. He performed an analysis with those patients removed (3/7 high dose and 2/3 low dose with TS were seizure free at 2 weeks) and the chi square statistic is 8.259 ($p>0.01$).

Despite the risk of visual defects, the standard therapy, ACTH, is itself associated with risks "much more significant than visual field disturbance." He clearly supports quick approval.

5. Comments

5.1 Visual Field Defects

The data thus far offer compelling evidence that vigabatrin causes peripheral constriction of the visual fields, more prominent nasally. The exact onset, localization, relationship to exposure, and reversibility remain unknown.

The sponsor plans to continue to collect visual data in those patients already chronically exposed to vigabatrin. I concur. This should provide useful long term data and help address the issue of reversibility of the defects.

I also agree in principle with the proposed prospective longitudinal study. However, I have the following questions and comments:

- It is unclear how many will be new VGB users (the outline states that they will be candidates to receive VGB)
- The study should include frequent and complete ophthalmologic exams (at least every three months) and visual fields (both central and peripheral to 60 degrees). Theoretically, the defect may be reversible if detected early. A six month interval may be too long and miss the reversible period.
- The sponsor should consider adding frequent electrophysiologic testing (VER, ERG) to asses the ability of these tests to predict ongoing or future visual loss.

For all proposed studies, the sponsor should also collect brain MRI's, to look for radiological evidence of intramyelinic edema (IME) in patients with known visual loss. Those without visual loss can act as controls. The localization of the visual loss is not clear, nor whether it is related in any way to the IME seen in animals.

5.2 Infantile Spasms

There are only 3 controlled trials, and only one of these was double blind (study 19). This was a small study (n=40) and the double blind treatment phase was

only 5 days long. The study was negative on the primary outcome measure, but positive (one markedly so) in key secondary measures.

The other studies are problematic and difficult to interpret, either because they were unblinded, or uncontrolled, or both. In the Italian study (Vigevano), ACTH beat vigabatrin. It is doubtful that these studies can be used to support the efficacy.

I believe the sponsor should perform a second adequate and well controlled efficacy study. The treatment phase should approximate the method that the drug will be used in clinical practice. It is not clear from the information provided that Dr. Shield's study is appropriate. There is no control arm, unless one uses low dose VGB as a control.

As far as the safety of the drug in this population is concerned, this raises more serious questions. We already know that the prevalence of asymptomatic, usually severe, and possibly irreversible visual loss in adults approximates 27% during chronic use. The effect of the drug on the visual system of children is completely speculative. The difficulty, of course, is that visual defects are either extremely difficult or impossible to assess in this population.

The sponsor proposes to evaluate the visual function of 40 children aged 8 years or older, who previously received vigabatrin. This seems reasonable, as a condition with a prevalence as high as 27%, we should be able to detect some cases if they are severe and long-lasting. It's important that the study include good exposure data, and that a complete ophthalmologic evaluation be performed, including electrophysiologic testing (*e.g.*, VER, ERG). They should also consider obtaining brain MRI's.

AOliva

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. 2/9/99

ao 2/5/99
cc:
HFD-120
NDA 20-427

351

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 22, 1998

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Not Approvable Action,
NDA 20-427, Sabril

TO: Robert Temple, M.D.
Director, ODE 1
&
File NDA 20-427

This memorandum conveys and explicates the basis for my recommendation that Hoechst Marion Roussel's (formerly, Marion Merrell Dow's) NDA 20-427, which allows for the use of Sabril (vigabatrin, gamma vinyl GABA, GVG) as an adjunctive treatment for adults with Complex Partial Seizures, be declared not approvable.

The PDUFA action date on this application is 10/27/98

Explication

Although my November 18, 1997 memorandum to the Sabril file recommended that the NDA be declared approvable, it also made clear that I considered vigabatrin to be a drug with a yet to be fully investigated capacity/potential to cause a variety of kinds of neural injury (i.e., intramyelinic edema, peripheral neuropathy, neuropsychiatric symptoms, etc.).

Because Sabril had been shown in clinical trials to be an effective AED and because so many members of the anti-epileptic drug class are also associated with very serious, even life-threatening, risks of use of their

own kind (e.g., Felbatol and aplastic anemia), I was persuaded that an expert, fully familiar with the management of patients with epilepsy, could responsibly conclude that Sabril, its numerous risks both known and potential not withstanding, had, within the meaning of the Act, been shown to be safe for use provided, however, that it was marketed under labeling that fully disclosed it risks, both realized and potentially realizable.

New information bearing on Sabril's association with visual field defects has emerged in the 11 months that have elapsed since the approvable action was taken, however. While the new information is still far less than one might want to possess at the point of reaching a definitive conclusion about a drug product's safety for use, I consider the new information of sufficient concern to cause me to rescind my conclusion that Sabril has been shown to be safe for use.

The significance of Visual Field Defects

In the assessment of drug associated risk, one must always be mindful that the absence of evidence is not evidence of absence. This is especially important when the risk involved 1) is one that can be asymptomatic at an initial stage in its evolution, and 2) is not, in its presymptomatic stage, readily detectable upon routine clinical or laboratory examination[1]. The visual field defects being reported with Sabril are a case in point.

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[1] Concerns about missing risks of this kind have loomed large in our evaluation of the safety of Sabril since recognition of the fact that it is capable of causing, by a yet unknown mechanism, intramyelinic edema in 3, arguably 4, different mammalian species.

Although the visual tract is a prominent sight of intramyelinic edema in dogs, we have never been certain how such a lesion, were it to occur in humans, would present clinically. We did have reason to believe, based on studies in dogs, that it might be detected electrophysiologically through the measurement of visual evoked responses (VERs). To date, however, the VERs that have been performed have not been positive.

Nevertheless, when I first learned of reports of visual field defects occurring in association with Sabril, I wondered whether they might be a reflection of some intramyelinic edematous process. At this point, our ophthalmological consultants believe that the visual field loss is most likely due to retinal injury

Among the yet to be fully evaluated risks that I identified as "untoward neurological findings of concern" in my November 1997 approvable action memorandum were visual field defects. I noted that although these were disconcerting, we knew far too little about them to reach even a preliminary conclusion about the nature of their association with vigabatrin (i.e., chance or causal), let alone their clinical importance.

Although the extent of our knowledge and understanding of these visual field defects continues to be relatively limited, at times even inconsistent, the evidence now accumulated, (see the reviews of Boehm, 8/24/98, Oliva, 8/28/98, and the supervisory overviews of Burkhart, 10/6/98 and Katz, 10/14/98)) lends reasonably strong support to a conclusion that the use of vigabatrin is responsible for at least some proportion of these reports[2].

It is still possible, of course, despite the fact that these visual defects are more often reported among epileptic patients being treated with Sabril than among those treated for with other AEDs[3], that some factor, other than a drug effect accounts for this finding (e.g., biased ascertainment and/or enhanced reporting fraction secondary to publicity). Acknowledgement of this possibility, however, does not change the fact set upon which we must act.

Regulatory options

The emerging evidence linking the use of Sabril to the occurrence of visual field defects clearly tips the risk benefit assessment of the product in an unfavorable direction. The question is how far.

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[2] What fraction of all field defects is attributable to Sabril seems impossible to determine in a meaningful manner, at least at this time. In part, the issue is one of case definition. My impression, and it is only that, is that if the case definition is limited to concentric field constriction more intense in a bilateral nasal distribution, the etiologic fraction may be considerably larger than if all kinds and variety of visual field constriction is considered.

[3] A possible exception may be Gabitril (tiagabine), another recently approved (9/97) AED with a presumed capacity to increase GABA levels, albeit by a different mechanism of action (uptake transport blockade)

In my judgment, the evidence extant supports the following conclusions:

> 1) that Sabril seems likely to be the cause of a unique kind of injury to the visual system, one that in an unknown proportion of patients is irreversible, perhaps even progressive, 2) that the incidence of this injury could be very high (e.g., the crude proportion of Sabril treated patients developing field defects was 28% in one Finnish study), and 3) that the documented benefits of Sabril as a treatment for partial onset seizures are not so great as to offset the potential harm signaled by these visual field changes (which must, even if initially "asymptomatic," be taken as indicia of a process that could evolve to symptomatic blindness).

In respect to the last point, I am mindful that some clinicians could be persuaded that Sabril does offer a unique advantage for some patients. Obviously, I am not in a position to contest opinions based on reports of personal clinical experience, but claims of advantage for any drug, especially a dangerous one, should, in my view at least, turn on valid evidence adduced in adequately and well controlled, comparative clinical trials that, by design, are capable of examining the risks and benefits of the products involved under conditions that allow for a fair comparison (e.g., give no advantage to any of the products being compared by virtue of the patient population sampled, the range of doses or treatment regimen followed, or the outcome assessments employed, etc.)

My personal beliefs about the nature of the evidence needed to sustain a claim of advantage notwithstanding, I am mindful that those who take a different view might be persuaded that the marketing of Sabril could be justified provided the product was marketed under highly restrictive labeling replete with dire warnings and cautions about its potential to cause serious harm. In fact, advised of the likelihood that the Division would offer an adverse recommendation concerning its pending NDA, the sponsor not only offered to accept such restrictive labeling as a condition of marketing, but volunteered to eschew all promotional activities on behalf of Sabril as well.

Although I acknowledge that the argument for approval is not entirely without merit, I find it unattractive and fraught with peril, especially in

light of the fact that any legally marketed drug product may enjoy widespread off label use.

Accordingly, I am persuaded that it would be best to disapprove the Sabril NDA at this time. In dosing so, however, I believe it would be important to make clear to the sponsor that the agency stands ready to reconsider its conclusions about the risk and benefit of the product upon the presentation of persuasive evidence that would allow a disinterested expert to discount the importance of the visual field defects. This might become possible if new information about either the nature of the findings[4] and/or the comparative effectiveness/clinical value of Sabril or both were to be presented.

Recommendation:

Issue the not approvable action letter

Paul Leber, M.D.
October 22, 1998

[4] For example, if visual field defects (a consensual case definition has yet to developed to my knowledge) were found to be common among patients with epilepsy, or among epileptics long treated with multiple AEDs, the importance that is currently attached to the visual field defects reported would obviously change. Whether the change would be enough to allow the approval of Sabril, let alone if it did, the specific conditions of use under which it could be marketed, are questions that cannot be addressed at this time.

Cc:

NDA 20-427
HFD-101
Temple
HFD-120
Katz
Burkhart
Boehm
Oliva
Malandrucco

OCT 14 1998

MEMORANDUM

DATE: October 14, 1998

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD- 120

TO: File, NDA 20-427

SUBJECT: Supervisory Review of Response to Approvable Letter for NDA 20-427, for the use of Sabril (vigabatrin) in Patients With Partial Seizures

Background

On 11/26/97, the Agency issued an Approvable letter to Hoechst Marion Roussel, Inc., for NDA 20-427, for the use of Sabril (vigabatrin) in patients with partial seizures. In that letter, numerous questions related to further characterizing the safety profile of the drug were asked, as were questions related to the description of these findings in labeling.

The sponsor responded to this letter in 3 separate submissions: a safety update (1/20/98), a "complete" response to the Approvable letter (4/24/98, and which serves as the basis for the current User Fee deadline of 10/27/98), and a further discussion of ophthalmologic findings (7/29/98). All 3 of these submissions have been reviewed by Dr. Gerard Boehm, of the division's Safety Unit (review dated 8/24/98). In addition, the 7/20/98 submission of ophthalmologic data was reviewed by Dr. Oliva (review dated 8/28/98), and data related to peripheral neuropathy and MRI were reviewed by Dr. James Sherry (review dated 8/25/98). Finally, Dr. Burkhart has written a supervisory review (review dated 10/6/98).

In the course of the Division's review of these submissions, serious concerns about the potential for Sabril to cause frequent, significant, perhaps irreversible, visual field defects (VFDs) were raised. As a result, the Division called the sponsor (8/27/98, a conversation in which Dr. Robert Temple, Director of ODE I, actively participated) to express these concerns and our view that the application could not be approved until additional data were submitted, reviewed, and determined to support the safe marketing of the drug.

In response to this call, the firm has made one additional submission, dated 9/23/98. In this submission, the sponsor proposed that the drug be marketed under very restrictive conditions (e.g., no journal ads, no detailing, no PDR placement, etc.). In a phone call to the sponsor on 9/24/98, the division informed the sponsor that we would still likely recommend that the application not be approved at this time.

In this memo, I will briefly review only the primary safety issue, (given that the other safety issues raised in our Approvable letter do not pose a difficult problem vis-a-vis the approvability of the application at this time), and offer my recommendations for action on the application.

Visual toxicity

As previously noted, the primary safety issue presented in the application now concerns the potential for Sabril to be associated with significant visual field defects.

According to Dr. Boehm, the sponsor reports on a total of 239 patients in whom reports of visual abnormalities have been recorded. Of these, 192 were reported to have visual field defects. These reports come from many sources, including clinical trials of various design (US and non-US) and post marketing sources. The vast majority of patients exposed to Sabril, in drug development cohorts as well as post marketing, have not had routine systematic assessments of their visual fields; as a result, most of the cases can be considered spontaneous reports which became known only after patient complaint. There are, however, several cohorts of patients treated with Sabril that have been systematically assessed with formal visual field testing.

Prospective cohorts

Study VI-PE-0192 was a randomized, parallel group, placebo controlled trial in children ages 4-16. The controlled portion of this trial lasted 17 weeks. Patients had formal testing of the visual system, including confrontational visual field testing, at baseline and at the end of the trial. In this study, no abnormalities were noted in either the treated or control groups.

After the 17 weeks, 44 patients entered an open, 28 week extension. Of these 44, 41 had visual system testing at the end of this extension. No abnormalities were noted.

One patient in this study, a 17 year old female, complained of visual difficulty during the extension trial, at which time her acuity was 20/25. At the end of the extension, her acuity was 25/25, with normal fields and a prolonged P100 latency with stimulation of the left eye on VEPs. Within several weeks of the end of the extension (she continued to be treated with commercially available vigabatrin), she developed pain and was noted to have visual field constriction. She apparently continued on treatment, subsequently developing pain and visual loss in the left eye after several additional months. At that time, she was noted to have nasal and temporal field constriction bilaterally, later described as a bitemporal hemianopsia. There was no further follow-up.

As far as I can tell from the reviews, there were no other data regarding visual field defects deriving from controlled trials.

The sponsor presented the results of systematic visual system testing in several other prospectively followed cohorts receiving Sabril.

Study VGPROO98 is an ongoing open label trial in adults in over 1000 patients. Of these, 146 had eye exams during earlier vigabatrin studies, and were therefore chosen to have repeat assessments. Unfortunately, visual field testing was not performed in these patients. However, one patient was noted to have had bilateral visual field defects 7 years after the initiation of treatment (by history, previous exams were normal, although it is not clear to me if these previous exams included visual field testing). A follow-up exam almost 6 months after the abnormality was noted was unchanged, although it is unclear when (if?) Sabril had been discontinued.

The sponsor also reported the results of systematic visual field testing in patients enrolled in 6 open, uncontrolled long term studies. Two of these studies were conducted in Finland, and were in patients receiving Sabril as monotherapy; the remaining 4 studies were conducted in Japan, in patients receiving Sabril as add-on therapy.

In these studies, patients were asked to undergo visual field testing at a single point in time (about 9 years after the start of the first study). A total of 219 patients were being treated in these 6 studies. Of these, 136 agreed to undergo testing. Two (2) of these patients had uninterpretable tests. Therefore, a total of 134 patients had useable data.

Formal visual field testing was performed on these patients, all of whom were asymptomatic (for the methodology used, see Dr. Oliva's review, page 2). Of the 134 patients with interpretable data, 38 (28%) had visual field defects. The data were independently reviewed by the firm's expert consultant, Dr. John Wild, of the UK. Of these 38, 31(82%) were considered moderate or severe. The constriction consisted of bilateral concentric constriction, worse nasally. The overall incidence was 5.9 cases per 100 patient-years. The distribution was reasonably similar between the 2 countries: 35% of patients in the Finnish studies, and 26% of patients in the Japanese studies had defects.

Another prospective cohort was evaluated by Krauss, et al, in an article "Vigabatrin associated retinal cone system dysfunction" (Neurology 1998;50:614-618). In this article, researchers at Johns Hopkins systematically evaluated the 4 patients they were treating in an HMR sponsored safety study (out of a total of 38 at their institution) who complained of visual symptoms. Of these 4, 2 complained of symptoms referable to visual field constriction, and 2 complained of blurred vision.

Three of these patients were noted to have formal visual field defects, and they all had cone system dysfunction. According to Dr. Burkhart (see his review, page 4), Dr. Krauss is currently assessing the remaining patients, who were asymptomatic. He has told Dr. Burkhart that he has assessed 10 control patients (matched by age and duration of epilepsy), and none have had demonstrable abnormalities.

Epidemiologically styled studies

The sponsor has presented the results of 2 epidemiologic studies.

The first study used a UK General Practitioner Database for this retrospective study. (My description of this study is taken entirely from that provided by Dr. Boehm in his review. There are a number of details about the methodology used that are not provided in Dr. Boehm's description; whether these details are provided by the sponsor is unknown to me). Patients in this database at the start date of the study with a diagnosis of epilepsy and no visual field defect recorded, as well as patients newly diagnosed with epilepsy during the study period and no recorded VFD, were included in the study.

For patients in whom a VFD was detected during the study, the day of detection was used as the index day; all AEDs they were receiving for the previous 120 days were recorded. For patients who did not develop VFDs, a day was randomly selected as an index day, and the same data as for cases was collected.

The sponsor sent questionnaires to the physicians of the patients with VFDs to collect the ophthalmologic data. These data were reviewed by 2 independent ophthalmologists, who classified the cases as probable/possible or probable.

A total of 16,447 patients were eligible for enrollment in this study. Of these, 54 had a VED recorded during the study period. In this study, the highest rate of VFD was associated with vigabatrin (31/10,000 patient-years for possible/probable cases, 10.3/10,000 patient-years for probable cases). The next highest rates of VFD were seen with carbamazepine (12.5/10,000 patient years for possible/probable cases, and 5.2/10,000 patient years for probable cases). It should be noted that the exposure to vigabatrin was considerably less than that for any of the other AEDs. For example, in this study, 285 patients were exposed to vigabatrin (968 patient-years), compared to 4,233 patients on carbamazepine, 15,248 patient years).

A second epidemiologic study was based on PEM data from the UK. This study compared experience among vigabatrin (10,178 patients), lamotrigine (11,316 patients), and gabapentin (3,100 patients). No cases of VED were found in the gabapentin treated group, no well documented case in the lamotrigine group, and apparently 5 cases were seen in the vigabatrin group. Of these 5 cases, one reportedly resolved, 2 continued after discontinuation of the vigabatrin, and there was no follow-up for the other 2. Details of the methodology of this study were not provided.

Other cases

The sponsor presents data about additional cases of VFD from other sources, namely post-marketing reports and various individual reports from various studies, compassionate use, etc. The number of such reports is not clear from the reviews of Drs. Boehm and Oliva. For example,

Dr. Boehm (page 31 of his review) lists 152"spontaneous" reports of any sort of visual abnormality; Dr. Oliva (page 3 of his review) lists 133 "spontaneous" reports from foreign sources. Dr. Boehm describes a total of 239 reports of visual abnormalities, Dr. Oliva describes a total of 221 reports.

According to Dr. Boehm, there were a total of 192 reports of visual field defects. Elsewhere in his review, he states that there were 27 spontaneous reports of VFD for which perimetry data was submitted, and that this represents about 14% of all spontaneous reports of VFD. This would be consistent with his statement that there were 192 reports of VFD (14% of 192=27), although the 192 are not all "spontaneous".

In any event, it appears that the number of perimetry documented spontaneous cases of VFD is 27. These 27 were also reviewed by Dr. Wild; he found 15 to be likely related to vigabatrin. As with the Finnish and Japanese data, he found these defects to be bilateral, concentric, more marked nasally. He offered the view that bilateral nasal VFDs are rare, and that the lesion was probably retinal.

According to Dr. Oliva (page 4 of his review), of the total 221 cases of visual abnormalities (I am not sure exactly how many of these are VFDs), vigabatrin was discontinued in 110 patients. Of these 110, the lesion was unresolved in 84. As he notes, the nature of the follow-up, etc., is unknown.

As described by both Drs. Boehm and Oliva, other visual and retinal abnormalities were noted.

Given the signal of ophthalmologic injury, the Division asked both the Epidemiology and Ophthalmologic Drugs review groups to address these issues.

Specifically, we asked the Epidemiology group to examine the SRS for similar reports for other recently approved AEDs. In a report dated 9/9/98, they note that there are no cases of VFDs reported in association with tiagabine, topiramate, and felbamate. One case of VFD was reported in association with valproate use. While there were numerous reports (mostly for valproate) of eye abnormalities, only one case of VFD was reported. A search of the literature also failed to find any cases of VFD is association with the use of these drugs.

In an ophthalmology consult dated 8/27/98, Dr. Wiley Chambers concludes that the lesion seen here is rare, not known to occur with other drugs, and might be significantly underreported, given concerns with the methodology used and the fact that there was no systematic assessment of asymptomatic patients. He also suggests that the character of the lesion is consistent with injury at perhaps multiple sites in the visual system, and not necessarily the result of a retinal lesion.

As noted earlier, the sponsor, aware of our reservations about approving the application in the face of these findings, submitted, on 9/23/98, a proposal for marketing the drug under the following restrictions:

No PDR placement ad
No journal ads
No Direct Mail programs to non-epileptologists
No commercial exhibits promoting Sabril
No sales force promoting Sabril
No direct to consumer or patient marketing

In addition, they propose announcing the drug's availability only to epilepsy centers, and working with the Agency to write restrictive labeling.

Beyond the ophthalmological findings, there were a number of other safety questions to which the sponsor responded; these are summarized in Dr. Burkhart's review. In particular, his comments on vigabatrin's capacity to cause liver injury are especially cogent.

Finally, Dr. Sherry has reviewed the MRI data and the evidence bearing on vigabatrin's capacity to cause peripheral neuropathy. In an attempt to further define this issue, the sponsor enlisted the aid of an expert, Dr. Cornblath, to construct a case definition and review potential cases of peripheral neuropathy. However, the sponsor did not provide requested information about the association of dose and/or duration of treatment to the onset, reversibility, etc. of the neuropathy, nor were adequate electrical studies provided. The sponsor did propose, though, that Phase 4 studies be performed to better characterize these aspects of any vigabatrin-induced neuropathy.

COMMENTS

The sponsor has submitted several sources of data that raise serious concerns about the capacity of vigabatrin to cause visual abnormalities of various type. This evidence is strongest for a drug induced visual field defect of fairly stereotypic type (bilateral concentric, predominately nasal). By most assessments, the lesion appears clinically to be retinal in origin.

Data from epidemiologically styled studies suggest that vigabatrin's ability to cause the lesion is, if not unique among AEDs, certainly unusual. However, as discussed in detail by Dr. Boehm, the nature of these studies is such that definitive conclusions about the rate of this lesion (absolute and comparative), as well as even its drug relatedness, cannot be made, although all evidence suggests that the rate of such a finding is extremely low in a similar population, suggesting, of course, that the lesion is treatment related.

The most compelling evidence for the existence, and estimated prevalence, of a Sabril induced lesion comes from the Finnish and Japanese data. In this study, 28% of asymptomatic patients had documented VFDs, 82% of which were gauged to be moderate or severe.

There is a great deal that is unknown about this lesion. As mentioned, the background rate (in particular, with other AEDs) is not known with any confidence, and so the relative risk of this event is impossible to know. In this regard, it is worth noting that I was informed by Dr. Cathy Peterson, of the Therapeutics Products Directorate of Health Canada, in a telephone conversation held 10/14/98, that a meeting was recently held by the Adverse Reactions Advisory Committee of the Australian drug regulatory authority on 9/25/98, at which reports of VFDs with AEDs was discussed. At this meeting, the committee discussed reports submitted by a single neurologist who he claimed that 50% of his patients on vigabatrin or tiagabine had constricted visual fields. Dr. Peterson faxed me a copy of a part of the confidential record of the committee's meeting. In this report is a list of 5 patients taking tiagabine in whom asymptomatic VFDs were noted (all of whom had received tiagabine for about 5 years and were receiving other AEDs). The report also contains a brief account of the sponsor's view (Sanofi Winthrop in Australia) that 4 of these cases were confounded.

Beyond this, however, we have no good data that speaks to the relationship of the occurrence and/or reversibility of the lesion to the dose and/or duration of treatment. Further, the sensitivity of the measures to detect the lesion early are unknown.

These lacunae in our knowledge about these fundamental parameters of this lesion make it impossible, in my view, to construct adequate labeling that would make the product safe in use. Specifically, despite the sponsor's proposal to severely restrict access to this drug, we still must be able to write labeling that adequately informs a prescriber about the risks associated with vigabatrin's use; given the lack of information about this risk, I do not believe that we can do this at this time. The sponsor has clearly not performed adequate tests by all methods reasonably applicable to show that the drug is safe for use under proposed labeling, as required by statute.

RECOMMENDATIONS

For the reasons stated above, I recommend that the application be Not Approved, and that the sponsor be required to perform studies in which large numbers of patients are adequately monitored (by appropriately sensitive methods) for a sufficient duration to evaluate the relationship of dose and duration of treatment to the occurrence of the lesion, and to document the incidence of the lesion as well as the comparative rates (perhaps to both a similar cohort treated with other AEDs as well as to an untreated cohort). Further, detailed study of the reversibility of the finding should also be undertaken, including adequately monitored follow-up of patients who develop VEDs. In addition, information about the risk of this event in association with other AEDs should be sought. Until this basic information is available, it would be difficult, in my view, to justify marketing.

When this additional data is received, the conditions of approvability can be further discussed. For example, approval might be contingent upon a demonstration of the superiority of Sabril to other available AEDs in a randomized controlled trial in which a direct comparison of the treatments is made.

Russell Katz, M.D.

cc:
NDA 20-427
HFD-120
HFD- I 20/Katz/Leber/BurkhartlBoehm/Oliva/Malandrucco

Review of Clinical Data

Safety Team Leader Comments on 4/24/98 Response to AE Letter

NDA:	**20-427**
Sponsor:	**HMR**
Drug:	**Vigabatrin**
Route of Administration:	**Oral**
Reviewer:	**Greg Burkhart, M.D., M.S.**
Review Completion Date:	**October 6, 1998**

On 11/26/97 the agency completed its review of the vigabatrin NDA issuing an AE letter along with proposed labeling for marketing. Included in the letter and embedded in the labeling were requests for additional analyzes that would be necessary to clarify a number of issues, most of which focused on vigabatrin's safety.

The sponsor submitted a response to the AE letter on 4/24/98, and in a 7/29/98 submission, provided additional data and findings on ophthalmologic events. The final safety update, which provided safety information up through 3/15/97, was submitted on 1/20/98.

Drs. Boehm, Oliva and Sherry have jointly reviewed the safety issues contained in these three submissions. Dr.Boehm, from the safety team, reviewed all three submissions and considered all the safety issues except for intramyelinic edema and events suggestive of peripheral neuropathy, which were reviewed by Dr. Sherry. Dr. Oliva, who completed a fellowship in neuro-ophthalmology, focused on ophthalmologic events and Dr. Chambers from HFD-550 also provided a consultative review of the ophthalmologic events.

Using the completed reviews from Drs. Boehm, Oliva, Sherry and Chambers, I will review and summarize the possible risks that may be associated with vigabatrin use.

Final Safety Update

Based upon Dr. Boehm's review of the final safety update, there are no new safety issues that have been associated with vigabatrin use.

One somewhat interesting observation, generally noted in Dr. McCormick's review of the NDA, is the several fold increase in the risk of hospitalization for events coded as "convulsions" for patients assigned vigabatrin compared to patients assigned either

placebo or an active comparator. (Dr. Boehm's review summarizes these data on page 7.) Although not shown in his review, Dr. Boehm confirmed that this apparent excess was present in both US and non-US controlled studies suggesting that it is unlikely to be due to chance. It occurs in the context of overall rates for "status" and "convulsions" that are about the same between groups, and it is unclear as to whether a particular seizure type(s) is responsible for the excess.

As per our request, the sponsor reviewed the safety experience of the 489 pediatric patients (<= 16 years of age) in the overall and update databases separately. While there were no findings specific to this age group, most of the experience was uncontrolled and the extent of use relatively small.

Response to AE Letter

As Dr. Boehm points out, the sponsor addresses all the issues the agency raised in the AE letter. I will review HMR's response by issue.

Hepatic Failure

In the AE letter, we proposed that vigabatrin labeling contain a warning about hepatic failure. In the warning we suggested that the sponsor describe the cases and estimate the reporting rate.

HMR estimated that there have been 350,000 PYRs of use based upon sales figures for the amount of vigabatrin sold and assuming [redacted] of use per patient-day. Using the 9 cases of reported liver failure with death and/or transplant gives a reporting rate of 2.6 per 100,000 PYRs of use. b(4)

While the sponsor provided no justification for choosing [redacted] per day, I don't think interpretation of the reporting rate depends on this assumption. Assuming that the average was [redacted] per day, person-time would be reduced by 50% effectively doubling the reporting rate. The rate, however, does not increase enough to material change the strength of the signal as discussed below.

In evaluating the signal of fulminate hepatic failure (death or transplant) for several of the division's drugs, a background rate range of 1 per million to 1 per 100,000 PYRs has been used. Thus, in my view, the reporting rate of liver failure with vigabatrin is higher than expected and, hence, represents a significant signal of risk.

HMR agrees that the liver failure and the reporting rate [redacted] because it is their belief that the background rate is higher in epilepsy patients than the general population, [redacted] HMR provides no supportive evidence for the belief. The division has also considered this possibility, but, to my knowledge, there is no evidence to support it. The only denominator-based data that I know of is the division's database of mortality with AEDs, being developed by b(4)

Dr. Racoosin. In this database, there are about 14,000 PYRs of experience for topiramate, tiagabine, lamotrigine and gabapentin and there are no deaths suggestive of hepatic failure. In the NDAs for these drugs, which contained the same patients, there were no cases of hepatic failure reported by the clinical reviewer. Alternatively, there have been cases of liver failure reported from post-marketing experience for felbamate, lamotrigine, and topiramate. With topiramate, there has been 1 foreign case reported, but no US cases reported in about 30,000 PYRs of use.

While I agree that it is possible that epilepsy patients in general or those who are taking several to many AED drugs could have an increased risk of liver failure compared to the general population, there is no evidence for such an assumption. Given the severity of the event and the fact that the actual incidence rate is likely to be 10 fold higher than the reporting rate because of under-reporting, [redacted] b(4)

Intramyelinic Vacuolization

In the proposed labeling included with the AE letter, the agency asked the sponsor to provide more detailed information about autopsy, MRI, and EP findings on IME. We also asked the sponsor specifically about their conclusion that vacuolization detected at autopsy in the absence of gliosis was an artifactual finding.

Dr. Sherry reviewed information submitted on these issues. In general, the sponsor provided the necessary data to clarify the enumeration of patients who had MRI, EP and/or autopsy findings [redacted] The sponsor, however, provided no supporting evidence that vacuolization occurring at autopsy is an artifact. Dr. Sherry also disagreed with the sponsor's arguments and additions [redacted] that were somewhat dismissive of the potential cases of IME [redacted] b(4)

Peripheral Neuropathy

In the AE letter, we asked for additional analyzes of patients who may have developed a peripheral neuropathy while on vigabatrin. While the sponsor reached the conclusion that vigabatrin causes peripheral neuropathy, they did not conduct the requested analyses on dose and time of occurrence. We still do not know whether this event is reversible upon vigabatrin withdrawal.

Visual Field Cuts

At the time of the AE letter, the division was aware of the PEM study finding of 3 cases of severe visual field cuts in 10,178 patients who had used vigabatrin. In fact, we included the PEM study findings in the warning section of labeling. We also made requests [redacted] ; for additional analyses of the NDA data. b(4)

In Dr. Boehm's review, he provides a good discussion of the ophthalmological findings that were submitted by the sponsor in final safety update as well as a 7/29/98 submission starting on page 23 of his review. The most striking finding was a 28% prevalence (38 of 136) of asymptomatic visual field cuts for patients enrolled in Danish and Japanese studies, the only group of patients in whom there was a systematic attempt to detect abnormalities. The sponsor's expert consultant judged 82% of these events as moderate to severe with some patients having significant disability - apparently these patients had not complained to the investigator about the visual changes. In addition, the consultant concluded that the perimetry findings were suggestive of a highly specific lesion – concentric narrowing that seems worse nasally. Drs. Oliva and Chambers agreed that such a finding was very unusual and not likely to occur in in the general population.

Also included in the response was a publication by Krauss in Neurology reporting that 4 of 38 patients with long-term vigabatrin use had symptomatic abnormalities on perimetry exam. In a teleconference with Krauss, he informed me that [redacted] perimetry exams on the remaining 34 patients who were reportedly asymptomatic. [redacted], he did say that there were 0 abnormalities in 10 "control" patients who had been matched by age and epilepsy duration. b(4)

While the sponsor seems to have concluded that this is a unique finding specific to vigabatrin, I am not so certain. In fact, to my knowledge, there is no other denominator-based data for any other AED where there has been a systematic evaluation of visual fields except for the small sample studied by Krauss. In trying to address this question as to whether other AEDs or epilepsy itself might be associated with visual field cuts, I checked the clinical reviews of the NDAs for lamotrigine, gabapentin, topiramate and tiagabine as well as their labeling for any mention of visual filed cuts. The only finding was with gabapentin where its labeling mentioned visual field cuts as being infrequently reported. However, I couldn't determine from the clinical review exactly what type of clinical abnormality was being coded as a visual field abnormality. DPE also reviewed the FDA and WHO databases looking for reports of visual field cuts with other AEDs, but could not find any actual cases. Of course, the patient population and the type of event may limit the reporting of such events.

In addition to an absence of data on the background rate of this event(s) with other AEDs, there is limited and somewhat conflicting information on its reversibility. There is significant concern that severe restriction in visual fields may not be reversible after discontinuation of vigabatrin. There have been, however, some patients with mild to moderate abnormalities whose abnormalities reversed upon discontinuation.

There also has been no systematic longitudinal study of the development of visual field cuts over time. Thus, while most of the prevalent cases have been detected in patients with long-term use, we really don't know the shape of the hazard by dose and time. Likewise, there has been no systematic study of screening strategies.

Other Issues

The AE letter raised questions about a number of other issues that were relatively minor in nature as follows. (1) The sponsor provided clinical descriptions of several poorly described events (dyspnea etc.) that occurred to greater extent with vigabatrin. There were no new striking findings from this information. (2) Dose-duration data showed that 106 patients had used ≥ 6 grams per day for longer than 1 year. (3) Urinalysis and coagulation data were submitted and were unrevealing. (4) Findings from new analyses were provided for cognitive events that, as with other AEDs, weren't particularly illuminating. (5) Anemia events were described showing that the apparent excess was probably not associated with recognized medical events and that these patients weren't evaluated for anemia. The occurrence of anemia was described in the labeling proposed by the division at the time of the AE letter. (6) The sponsor confirmed the marked decrease in ALT and AST that occurs with vigabatrin. (7) New analyses of the effect of time on common events suggested the events occur early in treatment. (8) The sponsor [redacted] about the possibility of absence seizure occurrence and enumerated the patients that were recognized to have such events in the NDA.

b(4)

In discussing the decline in AST and ALT, the sponsor also mentioned that vigabatrin seemed to be associated with amino aciduria and proposed labeling to mention this effect in addition to that on AST and ALT.

Conclusion

The safety profile of vigabatrin has changed significantly since the issue of the AE letter. Severe visual field cuts appear to be strongly associated with vigabatrin use and are much more common than we thought. Unfortunately, there is no longitudinal data to describe the hazard by dose and/or time, or the effectiveness of screening at preventing the event. Likewise, there is no longitudinal data in patients who have the event so that its course, and particularly its reversibility, can not be described. Finally, we don't know for certain that the event is specific to vigabatrin.

HMR addressed all but the peripheral neuropathy issues that were noted in the AE letter or the proposed labeling.

There appears to be an excess of hospitalizations for an event coded as "convulsions" in patients assigned vigabatrin, but do not know the nature of these events.

Recommendation

In my opinion, the labeling should remain mostly as we proposed. I don't think, however, that we can construct informative labeling for the visual field cuts that develop with vigabatrin use until we have additional data. HMR needs to conduct a randomized study that is carefully designed to detect visual field abnormalities in users of vigabatrin and other AED drugs. Since some type of perimetry exams will be used as the outcome, the study probably only the examiner would have to be blinded. Patients that develop abnormalities should also be longitudinally followed.

b(4)

HMR needs to describe the events that have been coded as "convulsions" that result in hospitalization and they need to conduct the analyses we requested in the AE letter for peripheral neuropathy.

Greg Burkhart, M.D., M.S.
Safety Team Leader
Neuropharmacological Drug Products

HFD-120/Leber/Katz/Boehm/Burkhart

MEMORANDUM

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

DATE: September 16, 1998

FROM: Allen Brinker, MD, MS
Epidemiology Branch
Division of Pharmacovigilance and Epidemiology, HFD-733

THROUGH: Ralph Lillie, RPh, MPH
Acting Director,
Office of Postmarketing Drug Risk Assessment

TO: Paul Leber, MD
Director,
Division of Neuropharmaceutical Drug Products, HFD-120

SUBJECT: Visual events reported in association with vigabatrin in comparison to other anticonvulsants.

INTRODUCTION

This consult updates and completes a synopsis delivered to Greg Burkhart, MD on August 27, 1998 on visual problems reported in association with vigabatrin and other anticonvulsants. It includes an analysis of WHO (international) and SRS/AERS (domestic) adverse drug events (ADEs) and suspect cases culled from a hands-on review of reports.

METHODS

As per request, WHO adverse drug experience reports for vigabatrin, tiagabine, felbamate, topiramate, and valproic acid were obtained from the Uppsala Monitoring Centre in Sweden. WHO reports of this nature contain only frequencies of ADE terms reported in association with a drug. Thus, as a case report can, and frequently does, contain more than one ADE, it is not possible to

determine how many individuals are represented in these WHO data. Therefore, in addition to frequency, the statistic of interest calculated in this analysis is an estimate of the proportion of visual field defect (one COSTART term) and vision abnormalities (containing 4 COSTART terms) to the total number of ADE terms reported in association with a specific drug. No attempt has been made to limit reports to those submitted prior to dissemination of the association in question in the medical literature. WHO data were prepared on July 17, 1998. There is one case report (published in BMJ) of visual field constriction in association with vigabatrin from January 1997.

In consideration of the many WHO languages, and after review of individual case reports where suspect "cases" were recovered under nonspecific ADE terms (e.g. "vision abnormal"), this analysis will examine reports classified as "visual field defect" and those containing any of the 4 following COSTART terms: visual field defect; vision abnormal; blindness; or eye disease. [This collection of terms will hereafter be referred to as "vision abnormality."]

Although specific interest was directed at GABA-specific agents, other anticonvulsants have been included in this analysis as the precise mechanism of action of these agents is not known but assumed to be through one or more of the following mechanisms: modulating voltage-dependent ion channels involved in the action potential propagation or burst generation; enhancement of GABA inhibitory activity; and/or inhibition of excitatory amino acid neurotransmiter activity.

REVIEW OF CASE REPORTS

As noted above, the AERS/SRS databases were searched for reports containing any of the 4 relevant COSTART codes in association to the anticonvulsants listed in Table 1. Copies of the actual case reports were then obtained for hands on review. Four case reports of nonspecific vision

abnormalities and one case report of visual field defect that included dechallenge/rechallenge information are summarized below and attached.

1) FDA# 1,667,937 (1995, dechallenge/rechallenge) 50 year old female with hx of Von Hippel-Lindau disease experienced "intermittent cloudy vision" 4-7 days after starting gabapentin. Gabapentin discontinued and symptoms resolved only to reoccur after gabapentin was reinstated.
2) FDA# 781,775 (1990, dechallenge) "Progressive loss of visual fields" in a 57 year old male following treatment with Dilantin (IV). Symptoms improved after drug discontinued.
3) FDA# 1,421,916 (1993, dechallenge) 42 year old female experienced "complete loss of vision [and speech]" 14 days after starting felbamate. Symptoms resolved after discontinuation of felbamate.
4) FDA# 1,865,053 (1996, dechallenge) 45 year old female experienced "blurred and cloudy vision" 4 days after starting gabapentin. Pt recovered after drug discontinued.
5) FDA# 1,699,884 (1995, dechallange) 31 year old male "lost vision in both eyes" 2 weeks after starting gabapentin. Symptoms abated after drug discontinuation.

An additional 12 cases which did not include dechallenge/rechallenge information were judged to be suspicious and are also attached. These contain reports of "tunnel vision", "vision loss", "blindness", blind spots", and "visual field defects/cuts." Of these 17 cases (5+12), time-to-onset was included on 10 reports: range of reported time-to-onset from starting drug - 4 to 90 days (median 17 days, average 33 days).

RESULTS

As shown in Table 1, the frequency and unadjusted proportion of the single ADE term "visual field defect" reported in association with vigabatrin is higher than for other selected anticonvulsants. Even after "diluting" the specificity of the case definition by examination of the frequency and proportion of vision abnormalities (Table 2), vigabatrin stands out.

Table 1 Frequency and unadjusted proportion* of the ADE term visual field defect reported in association with a specific anticonvulsants to US and WHO databases.

	US SRS			WHO		
Drug	frequency	total ADEs	proportion (%)	frequency	total ADEs	proportion (%)
Older agents						
phenobarb.	0	1,158	**0**			
phenytoin	3	13,110	**0.02**			
carbam-azepine	6	12,830	**0.05**			
valproic acid	1	15,815	**0.01**	5	6,288	**0.08**
clonazepam	4	1,786	**0.2**			
clorazepam	0	1,295	**0**			
Newer agents						
gabapentin	1	2,237	**0.04**			
lamotrigine	0	1,288	**0**			
felbamate	0	2,966	**0**	0	665	**0**
topiramate	0	120	**0**	0	565	**0**
vigabatrin				82	2,161	**3.8**
tiagabine				0	90	**0**

*denominator=total number of ADEs reported for specific drug

Table 2 Unadjusted proportion* of vision abnormality terms reported in association with a specific anticonvulsants to US and WHO databases**

	US SRS			WHO		
Drug	frequency	total ADEs	proportion (%)	frequency	total ADEs	proportion (%)
Older agents						
phenobarb.	3	1,158	0.3			
phenytoin	48	13,110	0.4			
carbam-azepine	65	12,830	0.5			
valproic acid	65	15,815	0.4	26	6,288	0.4
clonazepam	12	1,786	0.7			
clorazepam	2	1,295	0.2			
Newer agents						
gabapentin	21	2,237	0.9			
lamotrigine	8	1,288	0.6			
felbamate	9	2,966	0.3	4	665	0.6
topiramate	0	120	0	8	565	1.4
vigabatrin				114	2,161	5.3
tiagabine				1	90	1.1

*denominator=total number of ADEs reported for specific drug

**vision abnormality ADE terms include the following: visual field defect; vision abnormal; blindness; and eye disease

LITERATURE

As of August 27, 1998, there were 10 literature citations on visual field defects associated with vigabatrin (see attached). In contrast, there were no citations suggesting visual field defects in association with any of the other anticonvulsants included in this report.

CONCLUSIONS

The frequency and estimated proportion of both visual field defects and nonspecific vision abnormalities reported in association with vigabatrin are substantially higher in comparison to other anticonvulsants selected for this consult. [Note that estimates presented in this analysis DO NOT represent the proportion of individuals for an agent reported with visual field defects and vision abnormalities but the proportion of visual field defects and vision abnormalities to the total number of ADEs reported in association with a specific drug.]

Although the ADE term "visual field defect" has been reported in association with 5 of the 11other anticonvulsants included in this report, a qualitative comparison of cases reported in association with vigabatrin to cases reported in association with other agents is needed to justify the comparison. In addition, given the number of years comparison products have been on the market, and the corresponding number of exposed individuals, we believe that this analysis has understated the magnitude of the apparent association and a comparison of reporting rates based on drug exposure would result in a greater difference. [A comparison of drug reporting rates is not possible as CDER does not have access to foreign use drug use data.]

In addition to the 17 SRS case reports attached to this consult, all the SRS reports collected as part of this consult are available upon request.

Allen Brinker, MD

Concurrence:

DC 11/26/08

David Graham, MD

Evelyn Rodriguez, MD

cc:

HFD-120//Leber / Burkhart

HFD-730//Lillie

HFD-733//Rodriguez / Graham / Brinker

HFD-735//Chen / Mease

BMJ 1998 Jul 18;317(7152):206

Study is needed of visual field defects associated with any long term antiepileptic drug.

Rao GP, Fat FA, Kyle G, Leach JP, Chadwick DW, Batterbury M

Neurology 1998 Mar;50(3):614-618

Vigabatrin-associated retinal cone system dysfunction: electroretinogram and ophthalmologic findings.

Krauss GL, Johnson MA, Miller NR

BMJ 1998 Jan 17;316(7126):233

Severe persistent visual field constriction associated with vigabatrin. Asymptomatic as well as symptomatic defects occur with vigabatrin.

Mackenzie R, Klistorner A

BMJ 1998 Jan 17;316(7126):232-233

Severe persistent visual field constriction associated with vigabatrin. Benefit: risk ratio must be calculated for individual patients.

Harding GF

BMJ 1997 Jun 7;314(7095):1694-1695

Severe persistent visual field constriction associated with vigabatrin. Manufacturers have started several studies.

Backstrom JT, Hinkle RL, Flicker MR

BMJ 1997 Jun 7;**314(7095)**:1694

Severe persistent visual field constriction associated with vigabatrin. Four possible explanations exist.

Harding GF

BMJ 1997 Jun 7;**314(7095)**:1693-1694

Severe persistent visual field constriction associated with vigabatrin. Reaction might be dose dependent.

Wong IC, Mawer GE, Sander JW

BMJ 1997 Jun 7;**314(7095)**:1694

Severe persistent visual field constriction associated with vigabatrin. Patients taking vigabatrin should have regular visual field testing.

Blackwell N, Hayllar J, Kelly G

BMJ 1997 Jun 7;**314(7095)**:1693

Severe persistent visual field constriction associated with vigabatrin. Chronic refractory epilepsy may have role in causing these unusual lesions.

Wilson EA, Brodie MJ

BMJ 1997 Jan 18;**314(7075)**:180-181

Severe persistent visual field constriction associated with vigabatrin.

Eke T, Talbot JF, Lawden MC