

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-427

MEDICAL REVIEW(S)

MEMORANDUM

DATE: August 14, 2009

FROM: Russell Katz, M.D.
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Division of Neurology Products/HFD-120

TO: File, NDAs 20-427 & 22-006

SUBJECT: Overview Memo for NDAs 20-427 & 22-006, for the use of Sabril (vigabatrin) as adjunctive therapy for Complex Partial Seizures (CPS) in adults and as monotherapy for Infantile Spasms (IS) in children, respectively

NDAs 20-427 & 22-006, for the use of Sabril (vigabatrin) as adjunctive therapy for Complex Partial Seizures (CPS) in adults and as monotherapy for Infantile Spasms (IS) in children, respectively, have a long and complex regulatory history. NDA 22-006, for IS, was submitted by Ovation Pharmaceuticals on 12/28/07, but NDA 20-427, for CPS, was submitted initially in April, 1994. A response to the most recent action letter for that NDA, a Not Approvable letter that was issued on 10/26/98, was also submitted by Ovation Pharmaceuticals on 12/28/07.

These most recent submissions have been reviewed by Dr. Gerard Boehm of the division's safety group and Dr. Sally Yasuda, safety group team leader; a statistical review of NDA 22-006 (IS) performed by Dr. Julia Luan, statistician; a medical review of the efficacy and safety data for NDA 22-006 (IS) performed by Dr. Philip Sheridan of the division; a review of the ophthalmologic toxicity data, performed by Dr. Ron Farkas of the division; reviews of juvenile rat toxicity studies by Dr. Ed Fisher, pharmacologist, and Dr. Larry Schmued, neurotoxicologist of the Agency's National Center for Toxicological Research, and Dr. Lois Freed, supervisory pharmacologist; a review of the sponsor's proposed plans for risk management (a Risk Evaluation and Mitigation Strategy [REMS]), by the Sabril Risk Evaluation and Mitigation Strategy Review Team of the Office of Surveillance and Epidemiology; Dr. Sharon Watson, Division of Drug Marketing, Advertising, and Communications; Sharon Mills, Division of Risk Management; Dr. Judy Park and Linda M. Wisniewski, Division of Medication Errors and Technical Support (now DMEPA); the Interdisciplinary Review Team for QT Studies; Dr. John Duan, Office of Clinical Pharmacology; Dr. Monica Cooper, chemist; Dr. Katherine Bonson, Controlled Substance Staff; and Dr. Norman Hershkowitz, neurology team leader. In this memo, I will very briefly describe the regulatory history of these applications, as well as the effectiveness and safety data for both, and offer the division's recommendation for action on these applications.

NDA 20-247, for the use of Sabril (vigabatrin), as adjunctive therapy for Complex Partial Seizures (CPS) in adults

History

The IND for vigabatrin was submitted in 1980. In 1983, the Agency became aware of the occurrence of a unique histopathologic finding in animals (rats, dog, mice, and to a lesser extent, monkey) given vigabatrin. Specifically, at doses approximating those to be given to humans, vacuoles between the myelin lamellae (so-called intramyelinic edema; IME) was seen. The division placed the IND on clinical hold until the sponsor was able to develop a non-invasive method that could detect the occurrence of the lesion in a sufficiently early stage to ensure that it would be reversible if the drug was discontinued. After several years, the sponsor was able to validate visual evoked potentials and MRI (in the dog) as a sensitive test, and clinical testing was permitted to resume in 1989.

The NDA was submitted in April, 1994 and contained the results of two adequate and well-controlled trials in patients with CPS. The Agency issued a Not Approvable letter on 4/28/95. The basis for the action was largely deficiencies in the structure of the submission, primarily related to the safety data. A provisional judgment was made at that time, however, that effectiveness had been shown. The sponsor submitted a response to the Not Approvable letter in May, 1997. In response, the Agency issued an Approvable letter on 11/26/97. That letter conveyed the Agency's conclusion that the sponsor had submitted substantial evidence of effectiveness for vigabatrin as adjunctive therapy for CPS, but that it should be indicated as second line adjunctive treatment because of concerns related to IME. The letter also requested additional safety analyses.

The sponsor responded to the Approvable letter in April, 1998. By that time, the Agency had become aware of a unique visual field defect associated with the use of vigabatrin, and, as a result, the sponsor had proposed that vigabatrin be approved as a last resort treatment under very restrictive conditions. The Agency had concluded that the risk had not been sufficiently characterized to permit marketing at that point, so a third action letter, a Not Approvable action, was issued on 10/26/98.

After numerous discussions between the Agency and the previous and current sponsors, Ovation Pharmaceuticals submitted an acceptable response to the 1998 Not Approvable letter on 12/28/07. We decided to discuss both NDAs at a meeting of the Peripheral and Central Nervous Systems Advisory Committee in January, 2009.

Effectiveness

As noted above, the sponsor previously submitted the results of two parallel group trials in which patients were randomized to one of several doses of drug or placebo. The trials were multi-center trials performed in the United States. Also as noted, the Agency has previously determined that these trials establish substantial evidence of effectiveness for vigabatrin as adjunctive treatment for CPS in adults.

Study 24

A total of 183 patients treated with 1 or 2 AEDs were randomized to vigabatrin (N=93) or placebo (N=90) at 15 US centers. Patients were observed for 12 weeks, titrated up to 3 gms/day of vigabatrin or placebo over the next 4 weeks, then maintained on their dose for 12 weeks. The following charts display the results of the outcome measures:

Median Monthly Seizure Frequency

	N	Baseline	Final	P-value
Vigabatrin	92	8.3	5.3	.001-.0002
Placebo	90	8.3	7.5	

Proportion of Patients Achieving At Least 50% Reduction

	N	%	P-Value
Vigabatrin	92	43%	<.001
Placebo	90	19%	

Median Monthly CPS Seizure Frequency

	N	Baseline	Final	P-Value
Vigabatrin	84	8.5	5.0	<.0006
Placebo	89	8.0	7.0	

Study 25

A total of 174 patients were randomized in this multi-center parallel group study to either vigabatrin 1, 3, or 6 gms/day or placebo (the design was similar to Study 24, except the titration phase was 6 weeks long). The following table represents the results:

Median Monthly Seizure Frequency

	N	Baseline	Final	P-value
Vigabatrin 1 gm	45	8.5	7.7	NS
Vigabatrin 3 gm	43	8.0	3.7	.0001
Vigabatrin 6 gm	41	9.0	4.5	.0001
Placebo	45	9.0	8.8	

Proportion of Patients Achieving At Least 50% Reduction

	N	%	P-Value
Vigabatrin 1 gm	45	24%	.02
Vigabatrin 3 gm	43	51%	<.0001
Vigabatrin 6 gm	41	54%	<.0001
Placebo	45	7%	

Median Monthly CPS Seizure Frequency

	N	Baseline	Final	P-Value
Vigabatrin 1 gm	45	7.5	7.0	NS
Vigabatrin 3 gm	43	7.0	3.5	.001
Vigabatrin 6 gm	39	8.5	3.5	.0001
Placebo	44	8.8	8.3	

Safety

As noted by Dr. Boehm, the sponsor has submitted some safety data from over 4800 subject/patients exposed to at least one dose of vigabatrin. These data have been gathered over many years of development, under various conditions that were more or less well documented. According to the sponsor, 4,077 patients have been exposed in epilepsy trials for whom sufficient evidence to

evaluate adverse events (AEs) is/was available. Of these, 3,456 subjects were exposed for at least 6 months, 2,753 were exposed for at least one year, and 403 patients were exposed for at least 5 years. A total of 1,112 patients were exposed to a daily dose of between 3 and 4 gms for at least 6 months, and 587 patients were exposed to the same dose for at least one year.

Treatment with vigabatrin is associated with typical CNS toxicities (somnolence, dizziness, ataxia, diplopia), but also several other changes. Besides the special ophthalmologic toxicities to be described below, the following other AEs were noted:

Anemia; Changes in Hemoglobin, Hematocrit

Very slight mean decreases in hemoglobin and hematocrit were seen in controlled trials of vigabatrin, which appeared to be dose related. The following results were seen in Studies 24 and 25:

Mean Change From Baseline

	Pla	1 GM	3 GM	6 GM
Hemoglobin	0.53	0.58	-0.24	-1.39
Hematocrit	0.02	-0.12	-0.44	-0.91

There were 3 SAEs (.06%) and 3 (.06%) discontinuations due to related changes, and no cases of aplastic anemia.

Liver Function Abnormalities

Treatment with vigabatrin results in dose-related decreases in LFTs. The following results were seen in Studies 24 and 25:

Mean Change From Baseline

	Pla	1 GM	3 GM	6 GM
AST	-0.18	-1.51	-3.65	-3.88
ALT	-0.07	-11.82	-16.23	-19.12

In these trials, the majority of patients had a decrease in LFTs. There were no patients who had an increase in LFTs of 3 XULN with an increase in bilirubin of 2 X ULN. There were 4 patients in the development program who died with liver failure, but there were other factors more likely to be the cause. In post-marketing experience (all foreign), there were 3 cases of death or transplant without an obvious other cause, although all were taking other AEDs. The

reporting rate exceeds the background rate (although, again, these were all foreign cases), but these other AEDs may have been the cause, or may have contributed.

Weight gain

Vigabatrin use causes weight gain. Combined data from 9 controlled trials revealed 17% of vigabatrin-treated patients gained at least 7% of their baseline body weight compared to 8.5% of placebo-treated patients (a mean gain of about 3-4 kg compared to about 1.5-2 kg for placebo patients). Including open-label, uncontrolled data, a total of about 26% (484/1843) of treated patients gained at least 7% of their body weight. It was impossible to perform adequate dose-response analyses.

Edema

In 12 controlled trials there was a slight increase in the rate of peripheral edema in vigabatrin-treated patients compared to placebo-treated patients (4.3/100 PYs vs 3/100 PYs, respectively); there was a clear dose response based on an analysis of 5 fixed dose controlled trials (maximum rate of .23/100 PYs for >5 gms/day compared to .06/100Pys for placebo). Edema did not seem to be associated with other cardiovascular, renal, hepatic, or pulmonary signs or symptoms. A total of 215 patients in the database had an edema-related AE; 50 also had weight gain.

Depression

There was no important difference in the incidence of depression as an AE between drug and placebo-treated patients in a pool of Phase 2/3 trials (446 PYs of vigabatrin compared to 101 PYs of placebo), but there was an increase in the rate of SAEs of depression (2.2/100 PYs vs 0) and discontinuations due to depression (3.4/100 PYs vs 1/100 PYs); there was one suicide attempt. There was only one completed suicide in the epilepsy experience (N=4,855).

Ophthalmologic Toxicity

As noted earlier, in 1997 the Agency became aware that vigabatrin use was associated with a stereotypical concentric visual field defect, worse in the nasal visual field. As a result, the sponsor has performed numerous analyses of multiple data sources in an attempt to characterize the incidence of this lesion, as well as to characterize important other aspects, including the time of onset, whether the lesion increases with treatment discontinuation or continuation, and, importantly, whether or not the lesion can be detected early enough so that it

might be reversible. These data have been reviewed in great detail by Dr. Ron Farkas, ophthalmologist in the division. I will here very briefly review the most important findings and conclusions.

Adults

Several major data sources were used to evaluate these issues.

Study 4020

This was a multi-center study in 46 centers in France, South Korea, Italy, Spain, and Australia. Investigators enrolled only those patients with visual field defects they felt not likely due to another cause (e.g., glaucoma). Patients in this study were either taking vigabatrin for variable durations, or had discontinued its use. Patients were assessed with various methods of perimetry (methods use varied between patients, and sometimes within patients over time).

The sponsor divided the patients into 3 groups:

Group 1-Currently receiving vigabatrin

Average 4.2 years of treatment. 38 children, 149 adults

Group 2-Previously treated, not on current vigabatrin treatment

Average treatment duration-2.4 years. 47 children, 152 adults

Group 3-Never treated with vigabatrin

The first test occurred about 5 years after treatment initiation, on average. A total of 524 patients had at least one useable test.

According to the sponsor, 25% of adults and 15% of children had a confirmed VFD characteristic of vigabatrin. As noted by Dr. Farkas, in patients with 5 tests, 35% (12/33) adults continuing treatment had a progressive lesion, compared to 13% who were never treated with vigabatrin. The earliest time of onset of a VFD was 12 months in adults and 16 month in pediatric patients.

As described in great detail by Dr. Farkas, this study suffered from many and profound methodological deficiencies; many of these were noted by members of the study steering committee. In Dr. Farkas's view, these deficiencies make the results of the study unreliable.

Pooled Cohort Study

The sponsor presented results of a pool of 367 of the total of 403 vigabatrin-treated patients in multiple studies from Finland, Japan, US, UK, Canada, Spain, Germany, and Australia. The studies were of many different designs (e.g., monotherapy, adjunctive, varying durations, controlled or uncontrolled) and included 112 non-vigabatrin treated patients. Of the 367 vigabatrin patients, 335 had usable visual fields. Various testing methodology was used, and patients were tested only once, unless an abnormality was suspected.

Of the 335 vigabatrin patients tested, 105 had a VFD (31%). According to Dr. Farkas's review, about 1/3 of these VFDs were "profound". There were no VFDs in non-vigabatrin treated patients. According to Dr. Farkas, it appeared that a VFD had to be relatively severe (given the grading system used) for a test to be considered "positive". An amendment to the original study report added 119 patients, with only 7 additional patients noted with a VFD. The average duration of treatment with vigabatrin was about 3 years. There was no real relationship between severity of VFD with increasing duration of exposure or with cumulative dose. Interestingly, the report states that 8% of patients tested complained of symptoms that could be referable to the VFD.

Based on these data, the sponsor estimated the time of onset of the lesion. According to these analyses, the maximum incidence of VFD occurred before 1 year, then declined slowly over 8 years (although there were still some new events out in time). The prevalence of VFDs continued to increase over 8 years (with increasing variability in the estimate), but appeared to approach a plateau at about 4-5 years.

The incidence also seemed to peak at a cumulative dose of about 1 kg, and the prevalence reached a plateau at a cumulative dose of about 2 kg.

Study R003

This was a prospective study of 25 patients treated at 4 Canadian centers. Perimetry and ERG were performed every 3 months. The median duration of treatment was 500 days (range 2-988 days).

A total of 7 patients (28%) developed VFDs. In 3, the severity was Moderate at diagnosis. The median cumulative dose was about 1 kg. Dr. Farkas describes one patient, a 44 year old woman, who was treated for 63 days (cumulative dose about 82 gms), who was determined to have a moderately severe VFD 2 months after vigabatrin was discontinued (ERG was negative). This case clearly suggests that the lesion can occur before 2 months of treatment.

Study 4021

This was an observational study performed in Finland of 29 patients (currently receiving vigabatrin or who had previously discontinued treatment due to a VFD). Nine patients were noted to have a vigabatrin-induced VFD.

Pediatric Patients

Toronto Study

A total of 246 infants, mostly with IS, were examined at a tertiary care center that treats most of the IS patients in the Toronto region. A total of 117 patients had a baseline and at least one on-treatment exam, and 85 patients did not have a baseline exam. A total of 179 patients were treated with vigabatrin, and 117 of these discontinued treatment during the study. Patients were examined initially (including with ERG) every 6 months, and more recently every 3 months. The median age at the most recent ERG was about 2 years old.

The incidence of a "sustained" ERG abnormality (defined as an abnormality on the last 2 consecutive exams) was about 25%, with at least one abnormality seen in 63% of subjects. The sponsor concluded that no abnormality occurred earlier than 3 months, but, of course, testing was not performed before 3 months. In patients with a sustained abnormality, the average time to abnormality was 27-36 months (depending on the test performed). However, as Dr. Farkas notes, sustained abnormality was defined by the last 2 exams, so the time to this endpoint is confounded with the definition. The sponsor reports a frequency of visual field defects of 8%, but, as Dr. Farkas notes, the test used (confrontation) is likely not sensitive in this population.

Several cases described by Dr. Farkas are worth recounting. A 13 year old boy with autism had been treated for about 6 years prior to his first test, which was reported as "mildly" abnormal; he had no visual difficulties (parent report) at that time. Eighteen months later the parent noted that he was bumping into things; the ERG was markedly abnormal. This case implies that a significant abnormality can occur, in Dr. Farkas's words, "precipitously".

Additionally, a 13 month old boy with Trisomy 21 had a normal ERG after 5 months of treatment with vigabatrin. Six months later, the ERG was still within normal limits. Five months later (a total of 16 months of treatment), the ERG was "dramatically" reduced. Although the dose was reduced, 8 months later there was clinical evidence of a profound field defect. At that time, the drug was discontinued, but 3 months later the ERG was even more abnormal.

Study 4102

This was another cross-sectional observational study in 39 pediatric patients in 3 centers. Twelve patients were tested with perimetry, H-stimulus was used in 35, and ERG in 26. VFD was detected in about 1/3 of the patients.

Study 0201

This was a 1 year follow-up study in 210 pediatric patients who were studied with ERG, field exams, and VEPs.

On average, ERG flicker amplitude decreased from 83 mcV to 69 mcV in 88 patients followed for one year. A total of 23/51 patients with normal visual fields had ERG progression.

ERG/Visual Field Correlation

Dr. Farkas has reviewed numerous articles submitted by the sponsor in support of their contention that ERGs are an acceptably sensitive test of VFDs in patients who cannot cooperate with formal visual field testing. Some of the articles simply demonstrate that ERG can detect already existing significant VFDs, and other articles demonstrate a relatively poor correlation between ERG abnormalities and VFDs (see, for example, the article by McDonagh et al, which demonstrates that most patients with abnormal visual fields had normal ERGs; of 19 patients with a VFD, at least 13 had a normal ERG). No adequately reported and documented article adequately established the ability of ERG to detect a VFD very early in its evolution.

Post-Marketing reports

Although there have been post-marketing reports of VFDs, it is difficult to interpret these reports, and, of course, it is difficult to assess the incidence/prevalence of VFDs from this sort of data. What is of note, however, as Dr. Farkas points out, is that these data are consistent with the reasonable conclusion that VFDs are not likely to occur in the first few days of treatment with vigabatrin, and that treatment with vigabatrin is only very rarely likely to cause severe central acuity loss.

NDA 22-006, for the use of Sabril (vigabatrin) as a treatment for Infantile Spasms (IS)

As noted earlier, the sponsor submitted this NDA for the use of vigabatrin in IS in December, 2007. The application consists of reports of two randomized controlled trials, neither of which was performed by the sponsor. These studies have been reviewed in great detail by Drs. Sheridan and Luan. Here, I will very briefly review the pertinent findings.

Study 1A

This was a multi-center study in which patients were randomized to receive either low dose (18-36 mg/kg/day) or high dose (100-148 mg/kg/day) vigabatrin. The treating physician was unblinded to treatment assignment, but the parents and the readers of the EEGs were blinded (parents were blinded to dose). Patients were titrated for the first 7 days, and then left on constant treatment for another 7 days. If the patient became spasm-free within the first 14 days, an additional 7 days of constant dose was given.]

The primary outcome was the proportion of patients spasm-free for 7 days beginning within the first 14 days of treatment. This was to be confirmed by the caregiver and a CCTV EEG performed within 3 days of the seventh day of spasm-freedom.

The study was originally submitted as a "compassionate" IND, but was changed to be a controlled trial, in which 44 patients were to be enrolled. Subsequently, however, the sample size was increased on two occasions, first to allow up to 150 patients, then to allow up to 250 patients. According to the sponsor, an interim analysis was requested by the FDA in order to put language about pediatric use in the product labeling (presumably, this was at the time that the Agency was considering the approval of the CPS application). This first analysis included data from 62 patients out of 89 randomized patients. Then, a second analysis was performed with 142 patients out of 179 randomized patients, again apparently, according to the sponsor, at the request of the Agency. The results of this analysis were published in Neurology in 2001. Finally, the analysis presented as primary in this NDA submission included 221 patients out of 227 randomized patients. These analyses were not prospectively designated in the original protocol.

The following results for these various analyses are presented below for the primary outcome measure as defined above:

	First 44	First Interim	Second Interim	Final
Responders, High Dose	14%	28%	15%	16%
Responder, Low Dose	0%	15%	5%	7%
P-value	.23	.35	.09	.0375

It should be noted that the second interim analysis that was published in Neurology described a Responder Rate in the High Dose group of 36% and in the Low Dose Group of 11% (P<.001). However, this was a result of a difference in the application of the definition of a Responder.

In this study, it was difficult for the EEG to always be obtained within the protocol-specified 3 day window. The sponsor performed additional analyses that examined the outcome when the window for performing the EEG was widened. As can be seen in Table 22 of Dr. Sheridan's review (page 49), analyses become increasingly positive with increasing widening of this EEG window. Further, the a comparison between the two treatment groups on the Time to Spasm Cessation for 7 days, with or without EEG confirmation, the second secondary outcome to be tested, was highly significant in favor of the high dose group (p=0.0016).

The first secondary outcome to be tested, the Proportion of Patients Spasm-Free for 7 days and who remained spasm-free for the duration of the study, revealed 68% and 52% in the high and low dose groups, respectively.

Study W019

This was a double blind parallel group study of vigabatrin as monotherapy in pediatric patients with IS. In this study, patients underwent a 2-3 day prospective baseline, during which caregivers were to determine the time of day during which the patient's spasms were most frequent. Then, patients entered a 5 day double-blind period, in which they were initially randomized to vigabatrin 50 mg/kg/day or placebo. If spasms continued, the dose was increased to a maximum of 150 mg/kg/day.

The primary outcome measure was the percent change in spasm frequency evaluated during a pre-determined 2 hour/day window from baseline to the final 2 days of the double-blind period. The outcome on this measure is described below. In addition, although entirely post hoc, the outcome on this measure, but measured over 24 hours, is also given:

Percent Change in Mean Spasm Frequency

	2 Hours	24 Hours
Vigabatrin	54%	69%
Placebo	41%	17%
P-value	0.56	0.030

A total of 35% of the vigabatrin-treated and 10% of the placebo-treated patients were spasm-free on the final day of the double-blind phase (NS).

Study FR03 in Patients with IS and Tuberous Sclerosis

Because there was some evidence from Study 1A that patients with Tuberous Sclerosis might be particularly sensitive to the beneficial effects of vigabatrin, this study was designed to examine the drug's effects in this specific sub-group.

This study was designed to compare the effectiveness of vigabatrin (150 mg/kg/day) and hydrocortisone (15 mg/kg/day) in previously untreated patients with IS. Patients were randomized to one of the treatments for one month (evaluated every 2 weeks). If spasms did not completely cease, patients were crossed over to the other treatment after 4 weeks of treatment. This study was open-label, and there was no prospective statistical plan.

A total of 11 patients were randomized to receive vigabatrin first, compared with 12 randomized to receive hydrocortisone. None of the patients treated with vigabatrin first crossed-over; that is, all 11 were spasm-free. A total of 7 patients treated first with hydrocortisone were crossed over to vigabatrin; that is, only 4/12 of these patients were spasm-free ($p=0.001$). When these 7 patients were treated with vigabatrin, they became spasm-free.

MRI

Previous evaluation of MRI studies in patients revealed no lesions that could reasonably be associated with vigabatrin treatment. However, recently, the literature has contained reports of MRI changes in pediatric patients that have raised concerns. These lesions were considered to possibly represent a different lesion from IME (although, again, even if they represented IME, they would have been more or less the first detection of IME in humans) because they were located in the deep grey matter (IME in animals was a white matter lesion). For this reason, the sponsor undertook a retrospective analysis of MRI data from 5 studies. In addition, after we met with the sponsor in June, 2007 to discuss this issue, the sponsor undertook to retrospectively examine data from an additional 10 centers in which infants were studied, as well as a re-examination of previously reviewed MRI studies in older children and adults (this latter study was considered appropriate because it was possible that previous examinations of these studies might have missed deep grey matter lesions, given that this was not the area expected to become abnormal with vigabatrin treatment).

Retrospective Study of 5 centers

In this study, MRI studies of 204 patients treated with vigabatrin in Canada, US, and France were examined. Of these, 42 patients were noted to have T2 abnormalities. Of these, 23 were considered likely due to vigabatrin (only 2 had

baseline studies), 13 were considered of questionable relationship, and 10 were considered unrelated to treatment.

Of the 23 considered to have lesions likely related to treatment, 12 had complete or partial resolution of the abnormalities (7 continued on treatment, 5 had discontinued). The remaining 11 patients did not have repeat studies.

Retrospective Epidemiologic Studies

In this study, MRIs of 205 infants treated for IS (with vigabatrin or other treatments) were blindly examined by 2 pediatric neuroradiologists.

The prevalence of vigabatrin-like MRI lesions in this study was 21.5% in vigabatrin treated patients and 4% in patients treated with other drugs. The incidence was 36% and 6%, respectively. It appeared that the lesion was transient in many patients, but in most of these patients the drug was discontinued when the lesion was detected, and there was a suggestion of a dose response (of course, patients were not randomized to dose). There seemed to be no characteristic clinical signs or symptoms that routinely accompany the lesions.

Retrospective re-examination of previously reviewed MRIs

In this study, in over 400 adults and 200 children, the prevalence of vigabatrin-like MRI lesions was 14% in vigabatrin treated patients and 13% in those treated with other drugs. The incidence was 11% and 8%, respectively.

Juvenile Toxicity

The sponsor asserts that the MRI lesion seen in pediatric patients represents the well-known IME seen in multiple animal species, but in a location not previously noted before. Dr. Schmued concludes that the lesion seen in the juvenile rat (seen in the same anatomic locations as the MRI lesions in pediatric patients) are different from IME, in that the juvenile lesions are seen in deep grey matter, and appear to not be intra-myelinic edema, but may represent neuronal degeneration (though he notes significant limitations in the studies performed).

REMS

The sponsor initially proposed to market Sabril under specific conditions, including product labeling that would mandate a specific schedule of ophthalmologic monitoring (for patients with IS, every 3 months for the first 18 months, then every 6 months; for patients with partial seizures, every 6 months). Further, they proposed to require that prescribers must receive education about

Sabril's risks, and that the product would be distributed through specialty pharmacies only when prescribers had attested to understanding the risks and the monitoring protocol. In addition, patients were to receive educational materials, and physicians and patients were to agree to re-assess the appropriateness of continued treatment with Sabril after 12 weeks on therapy. The sponsor believed that the proposed ophthalmological monitoring in both adults and pediatric patients was adequate to detect visual loss at a relatively early stage.

SUMMARY

The sponsor has submitted what they believe is substantial evidence of effectiveness for Sabril as adjunctive therapy for adults with partial seizures, and as a treatment for infantile spasms in infants. We have previously concluded that there is substantial evidence of effectiveness for the former indication (but had previously concluded that the safety data, particularly the visual toxicity, precluded approval), but have not previously considered the application for the treatment of infantile spasms. In the latter case, the results and design of the controlled trials pose numerous interpretive challenges.

Further, the sponsor believes that the safety data presented are adequate to support approval of Sabril for both indications, under appropriate conditions of use, as proposed in their REMS.

Because of the complexity of the issues involved, we discussed these applications in a 2 day meeting of the Peripheral and Central Nervous Systems Advisory Committee on January 7 & 8, 2009, supplemented by experts in epilepsy, ophthalmology, pediatrics, and risk assessment.

Regarding NDA 20-427, for the use of Sabril in the treatment of patients with CPS, the committee voted unanimously (24-0) that the application should be approved for use in refractory patients. They clearly felt that its use should be reserved for those patients who had had an adequate trial of several AEDs, though they also felt that no additional effectiveness data should be required prior to approval (despite their conclusion that Sabril has not been shown to be more effective than other AEDs in a refractory population, and especially not compared to current AEDs). Regarding visual toxicity in this population, they concluded that continued treatment can result in clinically meaningful visual loss, that discontinuation of treatment has not been shown to prevent progression of the visual loss, that monitoring can detect visual loss before it is clinically meaningful (14 yes, 7 no, 3 abstain), and that it had not been adequately shown that Sabril does not cause central visual loss. They also concluded that Sabril should be available only under restricted conditions, with required visual testing performed periodically throughout treatment, and that continued access to the drug should be made contingent upon performance of visual testing (or

documentation that such testing was impossible in any given patient). The committee also concluded that there was no adequate data to address the relevance to adults of the intramyelinic edema seen in animals.

Regarding NDA 22-006, for the use of Sabril in patients with IS, the committee voted unanimously to recommend approval of the application (23-0). They also concluded that there is no evidence that Sabril treats or prevents other seizure types in these patients, although they agreed that Sabril causes cessation of spasms and can ameliorate the EEG in these patients. Regarding visual toxicity in this population, they concluded that there was no reliable way to adequately assess visual function in these very young patients, and that therefore visual toxicity may not be detected before it is severe and irreversible. In this regard, they recommended that parents/caregivers must be notified of this fact. The committee also recommended that, as for NDA 20-427, Sabril should be made available for IS only under restricted conditions, but did not mandate periodic ophthalmologic testing, because of its unreliability in this population. The committee also noted that there was inadequate data to address the relevance of the intramyelinic edema seen in animals to the MRI lesions seen in pediatric patients, although they did feel that the edema did not correlate with the MRI lesions. They also noted that there was inadequate data to address the relevance of the specific toxicity seen in juvenile animals to the MRI findings in this population.

Recommendations

NDA 20-427

The PCNS Advisory Committee has unanimously recommended that this NDA be approved under restricted conditions that include required periodic ophthalmologic monitoring. Dr. Hershkowitz, on the other hand, recommends that the application not be approved. He has concluded that the risks of visual toxicity do not outweigh the benefits seen. In particular, he notes that Sabril has not been shown to be superior to other available AEDs, and he notes that when these studies were performed, many of the current AEDs were not available, and so patients in these studies could not have been shown to have failed on any of the newer AEDs. Further, despite the sponsor's argument that the patients enrolled in these studies were particularly refractory (that is, had more serious epilepsy than the "typical" patient enrolled in regulatory studies), Dr. Hershkowitz believes that this is not the case.

I agree with Dr. Hershkowitz that there is no evidence that the patients enrolled in these studies had more refractory disease than those enrolled in other studies of new AEDs. Further, it is clearly true that most of the current AEDs were not approved at the time the Sabril studies were performed, so that clearly the patients enrolled in these studies could not have been shown to have failed on any of these drugs.

Despite these facts, I do believe that Sabril can be approved for patients who have failed (or cannot tolerate) a fair trial of other available AEDs.

First, refractory epilepsy is a serious, life-altering and life-threatening condition, and despite the availability of many newer AEDs, I believe that, if at all possible, additional therapies should be made available.

Although patients in these trials did not fail on the "newer" AEDs, they were "refractory" (by the usual definitions) to one or several of the standard AEDs available at the time (e.g., phenytoin, carbamazepine). Therefore, they were poorly controlled, and though the studies did not compare Sabril to another AED added to their background regimens (these studies never do), Sabril was shown to be clearly effective when added to these regimens (it should also be further noted that there is no good evidence that, in general, patients refractory to the older AEDs will be, or are, better controlled on the newer AEDs; indeed, there is a general view among epileptologists that the percentage of patients with epilepsy who were refractory to the older AEDs [widely considered to be on the order of 30%] is unchanged in the current era, despite the availability of many more AEDs).

Further, despite the occurrence of visual toxicity, it does not appear that there are many patients who have suffered significant visual loss. It must be admitted, to be sure, that we do not have the adequate follow-up of patients that we would like in this regard, but we are not aware of many patients who have significant disability related to Sabril-induced visual toxicity. Whether this is because the lesion had been detected early in some patients, or whether the lesion (in some patients) never progresses beyond a certain degree, even with continued treatment for some period of time, or whether patients can function reasonably well even with significant visual pathology, or other reasons, is not clear, but we do not have reports of significant visual impairment in many patients, even after years of treatment with Sabril. This is not to minimize the toxicity, but only to point out that patients have, generally, tolerated whatever pathology the drug has produced (here it should be noted that the drug has been available in many countries since the mid 1980's). In this regard, the REMS that has been discussed with the sponsor is fairly restrictive, and commits physicians to perform periodic ophthalmologic examinations (where possible) and be aware of the results before deciding to continue treatment. And although we do not have definitive evidence that the monitoring to be imposed under the REMS will definitely prevent toxicity (or detect it as early as we might like), we do believe that it is worthwhile, and is likely, at least in some patients, to detect any changes before they result in a clinically meaningful decrement in visual function.

For these reasons, then, I believe that Sabril can be approved for patients with refractory CPS, under the conditions imposed under the REMS and product

labeling (that is, with periodic monitoring and in patients who have failed a fair trial of available AEDs).

We will also require several post-marketing studies.

Under the Pediatric Research Equity Act (PREA) we will require a controlled trial in pediatric patients aged 10-16 years with CPS. We will waive the requirement for controlled trials in patients below the age of 10 years with CPS because visual toxicity is difficult to assess in these patients and other drugs are available to treat them.

As a Post-Marketing Requirement (PMR) under FDAAA, we will require the sponsor to analyze the visual data collected in the registry to be set up under the REMS (see below for a discussion of the elements of the REMS).

We will also require a study examining the effects of taurine on vigabatrin-induced retinal damage in rodents (see below for a further discussion of this issue).

Finally, we will ask the sponsor, as a Post-Marketing Commitment (PMC), to perform an in vitro study to evaluate Sabril's capacity to induce CYP1A2 and 3A4.

NDA 22-006

Regarding NDA 22-006, the committee voted unanimously to recommend approval. The clinical team agrees (in particular, despite the numerous flaws in the three clinical trials submitted, the committee and the review team concluded that there is substantial evidence of effectiveness in patients with IS, and I agree), but Dr. Fisher recommends that the application not be approved. Specifically, the sponsor most recently submitted the results of 4 and 9 week oral toxicology studies in the juvenile rat. Although the sponsor has concluded that these studies demonstrate the typical IME seen in adult animals (except that these lesions were seen in gray matter in addition to white matter), a Pathology Working Group constituted by the sponsor concluded that the lesions are "... not characteristic of intramyelinic edema.". Drs. Fisher and Schmued agree that there are lesions present in these studies that are different from IME. These lesions were seen at exposures to vigabatrin that are lower than those achieved in patients. In addition, seizures were noted in both studies.

Vigabatrin also caused retinal degeneration in the albino rat and mouse, but not in pigmented strains or species. There is also some evidence that vigabatrin-induced retinal toxicity can be prevented (or minimized) by taurine administration.

Dr. Freed agrees that the neurotoxicity seen in the juvenile rat studies differs from IME, but concludes that the application can be approved, with the company's commitment to perform additional studies after approval.

I agree.

As she (and the clinical team) notes, IS is a serious condition for which there are no approved treatments. Although there is no evidence that the control of the spasms that Sabril produces is associated with amelioration or prevention of the other deficits associated with IS (e.g., developmental abnormalities, occurrence of other seizure types), control of the spasms themselves produces a clear benefit in the lives of these children.

It is also true that there is general agreement among the experts we have consulted that there is no reliable method available to detect Sabril-induced visual toxicity at any early stage in these young patients. Nonetheless, the severity of the clinical condition being treated argues, in my view, for approval. Again, although we do not have the sort of prospective follow-up of these patients that we would like, we do not have reports of significant numbers of patients who were treated with Sabril as infants having important visual sequelae (here again it should be noted that Sabril has been used in this population for many years outside the US).

In addition, although we do not know the clinical consequences, if any, of the pathology seen in the juvenile animals, we are not aware of reports of significant decrements in functioning in these children after prolonged treatment with Sabril. Although it must be again acknowledged that we do not have adequate, prospective follow-up of these patients, we can take some (albeit admittedly minimal) comfort in the absence of reports of significant neurological "worsening" in these patients after such treatment.

As Dr. Freed notes, Dr. Schmued has recommended another toxicology study be performed in juvenile rats to better characterize the pathology, and Dr. Freed also recommends such a study in juvenile non-rodents. She also recommends that the sponsor be required to perform a study evaluating the effects of taurine on vigabatrin-induced retinal damage in the rodent. I agree that these three studies should be required as PMRs under FDAAA.

REMS

As noted above, the Advisory Committee has recommended that these applications be approved only with an adequate REMS in place. Also as noted above, the sponsor had submitted a preliminary REMS early in the current review cycle. This REMS has been reviewed by numerous Agency reviewers, including the OSE Vigabatrin REMS Review Team, and the sponsor's original proposal has been extensively revised.

The REMS is complex, and contains not only a Medication Guide and Communication Plan, but Elements to Assure Safe Use as well (as well as an implementation plan, and the required REMS assessments and a timetable for the submission of these assessments). I will point out several of the key aspects of the program.

Prescribers who wish to prescribe Sabril will be certified by the sponsor, meaning that, among other things, they will:

- 1) Document that they have read the PI and MedGuide,
- 2) Have experience treating patients with epilepsy,
- 3) Understand the risks,
- 4) Assess the effectiveness of Sabril within 4 weeks for IS and 12 weeks for CPS and will discontinue the drug if there is an insufficient response
- 5) Order and review appropriate visual assessments (to be performed by a practitioner with expertise in visual assessment) at baseline and every 3 months during treatment (although we acknowledge that formal visual testing is unreliable in patients with infantile spasms, the program still requires that some effort to assess visual function, however coarse, be attempted in these patients)
- 6) Educate patients
- 7) Report serious adverse events to the sponsor
- 8) Return to the sponsor ophthalmologic assessment forms every 3 months (with a grace period), documenting either the results of such testing or that such testing was not feasible.

Pharmacies will be certified by the sponsor and will ship Sabril only to those patients enrolled in the REMS and will be trained by the sponsor. In particular, the pharmacy will dispense Sabril only to those patients who the sponsor has documented have complied with the periodic ophthalmologic assessments.

Patients must agree to comply with the required assessments, read the MedGuide and understand the risks, and agree to be in a registry.

The REMS is comprehensive, and will ensure, to the extent possible, that appropriate visual monitoring is performed throughout treatment with Sabril.

We will also require the sponsor, as a PMR, to perform a study to assess the single and multiple dose kinetics in patients 1-5 months of age.

Finally, as a PMC, we will ask the sponsor to perform a controlled trial in patients with IS to characterize the minimum duration of therapy required to produce sustained remission of spasms.

For the reasons noted, then, I recommend that this application be approved,

under the constraints imposed by the REMS, with the described PMRs and PMCs, and under the conditions described in the package insert.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
08/14/2009

CLINICAL REVIEW
VIGABATRIN OPHTHALMIC ADVERSE EFFECTS

Application Type: NDA
Submission Number: 22006 (Infantile Spasms); 20427 (Complex Partial Seizures)

Letter Date: 28 December 2007

Reviewer Name: Ronald Farkas, MD, PhD
Through: Norman Hershkowitz, MD, PhD
Wiley Chambers, MD

Established Name: Vigabatrin
(Proposed) Trade Name: Sabril
Therapeutic Class: Antiepileptic
Applicant: Ovation Pharmaceuticals

Priority Designation: P

Formulation: Tablets and Powder
Indication: Seizure disorder
Intended Population: Children and Adults

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1. Introduction and Background

This review addresses the visual adverse effects of vigabatrin (VGB) in patients with complex partial seizures (CPS) (NDA 20427) and infantile spasms (IS) (NDA 22006). For VGB efficacy in these indications, see the reviews by Phillip Sheridan, M.D. For review of non-ophthalmic safety, see the reviews by Gerard Boehm, M.D.

VGB was first marketed in 1989 in a number of countries outside the U.S. Due to safety concerns about the potential for VGB to cause intramyelinic edema, FDA issued an approvable letter for VGB in 1997. However, shortly thereafter emerging data linking VGB with visual field constriction led FDA to issue a non-approved letter pending submission of adequate evidence of a favorable risk/benefit profile of VGB given the visual adverse effects. Information requested by FDA about the visual adverse effects of VGB included the following:

- *Character of adverse event.* Incidence, prevalence, location (e.g. central vs. peripheral visual loss), severity, latency, reversibility, and risk factors
- *Monitoring and Prevention.* Ability to detect and prevent adverse events in both adults and children

The sponsor states that the adverse visual effects of VGB are now well-characterized and that the current submissions contain adequate data and appropriate risk management to conclude that the drug has a favorable risk/benefit profile to support FDA approval in CPS and IS.

2. Executive Summary

Key sponsor conclusions about visual adverse effects of VGB are presented below, followed in bold by key review findings.

a. *Ophthalmic Adverse Effects in Adults*

1. VGB causes bilateral, concentric peripheral constriction of the visual field, ranging from mild to severe.

Review agrees.

2. Central vision is preserved even in cases of severely constricted visual field
Reviewer: Central vision appears to be only relatively preserved. While severe visual acuity loss from VGB is rare, mild or even moderate acuity loss (20/25-20/50) may occur. Observable damage can also occur in the central retina.

3. Visual field constriction does not begin immediately upon initiation of VGB-therapy but occurs slowly, with average onset after several years of treatment.

Review disagrees:

- **The time course of visual damage is highly variable among patients.**
- **Some cases occur after less than 2 months of VGB exposure, with the lower limit of time of onset not well-defined.**
- **It is important to distinguish between latency of onset and speed of progression of damage. Damage may not progress linearly over time, but instead may occur more precipitously.**
- **Peak incidence of field defect likely occurs at about 1 year.**
- **There is no reliable evidence for a 'safe' period of exposure in which visual damage will not occur.**

4. Most individuals treated with VGB who develop visual field constriction are unaware of its presence, but in a minority of cases, field defect is sufficiently severe to hinder daily activities.

Review findings partially agree.

- **Even though many patients are unaware of the presence of visual damage, this in no way demonstrates that the visual damage doesn't have negative impacts on their function (see below).**
- **Given the high percentage of patients that develop VGB visual damage, even a 'minority' of patients with more severe disability still reflects many people.**
- **Little data is available about visual ability in patients with VGB field loss. On the supposition that VGB field loss is in some respects similar to field loss from glaucoma, vigabatrin patients with more severe visual damage are likely to have difficulty with common daily activities. However, most patients likely would remain capable of independent self-care and conduct of necessary business. In children with IS, the functional consequences of given degrees of field loss are not as well understood, with case reports suggesting that visual disability in some cases can be profound.**

5. Careful questioning of VGB-treated individuals can reveal symptoms of functional visual deficits even in those who failed to spontaneously recognize them.

Review agrees.

6. Most studies support the finding of defect that occurs in approximately 50% of subjects or fewer.

Review findings generally agree. However, for the roughly 50% of patients that don't develop field defect after a number of years of VGB, some risk of late development of field defect might remain.

7. The field defect progresses to a maximal point, remains static, and does not progress inexorably to the central visual island.

Review findings disagree. Key questions about progression remain poorly understood:

- While wide inter-individual variation exists, in many patients field defects progress over months to a few years to roughly 25° or even closer to fixation.
- While field defects have not been documented to progress to closer than roughly 10 degrees of fixation, even after a decade or more of VGB exposure, ongoing damage to the central retina may continue.
- The available data can not exclude the rare occurrence of severe central vision loss from vigabatrin.
- While field loss ranging from mild to severe can, in some patients, remain seemingly stable for months or even years despite continued VGB exposure, further constriction occurs in some patients.
- Importantly, some patients appear to have progressive field loss even after VGB is discontinued. The risk, time course, and potential degree of continued progression after stopping VGB are poorly understood.

8. Improvement of the visual field defect is probably very rare, and can't be considered likely.

Review findings agree, stressing that even rare cases of improvement are not well documented.

9. Patients who develop a visual field defect generally experience a decrease in lateral vision from the normal 90 degrees to, on average, 71.1 degrees.

Review disagrees. The 'average severity' value presented by the sponsor is not based on reliable data. Moreover, 'average severity' is not a clinically useful measure of an adverse event of variable severity. While available data allows only rough estimate, by 5 years of exposure about 1/3rd of patients experience constriction, often to within 20 or 30 degrees of fixation, with perhaps 10% experiencing greater constriction, to roughly 10 or 20 degrees of fixation. It should be noted, too, that the sponsor's estimate is problematic because for any scotoma that is not absolute, defect size is dependent on technical factors that vary among the different perimetry methods used to examine vigabatrin patients, including stimulus size and intensity.

10. Uniform, highly sensitive screening tools, including confirmatory testing with a variety of techniques, ensure accurate assessment of field defects.

Review disagrees.

- Perimetry is often *not* highly sensitive.
 - Perimetry is a subjective test that depends on the skill and experience of the patient and operator. The first one or several tests are often unreliable. Perhaps 20% of adult VGB patients may never be able to perform perimetry well enough to be monitored by that method. In perhaps a similar proportion of

patients, perimetry may be possible, but with poor reliability. Inter-test variability often remains high even for patients experienced with perimetry, which may lead to a high risk of false-positive findings.

- Success of safety screening is intimately linked to the speed at which VGB damage progresses. It is not clear if damage progresses linearly over time, or if damage can occur precipitously after an unpredictable latency. Patients that progress precipitously may not be detected until damage has already occurred.
- **Electroretinography (ERG) does not appear useful for early diagnosis of vigabatrin visual damage. ERG may be able to diagnose severe damage that has already occurred.**
 - ERG appears less sensitive than perimetry for vigabatrin visual damage. ERG is often normal in patients with field defect.
 - ERG suffers from high inter-test variability, and apparent poor specificity as a result.
 - Critically, the clinical correlate of any given degree of ERG decrease is poorly understood. Data is simply inadequate to determine the sensitivity or specificity of ERG testing for vigabatrin visual damage.
- Little data is available about the potential usefulness of screening methods other than perimetry and ERG, such as field-specific visual-evoked potentials (VEP).
- As severity of VGB damage increases, reliability of diagnostic methods may increase. Since even severe visual damage often remains asymptomatic, perimetry and ERG might be clinically useful to identify patients in whom VGB should be discontinued due to severe damage that has already occurred.

b. Ophthalmic Adverse Events in Infants and Children

1. Children appear to develop the same peripheral VFD defect as adults. Review generally agrees, noting that data from children is limited, and that important undiscovered differences may exist.
2. Diagnosis in very young or cognitively-impaired children can be technically challenging
Review agrees, stressing that sensitivity for detection of vigabatrin visual damage in children appears to be poor
3. Overall, studies suggest that VGB-induced VFD is somewhat lower in children than adults.

Data is inadequate to support this conclusion. Comparison of rates is not possible because vigabatrin visual damage can not be reliably diagnosed in children.

4. In infants, the characteristic electrophysiological abnormalities associated with VGB-induced visual field defect do not occur rapidly, with onset generally after one year of therapy.

Review disagrees. Issues of sensitivity and specificity aside, ERG testing was conducted at 6-month intervals in the studies on which this conclusion is based, and patients were required to have 2 abnormal results before being defined as abnormal; thus field defects would not be confirmed until after one year of therapy due to study design. In some of the patients tested after 3 months of VGB, abnormalities were found, but again, this does not provide evidence about potential onset even earlier, prior to the first ERG test.

c. Risk Factors

1. The question is unresolved whether visual toxicity is unpredictable (“idiosyncratic”) or whether all subjects are vulnerable.

Review generally agrees. While there is little evidence that a single dose can cause visual loss, no ‘safe’ exposure is known.

2. Time of exposure and total dose are probably important risk factors.

Review generally agrees, stressing that at exposures for which data is available exposure and total dose are weak risk factors with limited clinical usefulness.

Reviewer Conclusions

- Many key questions remain unanswered about the characteristics of vigabatrin visual damage
- Current data allow a qualitative understanding of visual risks. Safety testing can *not* reliably prevent or lessen vigabatrin visual damage.
- Testing may more reliably detect severe visual damage, but the degree to which this would benefit patients is not clear..

Well-designed prospective, longitudinal studies needed to accurately characterize visual damage caused by vigabatrin were planned but never successfully conducted. Data submitted to FDA is mainly from less formally conducted, uncontrolled, potentially unrepresentative cross-sectional studies lacking full documentation. As a result, the available data supports only *qualitative*, not quantitative conclusions about the nature and extent of the visual damage caused by vigabatrin.

Vigabatrin causes both irreversible bilateral constriction of the visual field and, in at least some patients, mild or even moderate damage to central vision (rare cases of severe damage to central vision also can not be excluded). By about 5 years of treatment, roughly 1/3rd of patients will have visual field constriction, about evenly divided among mild, moderate, and severe constriction. Patients with more severe visual damage are expected to have increased difficulty with common daily activities, particularly those involving mobility and orientation. Although many patients with less severe vigabatrin visual loss are seemingly 'asymptomatic,' symptoms of visual loss may be incorrectly attributed to such factors as clumsiness or drowsiness.

The peak incidence of vigabatrin visual damage occurs at about 1 year, but onset at a few weeks or months is not rare. While some evidence suggests a weak time and dose dependence of vigabatrin damage, no 'safe' exposure is known.

Importantly, there is little reliable data addressing if visual damage can worsen *after stopping* vigabatrin; of concern, individual cases suggest worsening can occur. Long term visual function of vigabatrin patients is also threatened by the presumably additive effects of such common eye diseases of aging as macular degeneration and glaucoma.

It is far more difficult to *prevent* vigabatrin visual damage than to detect damage that has already occurred. Essentially no data supports the effectiveness of safety monitoring for preventing vigabatrin visual damage, and neither perimetry nor ERG appear able to do so reliably. Visual loss similar to the 'natural history' of vigabatrin visual damage is likely to occur in many adult and pediatric patients despite safety monitoring.

Even in adult patients in whom perimetry might theoretically be useful, experience in other ophthalmic disease suggests that the sponsor's monitoring plan is inadequate. Of particular concern, the sponsor's plan does not account for the nearly universal 'learning effect' that would confound detection of visual damage. In addition, while the speed of damage progression is not well-understood, the proposed 6-month monitoring interval appears too infrequent. Theoretically, intensive early testing to establish a reliable baseline, followed by an ongoing increased testing frequency could improve detection of visual damage in patients that can perform perimetry adequately. However, such intensive monitoring might be impractical for many patients, thus subverting the theoretical gains.

3. Data Sources

Visual adverse events were assessed in the following for both CPS and IS:

- Efficacy studies and open-label extensions
- Phase 4 studies of visual adverse events
- Published case series and case reports
- Periodic Safety Update Reports (PSURs), 1995 (PSUR 1) to 2007 (PSUR 19)

Following are the major trials conducted by the sponsor that were evaluated in this review:

CPS Safety Studies

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Safety-Subjects with Complex Partial Seizures	4020	Open, Multicenter Study of the Prevalence, Incidence and Clinical Course of Visual Field Defects in Adults and Children with Refractory Partial Epilepsy Treated with Antiepileptic Drugs	Multicenter, open, comparative, parallel group	Variable; subjects continued anti-epileptic treatment used at inclusion, unless the physician decided that a change was in the best interest of the subject	735 Enrolled	Refractory Partial Epilepsy	Variable	First Subject Entered Mar, 1999
					554 Included in safety analysis			Last Subject Enrolled Apr, 2003
								Report finalized June, 2006
								Report amended Oct, 2006
Safety-Subjects with Complex Partial Seizures	4021	Assess the Clinical Course, Prevalence and Risk Factors of Visual Field Constriction	Single center observational open, follow-up study	Film coated tablet and non-coated tablet 500 mg; powder for oral solution sachets 500 mg, 1 g, 2 g, and 3 g; granules for oral solution sachets 500 mg and 1 g	30 Enrolled	CPS	Study Duration: 2.5 years	Last subject completed Dec, 2001
					30 Currently using or previously used VGB			Report finalized June, 2002
					26 Completed		Treatment Duration: 6-7 study visits per subject over 2.5 years	
Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Safety-Subjects with Complex Partial Seizures	R003	Study to Detect Early Visual Field Defects, Their Frequency and Clinical Course in First-Time VGB Treatment for Refractory Partial Epilepsy	Multicenter, non-comparative, prospective, observational cohort study	N/A	25 Enrolled	Uncontrolled CPS	455 d mean duration (range: 2-988 d)	First subject enrolled Oct, 2000
					25 treated with VGB			Study ended Oct, 2003
					10 Completed			Report finalized May, 2004

CPS Efficacy Studies

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0101	Efficacy of Rational Polytherapy with Sabril vs. Carbamazepine or Phenytoin Monotherapy in the Management of Patients with Non-Refractory CPS (Complex Partial Seizures)	Multicenter, randomized, double-blind, placebo-controlled trial with 2 parallel groups	Oral VGB BID increasing weekly by 500 mg/d to a fixed maintenance dose of 3 g/d	268 enrolled 177 randomized to double-blind period (119 VGB; 58 placebo) 171 completed titration period (113 VGB; 58 placebo) 149 completed double-blind period (94 VGB; 55 placebo)	Partial Epilepsy	40-44 weeks: 12-week baseline; 4-week titration; 24-week maintenance; 4-week taper or transfer to open-label extension	Last subject completed May, 1997 Report finalized Oct, 1998
Efficacy – Subjects with Complex Partial Seizures	0118	Efficacy and Safety Evaluation of Oral Adjunctive VGB Therapy Compared to Placebo in Children with Uncontrolled CPS: a Dose Response Study	Multicenter, randomized, double-blind, placebo-controlled, parallel group	Oral VGB 20 mg/kg/d 60 mg/kg/d 100 mg/kg/d	173 Enrolled 126 randomized to receive study medication (94 VGB; 32 placebo) 108 Completed (80 VGB; 28 placebo)	Uncontrolled CPS	24-27 weeks 10-week baseline; 6-week titration; 8-week maintenance; 3-week taper or transfer to open-label study	Last subject completed (dosed) Sept, 1997 Report finalized Aug, 1998

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0221	Efficacy and Safety of Oral Adjunctive VGB Therapy Compared to Placebo in Children with Uncontrolled CPS: a Parallel Group Study	Multicenter, randomized, double-blind, placebo-controlled, parallel group	Oral VGB Initial dose: 10-30 kg: 0.5 g/d (0.25 g BID) > 30 kg: 1.0 g/d (0.5 g BID) Maintenance dose: 10-15 kg: 0.5-1.5 g/d 16-30 kg: 0.5-2.0 g/d 31-50 kg: 1.0-3.0 g/d >50 kg: 1.5-4.0 g/d Dosage regimen: BID	127 Enrolled 88 Randomized (43 VGB; 45 placebo) 68 Completed (36 VGB; 32 placebo)	Uncontrolled CPS	23-26 weeks 6-week baseline; 10-week titration; 7-week maintenance; 3-week taper or transfer to open-label study	Last subject completed (dosed) July, 1997 Report finalized Sept, 1998 Amended April, 1999

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0222	Efficacy and Safety of VGB 3 g/day vs. Gabapentin 1800 mg/d as Monotherapy in Patients with CPS	Multicenter, randomized, double-blind, double-dummy, parallel group	Oral VGB up to 3 g/d or gabapentin 1800 mg/d	44 Enrolled 19 Randomized 18 received study medication (9 VGB; 9 gabapentin) 3 Completed (1 VGB; 2 gabapentin)	CPS	29 weeks 8-week baseline; 5-week titration; 8-week withdrawal 8-week maintenance	Last subject completed (dosed) Sept, 1996 Report finalized Sept, 1998
Efficacy – Subjects with Complex Partial Seizures	0223	Dose-Response Study of Efficacy and Safety of VGB 1, 3, 4, and 6 g/day as Monotherapy in Patients with CPS	Multicenter, randomized, double-blind, dose-response, parallel group	Oral VGB 1, 3, 4, or 6 g/d BID	121 Enrolled 75 Randomized (17, 1 g/d; 18, 3 g/d; 19, 4 g/d; 21, 6 g/d) 13 Completed (2, 1 g/d; 3, 3 g/d; 4, 4 g/d; 4, 6 g/d)	CPS	30-35 weeks 8-week baseline; 6-week titration; 8-week withdrawal 8-week maintenance 5-week taper or transfer to open-label study	Last subject completed (dosed) Oct, 1996 Report finalized Dec, 1998

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0192	Efficacy and Safety of Oral Adjunctive VGB Therapy Compared to Placebo in Children with Uncontrolled CPS: A Parallel Group Study	Multicenter, randomized, double-blind, placebo-controlled, parallel group	Oral VGB Initial dose: 10-30 kg: 0.5 g/d (0.25 g BID) > 30 kg: 1.0 g/d (0.5g BID) Maintenance dose: 10-15 kg: 0.5-1.5 g/d 16-30 kg: 0.5-2.0 g/d 31-50 kg: 1.0-3.0 g/d >50 kg: 1.5-4.0 g/d Dosage regimen: BID	55 Enrolled 55 randomized (28 VGB; 27 placebo) 48 Completed (22 VGB; 26 placebo)	Uncontrolled CPS	23-26 weeks 6-week baseline; 10-week titration; 7-week maintenance; 3-week taper or transfer to open-label study	Last subject completed Dec, 1994 Report finalized Sept, 1998
Efficacy – Subjects with Complex Partial Seizures	0098	Clinical Experience and Use of Sabril in Patients with Partial Seizures	Multicenter, open-label, flexible-dose, long term	Oral 500 mg VGB BID increasing weekly by 500 mg/d not to exceed 6 g/d	1264 Enrolled	Partial Epilepsy	6-24 months	Last subject completed Mar, 2000 Report finalized Dec, 2000

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0242	Maintenance of VGB as Monotherapy in Patients with CPS	Multicenter, open-label, long-term, follow-up	Oral VGB 4g/d up to 6g/d	86 Enrolled 85 Evaluated for safety	CPS	Planned to be 52 weeks Study terminated	Last subject completed Oct, 1998 Report finalized Sept, 1999
Efficacy – Subjects with Complex Partial Seizures	0201	Maintenance Study of VGB as Adjunctive Therapy in Children with Uncontrolled CPS	Open-label, multicenter, long-term, follow-up	Oral VGB 40 mg/kg/d or 60 mg/kg/d up to the lesser of 100 mg/kg/d or 6 g	210 Enrolled 209 Evaluated for safety	Uncontrolled CPS	Planned to be at least 52 weeks Actual approximately 3 years	Last subject completed Nov, 1998 Report finalized Dec, 1999

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0294	VGB as Adjunctive Therapy in Children with CPS	Open label, multicenter, follow-up	Oral VGB Two dosing regimens depending upon which protocol was being extended 10-30 kg: 0.5 g/d (0.25 g BID) >30 kg: 1.0 g/d (0.5 g BID) or 10-15 kg: 1.0, 1.5 g/d 16-30 kg: 1.0, 1.5-2.0 g/d 31-50 kg: 1.5, 2.0-3.0 g/d >50 kg: 1.5, 2.0, 3.0-4.0 g/d Dosage regimen: BID	44 Enrolled 44 Received 38 Completed	CPS	24 weeks	Last subject completed June, 1995 Report finalized Sept, 1998

IS Safety Studies

Toronto Study

Single center, open-label, retrospective and prospective case series of \approx 200 children taking VGB for IS and CPS, focusing on ERG monitoring for VGB adverse visual effects. The study is ongoing.

Boston Children's Hospital Study

Single center, open-label retrospective case series of ≈ 50 children taking VGB for IS and CPS, focusing on ERG monitoring for VGB adverse visual effects.

IS Efficacy Studies

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy - Subjects with Infantile Spasms	1A	Clinical Experience and Use of VGB (Sabril®) in Subjects with IS	Multicenter, randomized, single-blind study with an open-label, dose-ranging, long-term follow-up	Oral VGB Low-dose: 18-36 mg/kg/d High-dose: 100-148 mg/kg/d	226 Enrolled 221 Modified ITT Cohort 219 Entered flexible dosing period	IS	14-21 d, with long-term follow-up of up to 3 years	Last subject completed Apr, 2002 Report finalized Nov, 2005 Report Amendment June, 2006
Efficacy - Subjects with Infantile Spasms	W019	A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of VGB vs. Placebo as First Line Therapy in the Treatment of Newly Diagnosed IS	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study with open-label follow-up period	Oral VGB at initial dose of 50 mg/kg/d with titration allowed to 150 mg/kg/d for 5 d, followed by 6 months of open-label VGB Placebo for 5 d, followed by 6 months of open-label VGB	40 Enrolled 40 Randomized (20 VGB; 20 placebo) 40 Completed double-blind phase 36 Entered open-label 28 Completed 24 weeks of study	Newly-diagnosed IS with no prior treatment	Baseline: 2-3 d Double-blind: 5 d Open-label follow-up: 6 months	Last subject completed Jan, 1996 Report finalized Mar, 1997
Efficacy - Subjects with Infantile Spasms	FR03	VGB vs. Hydrocortisone in IS due to Tuberous Sclerosis	Multicenter, randomized, open-label, comparative, response-mediated cross-over study	Oral VGB 150 mg/kg/d for 4 weeks (if no response, then cross-over to hydrocortisone for 4 weeks) Hydrocortisone 15 mg/kg/d for 4 weeks (if no response, then cross-over to VGB for 4 weeks) Long-term follow-up optional for both groups	VGB 11 Enrolled 11 Completed (No subjects crossed-over to receive hydrocortisone) Hydrocortisone 12 Enrolled 11 Completed (7 subjects crossed-over to receive VGB)	Newly-diagnosed and previously untreated IS due to tuberous sclerosis	2-month randomized period (No specific dosing data are available for the follow-up period, but some subjects were followed for ≥2 years)	Last subject completed Oct, 1994 Report finalized June, 1995

4. Ophthalmic Safety Data from Early Studies

In efficacy studies of children with IS, a large variety of visual abnormalities occurred in both VGB- and placebo-treated patients, ranging from strabismus to cortical blindness. The power of these studies to detect even large deleterious effects of vigabatrin on vision was thus low. For the current submission, the division reasoned that long-term ophthalmic exam data from the children in the original IS studies might be informative about long-term visual outcome in children treated with VGB. Of 279 originally enrolled patients, the sponsor was able to obtain some follow-up information about visual function for 55 (Table 1). None of these 55 patients had been noted by current caregivers to have severe VGB-related field defect, but 24 had been diagnosed with 'severe non-VGB related' field defect. Forty-eight patients were said to have normal vision.

Table 1: Long Term Vision of IS Study Patients

Investigator ^a	Total Enrolled	With Absence of Vision at Baseline	With Follow-Up after Subject Exited Study	With Follow-Up Vision Exam Performed ^b	With Severe VGB-Related VFD	With Severe Non-VGB-Related VFD	Normal Vision ^c
Appleton ^d	40	Unknown	10	3	0	0	3
Bebin	58	2	24	13	0	2	13
Chiron ^e	23	4	11	9	0	4	9
Conry	1	0	1	1	0	0	1
Crumrine	18	1	16	9	0	1	6
Elterman	47	0	13	13	0	4	9
Marks	6	1	6	0	0	1	Unknown
Mitchell	23	2	20	3	0	2	3
Shields	47	5	26	4	0	10	4
Trevathan (Bauman)	3	Not Available	No Follow-Up Data	No Follow-Up Data	No Follow-Up Data	No Follow-Up Data	No followup Data
Wyllic	13	Not Available	No Follow-Up Data	No Follow-Up Data	No Follow-Up Data	No follow-Up Data	No followup Data
Total	279	≥15	127	55	0	24	48

a Investigator participated in study 1A unless otherwise footnoted.
b Or near complete absence of vision, defined as light perception only
c Of those with vision at baseline
d By method or methods tested, depending upon subject included Goldmann perimetry, confrontation fields, measures of visual acuity or quadrant fixation testing, in various subjects
e Investigator for Study W019
f Investigator for Study FR03

[From Table 71, visualdysfunc.pdf, page 169 of 304]

Reviewer Discussion

Review of safety data from the original VGB studies confirms the findings of the original safety review that VGB is associated in CPS with a low incidence of at least severe *acuity* loss. It seems clear, too, that symptoms of visual field loss in CPS patients were not so gross as to be detected.

Since children, particularly those with IS, would not be expected to be able to report symptoms of visual loss, the original safety and efficacy studies in IS provide less reassurance that severe visual loss did not occur in these patients. The long-term follow-up data available from the children in the original studies is too incomplete for reliable conclusions.

5. Ophthalmic Safety Studies in CPS

a. Reviewer Introduction

After postmarketing reports emerged associating VGB with visual field constriction, phase 4 studies were initiated to characterize this adverse effect. Several large studies were to be conducted prospectively, or with randomly selected retrospective samples designed to represent the overall VGB patient population. However, as detailed below, most studies were plagued by serious shortcomings in design and execution, including low enrolment, non-random patient selection, high dropout rate, poor quality assurance, and post-hoc analysis.

The sponsor's conclusions about the natural history of VGB visual damage in adults are based largely on study 4020, which is described below. However, due to multiple problematic study design and execution issues, this review concludes that most data from study 4020 is unreliable.

The 'pooled cohort' study described below is based on visual field exams at a single time point in a cross-section of several hundred patients enrolled in VGB clinical studies. The current sponsor did not submit detailed information from this cohort study, and did not rely upon it for major conclusions. However, this review considers the study particularly important because, while it is not a random population, it may represent a relatively unbiased view of field defect in patients with various VGB exposures.

Study R003 is particularly valuable as one of the few prospective studies of VGB visual effects. The study enrolled only 25 out of a planned 200 subjects, but despite the small number of patients, the study provides one of the only available estimates of the performance of perimetry in safety monitoring of patients starting VGB.

b. Study 4020

Study 4020 was an open-label, multicenter study at 46 centers in France, South Korea, Italy, Spain, and Australia conducted to examine the characteristics of the visual field defect associated with VGB. Anti-epileptic treatment was selected by the treating physician.

The original study plan called for selecting a random sample of patients, but this plan was later abandoned. Investigators had knowledge of the severity of visual defect prior to patient enrollment, and excluded patients thought to have visual abnormalities not related to VGB, such as glaucoma.

Reviewer: Many profound biases could have been introduced by this patient selection. For example, visually disabled patients might be under-represented due to difficulty traveling to clinic.

Prior to enrollment patients had taken VGB for variable lengths of time, often several years, or had stopped VGB variable lengths of time in the past.

Reviewer: This confounded the sponsor's calculations of time to diagnosis and time of onset of visual damage.

Visual system tests:

- Perimetry
 - Static and kinetic perimetry were planned
 - The recommended static perimetry method was Humphrey Field Analyzer (HFA) 135 or 120 age-corrected 3 zone or Octopus 2 level and, whenever possible, Program 30-2 or 32 of the HFA, Octopus or equivalent.

Reviewer: Consistent perimetry methods were not followed, for different patients or even when longitudinally following a single individual. This greatly hinders interpretation.

- Ophthalmic exam
 - Ocular history
 - Best corrected visual acuity (rated on a scale of zero to ten)

Reviewer: The sponsor notes that visual acuity data was not properly recorded and not analyzable.

- Manifest refraction
- Ocular symptoms
- Slit-lamp biomicroscopy
- Intraocular pressure
- Bilateral dilated ophthalmoscopy
- Gonioscopy (if not done within the last year)
- Evaluation of if ocular findings might explain the visual field results
- Visual disability as assessed by questionnaire.
- Adverse event reporting

Endpoints:

- Estimated prevalence rates for peripheral VFD.

Major Inclusion Criteria:

- Age \geq 8
- refractory partial epilepsy for at least one year

Major Exclusion Criteria:

- Patients with identified secondary ophthalmological disease of known etiology at inclusion were excluded.
- Progressive VFD of identified etiology unrelated to VGB

Reviewer: Importantly, the above 2 criteria might have excluded VGB patients with ophthalmic adverse events incorrectly classified as unrelated to VGB.

- Unreliable perimetric data

Reviewer: Patients with visual damage may be over-represented among patients with unreliable perimetric data, thus underestimating VGB visual damage.

The sponsor divided enrolled patients into groups for additional comparative analysis:

- Group 1: treated with VGB prior to study, and remaining on VGB
 - Average 4.2 years VGB treatment prior to entry
 - 38 children
 - 149 adults
- Group 2: previously treated with VGB but discontinued prior to study entry
 - Treated for average of 2.4 years
 - 47 children
 - 152 adults
- Group 3: subjects who never received VGB.
 - 7 of these subjects started VGB while on study, but for an average of only 4 months

On average the first field test in study 4020 occurred about 5 years after starting VGB.

Study populations

- 2,583 patients were screened
- 735 subjects were enrolled
- 524 subjects were considered evaluable (patients having at least a single conclusive visual field test)
- 354 subjects had an evaluable field at inclusion
- 46% of patients discontinued prematurely

Reviewer: In addition to initial non-random patient selection, patient attrition between screening and study completion was extremely high, and might have profoundly biased study results.

Data Analysis

- Prevalence was defined by Aventis as the number and percentage of subjects with field constriction on first conclusive examination. Two different definitions of conclusive examination were used. The strict definition was 'normal' or 'abnormal' and the broad definition also included 'inconclusive.' Abnormal was further categorized as abnormal of identified etiology and abnormal of unidentified etiology. Fields of unidentified etiology were further categorized as bilateral concentric peripheral constriction or other pattern.

Reviewer: Notably, the study report discusses how an initial analysis of field defects was deemed unacceptable because too high a percentage of patients who had never taken VGB were found to have VGB-like visual field defects. This led to changes in the definitions used for abnormal fields. Such post-hoc

changes to analysis methods decrease the confidence that can be placed in study findings.

- **Period prevalence was defined by Ovation as at least one occurrence of ‘bilateral concentric peripheral constriction’ (BCPC) upon entry into or over the course of the study.**
- **The submission describes how methods of field analysis were modified based on initial analysis of the data:**

“The metric properties of the outcomes are not yet known, although the interpretation of the results depends on these properties and this may lead to erroneous conclusions on clinical course. Therefore the inter-techniques agreement will be studied from the 5th IA [interim analysis] onwards to find out the extent to which different techniques lead to different conclusions.”

“There is no final statistical analysis plan, as the tests used will depend on the results obtained with the current plan. The statistics will evolve as required.”
[study4020.pdf, page 572-573 of 3105]

Data Integrity

Discussions from the study steering committee excerpted below offer insight into problems with study design and data analysis:

“As a general consideration, the experts stressed the difficulty to obtain perimetries of good quality: only 10% Goldmann and 50-60% suprathreshold and threshold perimetries are of good quality.” *October 1999*

Reviewer: Few of the visual fields were submitted to FDA, and reliability of findings could not be adequately evaluated.

“Concern [was] expressed by the neurologists regarding a “selection bias”: current vigabatrin patients have already undergone visual field assessment(s). Since the vigabatrin is withdrawn in most cases where a typical VFD is diagnosed, as a consequence nearly all patients remaining under vigabatrin have no VFD.”

September 1999

Reviewer: Potentially also patients with mild defects would have preferentially remained on VGB, biasing the average to less severe defects.

“The company stressed again that they had concerns regarding the reliability of the data currently gathered by the 4020 study. The CPMP [Committee for Proprietary Medicinal Products, responsible for preparing opinions on questions concerning medicinal products for human use for the EMEA] had also expressed concerns over methodological issues and the data quality.” *February, March 2002*

“It was noted that the majority of data presented was derived from centres in France and that the centres may have not used the recommended perimetry techniques or may not have carried out the tests under optimal conditions.” *January 2003*
Reviewer note: Centers in France enrolled the majority of patients, 437/735

“Although at one point in the study there was an attempt to standardise the perimetry technique, not all centres complied. In addition, no allowance is made for increased patient compliance over visits (learning effect) or for the increased confidence of the expert in designating what is or isn’t field loss. The importance of the latter may vary, depending on which technique was used. Time to onset is not equivalent to the time to detection. The clinical course also has to be considered. For a given patient this might only apply from when the perimetry was changed or, if the right technique was used in the first place, it might apply from baseline.”
January 2003

“The original patients included in France were generally evaluated using kinetic perimetry methods. These have since been largely superseded by static perimetry”
January 2003

Reviewer: Even longitudinal data for individual patients appears suspect because the methods of perimetry changed during the course of follow-up. Depending on the ability of the patient and tester, a given perimetry technique can be more or less sensitive and reliable than another.

“Disparities in the frequency of visual field defects observed between countries, between the study populations and over time all indicate that bias may have been introduced into the study, affecting the representativity of the results.” *June 2004*

“Much of the recruitment in countries other than France has occurred after the implementation of the educational programme aimed at training investigators in the optimal use and interpretation of perimetry testing.” *June 2004*

Reviewer: Study quality control is not well described in the submission, but appears to be poor.

Disqualified Centers

A site in Italy was found to have committed scientific fraud, and the 18 patients enrolled from that site were not included in data analysis.

No data validation plan was developed for the study, and there was no data monitoring committee.

Major findings from study 4020.

The sponsor notes that the study authors concluded that a true prevalence rate could not be established from this study, due to limitations in study methodology, randomization issues, the exclusion of subjects with preexisting peripheral VFD, and the large proportion of subjects lacking conclusive perimetry data. The sponsor makes the following conclusions:

- Fields defined as having the typical ‘bilateral concentric constriction’ caused by VGB had more marked nasal severity.
Reviewer: While this pattern of field defect often occurs, concern remains that other types of field defect might have been missed because they did not fit the ‘expected’ pattern.
- The prevalence of a confirmed Sabril-induced peripheral VFD was approximately 25% of adult patients and 15% of children receiving long-term Sabril therapy
Reviewer: Even in this potentially biased sample, ‘Confirmed’ field defects sets only a lower limit for the proportion of patients with field defect, and can not be considered a reliable estimate of the actual risk of developing visual field defect.
- Individuals who do develop VFD generally experience a decrease in lateral vision from the normal of 90 degrees to, on average, 71.1 degrees
Reviewer: Average severity of defect is highly sensitive to bias from false positive fields showing apparent mild defects. Incidence of false positives is unknown in this study, but may be substantial because of the small number of fields completed by most patients and the fact that perimetry is subject to large patient learning effects and inter-test variation. Also, it should be noted that lateral vision is often the least affected by VGB; nasal fields were constricted to a median of 18 degrees, severely decreased from the normal of 60 degrees.
- Bilateral concentric peripheral constriction appeared to have deteriorated over serial perimetry assessments in 29% of overall cases. In patients with five field assessments, 12 of 33 adults (35%) still taking VGB deteriorated compared to 3 of 17 (13.0%) who never took VGB.
Reviewer: The high incidence of deterioration in patients who never took VGB raises concern about a high false-positive rate. The higher progression rate in VGB patients versus controls still suggests progression occurs in patients on VGB, but the magnitude of progression can not be reliably estimated from this data. The submission notes that the sensitivity of the method used to determine progression is not known, and that this rate should be considered a preliminary estimate. Progression was only evaluated for fields that were already abnormal, and thus does not capture fields deteriorating from normal to abnormal.
- Risk factors for the development of BCPC visual field defects included treatment duration, average daily dose, and gender.
 - Males were ≈ 1.5 times more likely to have field constriction than females
Reviewer: No clear bias was evident in the derivation of this number, and a number of other published case-series also suggest increased prevalence in males. However, non-random enrollment and other potential biases weakens confidence in this finding.
 - Logistic modeling of visual field loss identified a strong relationship between vigabatrin exposure and development of visual field defects, with the risk being greater the longer the cumulative treatment exposure. The model demonstrated progressive accrual of risk with continued exposure and revealed no evidence for a plateau over a ten-year period.

Reviewer: Since modeling is based on potentially biased data, results may not be reliable.

- The sponsor concluded that results from the ophthalmic disability questionnaire were inconclusive
 - The sponsor reports that at least one disability item was endorsed by 27% of children and 32% of adults, but the proportions were similar in subjects with abnormal visual fields (35%) and normal visual fields (30%).

Review agrees.

- The average time to a confirmed peripheral VFD in patients exposed to Sabril was 6.3 years in adults and 6.5 years in children.

Reviewer: This is strongly biased by the time between starting VGB and enrolling in the study, and does not reflect the biology of VGB adverse visual effects.

- The earliest onset of the peripheral VFD was 12 months in adults and 16 months in children.

Reviewer: The average time of VGB treatment before enrollment was 2- to 4 years, such that the study was poorly designed to measure earliest onset of field defect. This estimate provides only an upper bound of when field defect develops, not a lower bound.

Additional findings

- There was a strong association between the presence of field constriction and the use of the recommended static perimetry technique

Reviewer: Reliable perimetry depends on the skill of both the patient and the operator. While this finding suggests that static perimetry may be more sensitive than kinetic perimetry for detecting VGB-induced field defects, it may also reflect differences in execution of kinetic versus static perimetry.

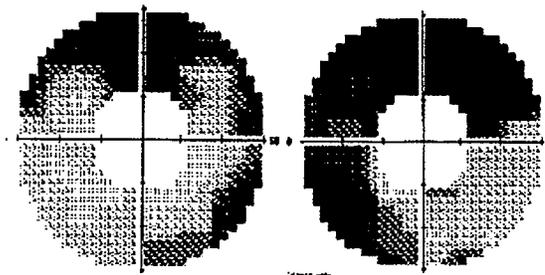
Cases of interest

Case 1

Subject 006, Center 3

63 days of VGB use

Peripheral fields (30-60 degrees), show ring scotoma with temporal sparing, consistent with most common pattern of VGB-associated field defect.



Reviewer: This case suggests onset of VGB visual field loss at 2 months or less.

Cases 2 and 3

Reviewer: The difficulty of perimetric monitoring in epilepsy is illustrated by the narratives of these 2 cases (paraphrased from submission), which are typical of many case reports in study 4020:

Site 17, subject 17

This 18 year old man had taken VGB 1g/day for 6 years prior to enrollment, and continued the same dose during the study. He had an ocular history of amblyopia, strabismus, and nystagmus. The first field test was technically limited. Results of visits 2 and 4 were inconclusive. Visits 5, 6, and 7 showed a field defect related to his right neonatal intracranial hemorrhage. The sponsor noted that 'underlying visual disorder makes it difficult to interpret any vigabatrin related defects in this subject.'

Subject 023

This 28 year old male had a history of vigabatrin usage 1000-1500 mg/day for about 1 year, stopping prior to the start of study 4020. He had no symptoms per questionnaire initially but later reported he noticed difficulty in lateral vision to the left and right, and noticed worsening of vision for shapes, and had vision disorder when walking in the street. His initial visual fields were read as normal at visits 1, 2, and 4. Visits 3 and 5 were technically correct but outcome inconclusive. His visual field at visit 6 was read as VGB-attributed visual field loss.

Reviewer: discussion of study 4020.

Study 4020 suffers from multiple serious shortcomings in study design, execution, and analysis. The method of selection of study population was susceptible to multiple types of bias, perimetric data was collected using inconsistent methods (even within-patient), and data analysis methods were modified post-hoc, potentially biasing findings towards prior expectations. As a result, this review finds most of the data and conclusions unreliable. This is particularly true for estimates of incidence, prevalence, and severity.

c. 'Pooled Cohort Study'

As described briefly first in PSUR 5, a cohort of VGB users was assembled from a variety of studies (Table 2) and tested for visual field defect. The cohort apparently consisted of 367 of the total 403 VGB-exposed patients from these studies. Of the 367 patients, 335 had usable visual fields, while the remaining 32 were excluded from analysis as either unreliable or uninterpretable.

Reviewer: Perimetry data from a high percentage of a defined group of study patients exposed to VGB for varying lengths of time was thus apparently captured.

Table 2: Studies contributing to cohort study of field defect

Country	Study Number	Phase	Treatment Regimen	Vigabatrin N=403	Non- Vigabatrin N=112
Finland	71754-3-W-007	III	Vigabatrin monotherapy	11	
	097.335	III	VGB monotherapy	23	
Japan	JGVG-CL-201*	IIa	VGB add-on therapy	3	
	JGVG-CL-202	IIb	VGB add-on therapy	33	
	JGVG-CL-301	III	VGB add-on therapy	37	
	JGVG-CL-302	III	VGB add-on therapy	29	
US	VGPR0098	IIIb	VGB add-on or monotherapy	39	11
US	201			70**	
UK	VIGAB/4001	IV	VGB add-on or monotherapy	26	5
Canada	Ottawa	IV	VGB add-on or monotherapy	37	
Spain	Valencia	IV	VGB add-on therapy	30	
Germany	BRD/S2	IV	VGB add-on or monotherapy	32	39
Germany	M071754/4017	IV	Non-GABA-ergic AED		42
Germany	Pilot study	IV	Non-GABA-ergic AED		15
Australia	Matched pairs	IV	VGB add-on therapy	33**	

* Includes one patient on compassionate use; ** include a total of 36 children <14

Baseline variables including age, duration and cumulative dose of VGB, duration of epilepsy, and weight differed among the studies (Table 3)

Reviewer: Baseline differences among studies weaken confidence in modeling derived from combined analysis.

Table 3: Baseline Characteristics in Cohort Study

	Male gender		Age (yrs)		Duration of vigabatrin Rx (yrs)		Duration of epilepsy (yrs)		Weight (kg)		Cumulative dose (kg)	
	N	(%)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Adults												
Finland	11	39	36.4	15.7	6.1	2.2	9.7	7.3	73.9	16.0	5.9	3.2
Japan	102	49	31.5	11.1	2.4	1.9	24.2	9.9	57.9	10.2	2.1	2.0
US	32	52	27.8	16.0	3.1	1.5	-	-	-	-	4.3	2.5
UK	10	40	29.8	10.9	5.4	2.1	22.6	11.5	74.6	15.9	4.3	2.5
Germany	19	50	40.6	10.8	2.7	2.5	-	-	-	-	2.3	2.4
Canada	15	52	33.5	11.4	2.8	1.8	-	-	-	-		
Spain	16	59	32.6	14.0	2.8	1.6	16.0	13.5	-	-	2.4	1.7
Australia	18	50	31.7	12.4	4.2	2.3	18.5	11.2	-	-	3.8	2.4
Total Adults	223	49	32.2	12.8	3.1	2.2	21.5	11.2	65.4	16.2	3.8	2.4
Children	12	44	9.6	2.0	2.5	1.4	-	-	-	-	3.0	1.7

Visual fields were measured with a variety of instruments and examination techniques. Each patient underwent field exam at only one time point, with repeat exam if abnormality was suspected or if the results were deemed unreliable (as described in Wild et al., 1999¹). The PSUR states that fields were assessed independently of drug exposure using a pre-specified algorithm.

As described in PSUR 5, of the 335 usable patients, 105 had visual field loss. The prevalence of VGB field defect was 31% (95% CI 25-36%), and for patients with more than 3 years of treatment was 36% (95% CI 29-43%). The severity of field loss ranged between a localized nasal defect between 30 and 40 degrees from fixation to severe concentric constriction. Field defect was considered to be 'profound' in about 1/3 of patients.

Reviewer: Severity was further graded on a 4-point scale of increasing severity, but the correlation of the 4-point severity scale with degrees of field loss was not provided in the study description in the PSURs. The sponsor indicated that the severity scale was defined in Wild et al., 1999. However, this publication described a 3-point scale of mild, moderate, and severe field defect, not a 4-point. It is not clear if 'grade 1'

¹ Wild, J.M. et al.. Characteristics of a Unique Visual Field Defect Attributed to Vigabatrin. *Epilepsia* 1999;40:1784-1794.

represents normal field, as the sponsor asserts. To summarize the grading method of Wild et al.², mild defect was to within about 30 to 35 degrees of fixation, moderate was within 20 to 25 degrees, and severe was closer than 15 or 20 degrees to fixation. The field severity in this study was grade 1 for 20 patients (22%), grade 2 for 29 (31%), grade 3 for 25 (27%), and grade 4 for 18 (20%).

For 165 evaluable patients unexposed to VGB, the overall prevalence of visual field defect was zero (upper 95% CI 2.2%)

Reviewer: It is striking that none of the control patients was diagnosed with a field defect. While findings were not described in detail, specificity may have been kept high by requiring field defects to be fairly severe before being called positive. This is supported by the grading scale, which somewhat surprisingly considered a deficit to within about 30 or 35 degrees of fixation to be only 'mild.'

In PSUR 7, data was added to this study for an additional 119 patients, for a total of 454 evaluable adult vigabatrin patients. In this larger cohort, 112 had a vigabatrin-attributed VFD.

Reviewer: The prevalence of VGB field defect was strikingly lower in the patients added between PSUR 5 and PSUR 7. There were only 7 cases in the additional 119 patients (6%) in PSUR 7, compared to 105 out of 335 patients (31%) reported in PSUR 5. It is not clear if factors such as shorter exposure in the added patients could explain this difference.

PSUR 7 reported that in 27 children ≤ 12 years old, prevalence of VGB field defect was 19% (95% CI 6%-38%).

Analysis of field severity by treatment duration showed that mean severity score was similar, about 2.5 on the 4 point severity scale, across groups exposed for a range of years from <1 to >7 . Likewise, there was little relationship between cumulative VGB dose and field severity (Table 4).

² Wild, J.M. et al.. Characteristics of a Unique Visual Field Defect Attributed to Vigabatrin. *Epilepsia* 1999;40:1784-1794.

Table 4: Mean Field Severity by VGB Duration and Cumulative Dose

Treatment duration	Grade of VFD severity	
	N	Mean
<1 year	2	2.5
1 – 3 years	18	2.1
3 – 5 years	45	2.5
5 – 7 years	26	2.5
> 7 years	8	2.5
Total	99	2.4

Cumulative VGB dose	Grade of VFD severity	
	N	Mean
<1 kg	5	2.6
1 – 3 kg	27	2.4
3 – 5 kg	26	2.3
5 – 7 kg	15	2.5
> 7 kg	13	2.9
Total	86	2.5

Reviewer: This result should not be taken as evidence that an *individual* patient's defect stays of moderate severity even after many years of exposure. A more likely explanation is that the average stability of the cohort derives from some patients developing field defects early and progressing rapidly, combined with others developing field defects later and progressing more slowly. Thus, at <1 year, 2 patients who were presumably very sensitive to VGB adverse effects already developed moderate field defects. At year 2, even if these patients worsened, the *group* average would stay about the same if additional patients with newly developed *mild* field defects then entered the average. The average field severity of patients *with field deficits* wouldn't strikingly worsen until all at-risk patients developed field defect, thus halting the influx of less severely affected patients over time. In contrast, the average severity of *all patients* would behave more intuitively, worsening steadily with increasing exposure.

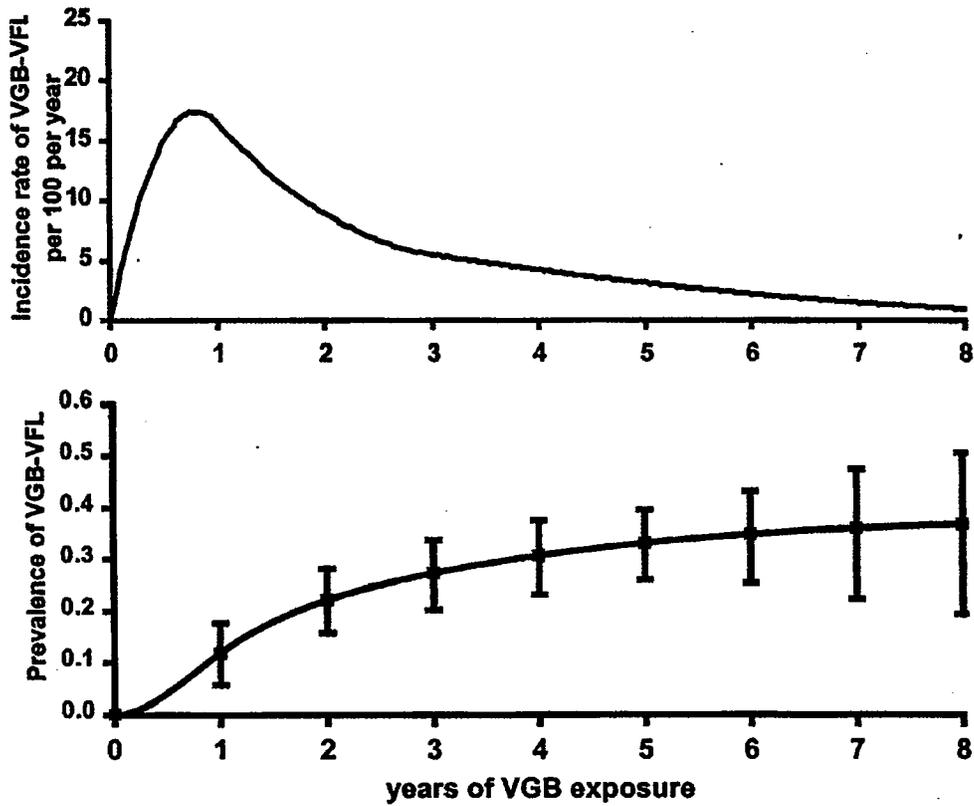
The PSUR notes that "only 8% of the patients tested had spontaneously complained of symptoms that could be related to the visual field defects."

Since patients in this cohort were tested after treatment with VGB for varying lengths of time (Table 5), it was possible for the sponsor to estimate the time to onset (Figure 1) and cumulative dose (Figure 2) to onset of visual field defects using a statistical approach that estimated the most likely time before the visual field test that the defect would have occurred. The maximum incidence of field defect occurred early, at less than 1 year, and then declined slowly over 8 years, but still with additional occurrences.

Table 5: VGB Dose and Duration at Time of Visual Field Test

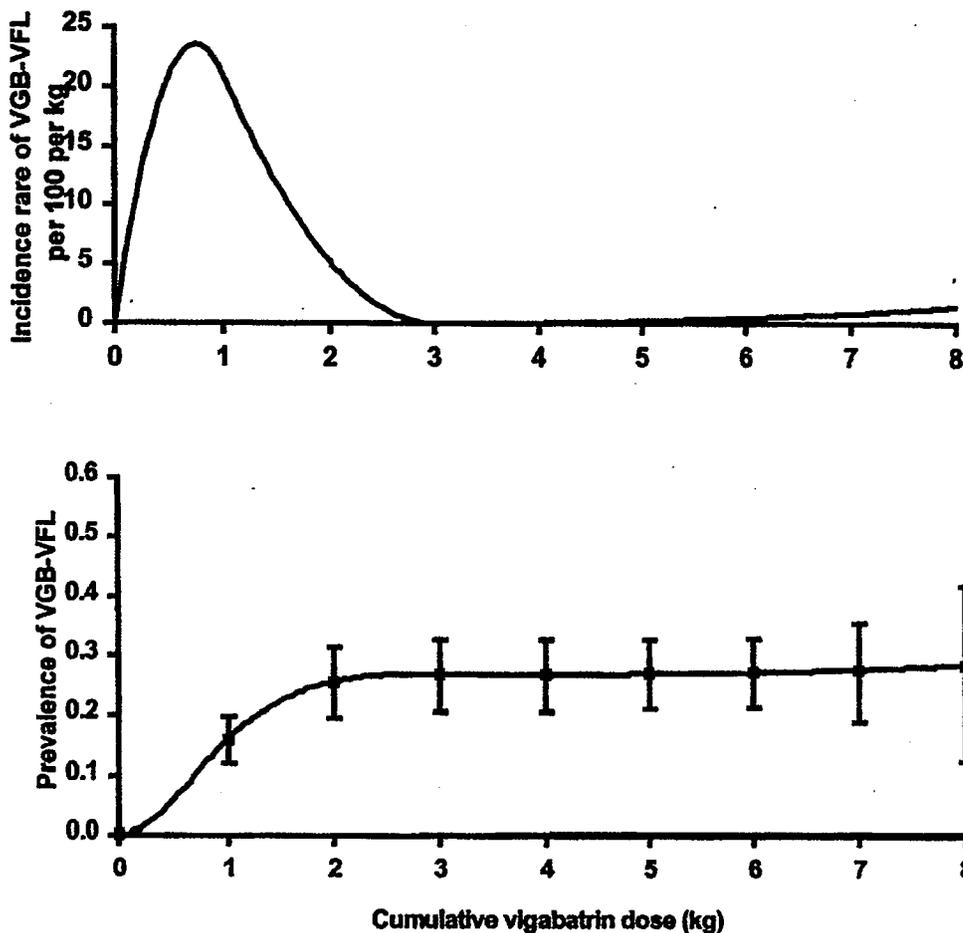
Cumulative VGB dose	Subjects	Duration of VGB therapy	Subjects
0-0.5 kg	79	0-0.5 year	64
0.5-1 kg	46	0.5-1 year	50
1-2 kg	54	1-2 year	59
2-3 kg	58	2-3 year	52
3-4 kg	50	3-4 year	84
4-5 kg	42	4-5 year	41
5-6 kg	37	5-6 year	57
6-7 kg	18	6-7 year	23
7-8 kg	13	7-8 year	10
8-9 kg	7	8-9 year	3
9- kg	12	9- year	8
Total	N=416	Total	N=451

Figure 1: Incidence and Prevalence of VGB Field Defect by Duration of Exposure



Reviewer: The data indicate a rapidly increasing risk of field defect in the first few months of VGB exposure, with risk of developing field defect still present for patients exposed for 8 years, albeit at a decreasing yearly rate.

Figure 2: Incidence and Prevalence of VGB Field Defect, by Cumulative Dose



Reviewer: Cumulative exposure is correlated with time of exposure in this population. Since cumulative dose is both a function of daily dose and time on treatment, the greater flattening of the dose curves compared to the time on treatment curves argues against a strong dose-dependence of risk of field defect, at least in the relatively narrow range used in these studies.

Risk Factors

Field defect occurred in 31% of all males (70/112) and 17% of all females (40/112). This increased prevalence in males was present in all countries from which patients were enrolled (Table 6).

When duration of VGB was stratified by high (>3 g/day) and low (<1.5 g/day) dose, the incidence rate for the high dose peaked at 0.75 years, while the incidence rate for the low dose peaked after 2.3 years.

Reviewer: This finding highlights the need to consider risk factors not only for occurrence of field defect, but also for time to onset of field defect.

The risk of field defect increased with duration of VGB use, but this finding was confounded by effect of cumulative VGB dose.

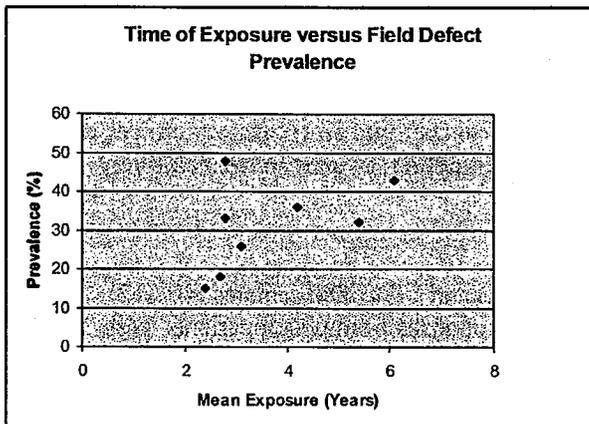
Type of epilepsy or ethnic origin was not reported to be a risk factor (Table 6).

Table 6: Field Defect by Country and Gender, Cohort Study

Country	Vigabatrin attributed VFDs			Total* N=454
	Male gender n=223	Female gender n=229	Total VFD	
Finland	6 (55%)	6 (35%)	12 (43%)	28
Japan	19 (19%)	12 (11%)	31 (15%)	208
US	11 (34%)	5 (17%)	16 (26%)	61
UK	5 (50%)	3 (20%)	8 (32%)	25
Germany	5 (26%)	2 (11%)	7 (18%)	38
Canada	9 (60%)	5 (36%)	14 (48%)	29
Spain*	6 (38%)	3 (27%)	9 (33%)	29
Australia	9 (50%)	4 (22%)	13 (36%)	36
Total	70 (31%)	40 (17%)	110 (24%)	454

*Gender unknown for 2 patients

Reviewer note: Baseline characteristics and exposure differed by country. For example, duration and cumulative dose in Japan was lower than in other countries, possible explaining the lower prevalence of field defects. The chart below shows prevalence of field defect in each country plotted against average years of exposure, and suggests that increase of field defect prevalence with exposure time may explain differences among countries.



In smokers or ex-smokers (N=111) no difference in relative risk of field defects was found (relative risk 0.9, 95% CI 0.5-1.5).

Reviewer Conclusions and Discussion, Cohort Study

While this study was not described in detail in the submission, several key characteristics of the study suggest that important insight can be gained into the VGB-induced visual field defect.

Most importantly, the study captured interpretable fields from a high percentage, perhaps close to 80%, of an identifiable cohort of patients that had been exposed to VGB for various lengths of time (although the cohort still reflects only those patients who had not dropped out of previous studies). This allowed the sponsor to model incidence and prevalence of field defect by time and total exposure. This model must still, however, be considered with caution because it is derived from combined data from studies of patients with different baseline characteristics and exposures, ranging from ≈ 2 years in Japan to ≈ 6 years in Finland.

While little information was provided about perimetric methods or data analysis, the low (zero) incidence of any field defects in the unexposed control population, and high incidence of severe field defects in VGB patients suggests that false-positive results were not a major confounder despite the fact that each patient was only tested at one time point. It appears that false-positives were kept low by not diagnosing even mild field defects until constriction to within about 30 or 35 degrees of fixation. Thus, the 'true' incidence of field constriction, as judged against normal fields that would be expected to be about 60 degrees on average, might have been underestimated by the study.

The following conclusions are drawn from this study:

- The incidence model suggests that visual field defects may begin within only weeks or a few months of starting VGB treatment.
- Peak incidence appears to occur after treatment of less than 1 year.
- $\approx 1/3$ of patients developed visual field defects in the first few years of VGB use.
- $\approx 1/3$ of field defects are severe, encroaching to within about 20 degrees of fixation.
- A continued risk of developing field defect extended past 8 years exposure, the limit of the data.
- Risk of field defect appeared higher (or occurred earlier) in men than in women.

d. Study R003

This non-comparative, *prospective* observational study enrolled 25 subjects from 4 centers in Canada (out of a planned 200 subjects). Subjects were treated with vigabatrin according to the clinical judgment of the investigator in accordance with the indication of VGB. The decision to treat patients with vigabatrin was independent of the trial protocol.

Static perimetry and ERG were performed every 3 months for all adult patients, and were evaluated by central evaluators. Suprathreshold perimetry using 120 point [60 degree] 3-zone strategy was the perimetry method of choice.

The median cumulative dose of VGB was about 1,100 g, and the median duration of treatment was about 500 days (range 2 to 988 days)

Seven patients (28%) developed visual field defect (Table 7). In 4 of these 7 the defect was graded as mild, while in 3 the defect was deemed moderate at first diagnosis.

Reviewer: The correspondence of severity grades to degrees of field constriction is not specified. John Wild was consulted for visual field interpretation, suggesting that as in the cohort study described above, mild defect corresponds to constriction to within about 30 to 35 degrees of fixation, and moderate corresponds to constriction to within about 20 to 25 degrees of fixation.

Table 7: Study R003 Serious Adverse Events

Subject number	Age/ Sex/ Race (i)	Adverse event as coded	Period (ii)	Exposure (iii)	Cumulative dose at SAE onset (g) (iv)	Duration of event (days)	Possible relation to vigabatrin	Intensity (v)	Action (vi)	Outcome (vii)
0300001	37/M/Asian	*Visual field defect	Post	680	1506.0	123	No	Mld		R w/o seq
0300005	40/F/White	*Visual field defect	On		2118.5		Yes	Mod	D/Cevn	Ongoing
0405001	50/F/White	*Depressed mood	On	11	7.5	20	Yes	Sev	D/Cevn	R w/o seq
		*Restless legs syndrome	On	11	7.5	20	Yes	Mod	D/Cevn	R w/o seq
		*Hallucination, visual	On	11	7.5	20	Yes	Mod	D/Cevn	R w/o seq
		*Convulsion	Post	37	18	3	No	Mod	Other	R w/o seq
0405003	43/F/White	*Mood swings	On	14	82.5	70	Yes	Mod	D/Cevn	R w/o seq
		*Visual field defect	Post	148	82.5		Yes	Mod		Ongoing
0405005	33/M/White	*Visual field defect	On	706	1553.0		Yes	Mld	N/C	Ongoing
0405007	32/M/White	*Visual field defect	On	402	1908.5		Yes	Mld	N/C	Ongoing
0405010	58/M/White	*Visual field defect	On	254	423.5		Yes	Mod	D/Cevn	Ongoing
		*Convulsion	Post	519	631.5	1	No			Death
0405011	32/F/White	*Drug hypersensitivity	On	1	1.0		Yes	Mod	D/Cevn	R w/o seq
0415008	52/F/White	*Visual field defect	On	444	867		Yes	Mld	N/C	Ongoing

Note: (i) Sex: M=male, F=female
(ii) On = On-treatment; Post = Post-treatment
(iii) Day of study medication when event occurred
(iv) Cumulative dose calculated from Appendix C.1.2 Listing 17
(v) Mld = mild; Mod = moderate; Sev = severe
(vi) N/C = no change; D/Cevn = discontinued due to the event
(vii) R w/o seq = recovered without sequelae

Key to symbols: * = serious adverse event; † = alert term; & = sponsor assessment of possible relationship differs from that of investigator assessment given in table

The following patient is particularly remarkable for showing that field defect can develop rapidly, escape perimetric diagnosis until of moderate severity, and totally escape ERG diagnosis.

Subject 405003

The subject is a 44 year old woman who took VGB for 63 days, beginning at 500 mg/day and increasing to 2000 mg/day, with a cumulative dose of 82.5 g. Her initial baseline static field test was outside of normal limits, but on repeat testing was “within normal limits”. Two months after study medication was discontinued for a non-ophthalmic adverse event, visual field testing showed moderate superior nasal defects. Repeat exam confirmed the field defect.

ERG did not detect retinal abnormality (Table 8):

Table 8: Flicker, subject 405003

<u>Treatment day</u>	<u>Flicker (µV)</u>
-28	49
28	55
56	57
148	57
317	69

Only one subject (0405010) had a visual field defect detected by ERG examination. The subject had an asymptomatic bilateral nasal peripheral acquired field defect that was considered to be moderate in intensity.

Reviewer Discussion

While this study was small, it is valuable for several reasons. The study was prospective, and should represent a less biased patient sample. Patients were monitored with perimetry in a manner similar to what might occur in clinical practice, thus providing an estimate of how successful safety monitoring might be at detecting early field constriction. ERG flicker testing was also conducted, providing information on how field defect correlates with ERG. This review concludes the following from this study:

- Visual field defect occurs in about 1/3rd of patients after less than 2 years of treatment.
- Early onset of visual field defect is common. In patient 405003, field defect was detected after only 63 days of treatment (including titration period starting at a low dose of 500 mg/day) and a cumulative dose of 82.5 g. Importantly, the defect diagnosed after 63 days likely did not *occur on the day of diagnosis*, but rather developed some time *before* diagnosis. This suggests that this field defect of moderate severity developed at *less than 63 days* of treatment. If the study had been larger, likelihood suggests that outliers would have been identified even earlier after initiating VGB. Patient 405010 had onset of field defect of moderate severity after only 254 days and a cumulative dose of 423.5 g, again with true onset of the defect likely at less than the time to diagnosis.
- *Perimetry appears unable to reliably detect mild field defects.* Only 4 of 7 defects were identified while mild. The remaining 3 were not detected until of moderate severity. Moderate severity defects under the grading scale likely used in this study correspond to constriction to within about 20 or 25 degrees of fixation.
- *ERG appears ineffective at detecting retinal damage corresponding to mild or even moderate field defects.* None of the mild defects and only 1 of 3 moderate defects were detected by ERG.

e. Study 4021

This was an open-label observational study conducted in a single center in Finland. The study enrolled 29 current or previous VGB patients from a single center, who were either still undergoing therapy or had discontinued due to VFD. Nine of 29 patients had a visual

field defect attributed to VGB, and 1 had a field defect attributed by the investigator to other causes. Seven of 18 patients who underwent ERG had abnormalities, but the investigator concluded that concordance between ERGs and peripheral VFD could not be confirmed due to methodology used for the ERG assays. Over 2.5 years of follow-up, 14 patients were monitored. Nine had no apparent change in visual fields, one demonstrated progressive field loss in one eye, and 4 showed apparent lessening of field defect, but the investigator concluded that reliable evaluation of progression or regression could not be made owing to variability in field assessments.

Reviewer discussion

Few reliable conclusions can be made from this data. If anything, the study adds supports that ERG findings are difficult to correlate with perimetry, and that perimetry is difficult to perform reliably.

f. Study 4103

The study called for 170 patients from 5 countries, but only 2 centers enrolled 23 subjects, and the study was terminated.

Reviewer discussion

Little can be concluded from this study

g. Sabril/Sabrillex (Scope) Study

This was a survey study designed to assess the compliance of VGB prescribers in the European Union (EU) with guidelines for ophthalmic monitoring of patients given VGB. The survey was completed by patients, but only 22% responded. The study was terminated early and deemed not to have met objectives.

Reviewer discussion

Insufficient response renders the study uninterpretable.

h. Glasgow study

This study is only briefly described in the submission, but is noted to be the same as McDonagh et al.³. The sponsor presents data on color vision and visual acuity from 56 patients on VGB and 49 previously on VGB. Compared to patients either on other GABAergic drugs or never on GABAergic drugs, there were no apparent differences in color vision or visual acuity associated with VGB.

Reviewer discussion

³ McDonagh et al., Peripheral retinal dysfunction in patients taking vigabatrin. *Neurology* 2003;61:1690-1694.

Insufficient data is presented in either the submission or the publication to judge the reliability of study findings (see additional discussion under Visual Acuity, section 10a).

6. Ophthalmic Safety Studies in Infantile Spasms and Children

a. Toronto Study (Westall)

This ongoing study was conducted by Carol Westall who heads the vision testing laboratory at the Hospital for Sick Children in Toronto. The sponsor has supported the study since 2005. No formal study protocol was available for review.

The majority of IS patients in the region are treated at this center, and the sponsor asserts that the study subjects should therefore be representative of the overall population of VGB-treated IS patients.

Reviewer: Speculatively, a center highly specialized in the technically difficult ophthalmic exam of IS patients may provide more reliable diagnosis than might be provided in less experienced centers that might provide the bulk of care to U.S. patients.

Ophthalmic exam including ERG was conducted every 6 months, although ongoing examinations now occur every 3 months (the sponsor notes that this is a limitation in interpretation of these data).

The study had both a prospective and retrospective component. Prospective patients had baseline exams near the time of initiating VGB, while retrospective patients were followed after varying times of VGB treatment.

Study population:

- 246 total infants (most with IS)
- 117 with baseline and at least one post-baseline exam (prospective arm)
- 85 with at least one exam, but no baseline exam (retrospective arm).
- 179 treated with VGB, with 117 discontinued VGB during study
- Median age of all subject at most recent ERG test was 2.2 years

Reviewer: While this study was relatively large and had a prospective arm, patients were not followed very long, such that important questions about defect progression or functional outcome can not be addressed.

Table 9 displays the number of visits for prospective and retrospective patients. The average patient had just over 2 exams, and was followed for between 6 and 12 months (Table 10).

Reviewer: While this study was relatively large and had a prospective arm, patients were not followed very long, such that important questions about defect progression or functional outcome can not be addressed.

Table 9: Number of Post-Baseline ERG Tests, Toronto Study

Number of Post-Baseline ERG tests	Prospective (N=117) n (%)	Retrospective (N=85) n (%)	Prospective + Retrospective (N=202) n (%)
1	28 (23.9)	21 (24.7)	49 (24.3)
2	28 (23.9)	19 (22.4)	47 (23.3)
3	26 (22.2)	19 (22.4)	45 (22.3)
4	17 (14.5)	10 (11.8)	27 (13.4)
5	13 (11.1)	7 (8.2)	20 (9.9)
6	3 (2.6)	3 (3.5)	6 (3.0)
7	1 (0.9)	1 (1.2)	2 (1.0)
8	0 (0.0)	3 (3.5)	3 (1.5)
9	1 (0.9)	1 (1.2)	2 (1.0)
10	0 (0.0)	1 (1.2)	1 (0.5)

Note: Prospective subjects have a baseline ERG and at least one post-baseline ERG.
Retrospective subjects have no baseline ERG.
t_visits_after.sas

Table 10: Duration of VGB Therapy, Toronto Study

Duration of Therapy	Prospective (N=117) n (%)	Retrospective (N=85) n (%)	Prospective + Retrospective (N=202) n (%)	Baseline Only (N=44) n (%)
>1 wk-<3 mo	9 (7.7)	7 (8.2)	16 (7.9)	42 (95.5)
3-<6 mo	18 (15.4)	8 (9.4)	26 (12.9)	1 (2.3)
6-<12 mo	37 (31.6)	19 (22.4)	56 (27.7)	1 (2.3)
12-<18 mo	16 (13.7)	9 (10.6)	25 (12.4)	0 (0.0)
18-<24 mo	18 (15.4)	9 (10.6)	27 (13.4)	0 (0.0)
24-<30 mo	9 (7.7)	5 (5.9)	14 (6.9)	0 (0.0)
30-<36 mo	3 (2.6)	3 (3.5)	6 (3.0)	0 (0.0)
3 yrs	2 (1.7)	6 (7.1)	8 (4.0)	0 (0.0)
4 yrs	2 (1.7)	5 (5.9)	7 (3.5)	0 (0.0)
5 yrs	1 (0.9)	5 (5.9)	6 (3.0)	0 (0.0)
6 yrs	2 (1.7)	2 (2.4)	4 (2.0)	0 (0.0)
7 yrs	0 (0.0)	2 (2.4)	2 (1.0)	0 (0.0)
8 yrs	0 (0.0)	2 (2.4)	2 (1.0)	0 (0.0)
10 yrs	0 (0.0)	2 (2.4)	2 (1.0)	0 (0.0)
11 yrs	0 (0.0)	1 (1.2)	1 (0.5)	0 (0.0)

Note: Prospective subjects have a baseline ERG and at least one post-baseline ERG.
Retrospective subjects have no baseline ERG.
Note: Duration of therapy measured from first dose to last dose. A missing last dose is taken as ongoing therapy, in which case duration is measured from first dose to last ERG visit. Subjects with last ERG visit prior to first dose have duration of 0.
t_demog1.sas

Of the patients already taking VGB before first exam, 49 of 85 began ≤ 6 months previously.

In the prospective cohort, most subjects (77%) had an ERG on the day of first dose or within the week immediately following the first dose. Eight of the 117 patients in the prospective cohort had ERG >2 months after starting VGB, and another had ERG >1 month after starting VGB.

In the sponsor's analysis, a replicated abnormality on ERG testing was defined as abnormality on two consecutive exams, and a sustained abnormality was defined as abnormality observed on the *last* two examinations.

Reviewer: The true sensitivity and specificity of ERG testing is not reflected in these definitions. A 'sustained' abnormality is in no respects equivalent to a 'true positive.' ERG results suffered from high noise, such that two consecutive abnormal results could have occurred by chance alone. Available data is fundamentally insufficient to determine the relationship of the sponsor's measures to true test performance. .

Significant change was defined as 30 Hz flicker amplitude less than lower limit of age matched control data (2.5th percentile) *or* a significant worsening of the ERG (change in ERG between visits is greater than normal inter-visit change).

Reviewer: 'Significant worsening' was not adequately defined, for example as a certain percent decrease.

The definition of an ERG abnormality also took into account that each ERG session could produce interpretable results from one eye, both eyes, or neither eye. The Toronto investigators developed a 'decision matrix' to define replicated or sustained abnormalities given the various combinations of results that could arise from two eyes over two ERG exams (Table 11).

Table 11: ERG Abnormality Decision Matrix

Toronto ERG Abnormality Analysis: Decision Matrix for Replicated and Sustained Abnormalities						
Left eye	Right eye	Left eye	Right eye	Patient-level assessment for replicated or sustained abnormality	Rule	Description of rule
Normal	Normal	Anything	Anything	Normal	A	Normal in both eyes at a visit precludes two abnormalities in a row.
Normal	Abnormal	Normal	Abnormal	Abnormal	B	One eye consistently abnormal on the two visits
Normal	Abnormal	Normal	No data	Normal	D	No evidence of abnormality at either visit, or abnormality not confirmed
Normal	Abnormal	Abnormal	Normal	Normal	D	
Normal	Abnormal	Abnormal	Abnormal	Abnormal	B	
Normal	Abnormal	Abnormal	No data	Abnormal	F	
Normal	Abnormal	No data	Normal	Normal	D	
Normal	Abnormal	No data	Abnormal	Abnormal	B	
Normal	Abnormal	No data	No data	n/a	n/a	These cases, where both eyes provide no data, are listed as a formality and are not applicable. That is, if there is no data on either eye at a particular visit, it's as if that visit didn't exist and the algorithm has to search for a different visit to examine.
Normal	No data	Normal	Normal	Normal	A	
Normal	No data	Normal	Abnormal	Normal	D	
Normal	No data	Normal	No data	Normal	D	
Normal	No data	Abnormal	Normal	Normal	D	
Normal	No data	Abnormal	Abnormal	Normal	D	
Normal	No data	Abnormal	No data	Normal	D	
Normal	No data	No data	Normal	Normal	D	
Normal	No data	No data	Abnormal	Normal	D	
Normal	No data	No data	No data	n/a	n/a	
Abnormal	Normal	Normal	Normal	Normal	A	
Abnormal	Normal	Normal	Abnormal	Normal	D	
Abnormal	Normal	Normal	No data	Normal	D	
Abnormal	Normal	Abnormal	Normal	Abnormal	B	
Abnormal	Normal	Abnormal	Abnormal	Abnormal	B	
Abnormal	Normal	Abnormal	No data	Abnormal	B	
Abnormal	Normal	No data	Normal	Normal	D	
Abnormal	Normal	No data	Abnormal	Abnormal	F	This takes a conservative point of view. Although there is no confirmation of the abnormality in one eye because there is missing data, we accept the occurrence of the abnormality in the other eye at the second exam as surrogate confirmation to declare the patient abnormal.
Abnormal	Normal	No data	No data	n/a	n/a	
Abnormal	Abnormal	Normal	Normal	Normal	A	
Abnormal	Abnormal	Normal	Abnormal	Abnormal	B	
Abnormal	Abnormal	Normal	No data	Normal	D	
Abnormal	Abnormal	Abnormal	Normal	Abnormal	B	
Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	B	
Abnormal	Abnormal	Abnormal	No data	Abnormal	B	
Abnormal	Abnormal	No data	Normal	Normal	D	
Abnormal	Abnormal	No data	Abnormal	Abnormal	B	
Abnormal	Abnormal	No data	No data	n/a	n/a	
Abnormal	No data	Normal	Normal	Normal	A	
Abnormal	No data	Normal	Abnormal	Normal	D	
Abnormal	No data	Normal	No data	Normal	D	
Abnormal	No data	Abnormal	Normal	Abnormal	B	
Abnormal	No data	Abnormal	Abnormal	Abnormal	B	
Abnormal	No data	Abnormal	No data	Abnormal	B	
Abnormal	No data	No data	Normal	Normal	D	
Abnormal	No data	No data	Abnormal	Abnormal	F	
Abnormal	No data	No data	No data	n/a	n/a	
No data	Normal	Normal	Normal	Normal	A	
No data	Normal	Normal	Abnormal	Normal	D	
No data	Normal	Normal	No data	Normal	D	
No data	Normal	Abnormal	Normal	Normal	D	

Reviewer: The matrix assigns the label 'normal' or 'abnormal' in situations in which there appears to be little certainty as to the clinical condition of the patient. For

example, a patient is 'normal' if the left eye is normal on two consecutive exams, while the right eye is abnormal on the first and 'no data' is available for the second exam.]

The following are the major findings and conclusions of the sponsor:

- There is a high background rate of abnormality on 30 Hz flicker (37%) and cone b-wave (18%) in children not exposed to VGB

Reviewer: Importantly, the sponsor does not discuss how testing would be interpreted in patients with abnormal baseline exams, who constitute a high percentage of all patients.

- Most subjects on VGB retained normal ERG parameters over 2 years

Reviewer: Findings do not support the validity of this observation. While high inter-test variability prevented concluding with certainty that most subjects had *abnormal* ERG parameters, this is not equivalent to concluding that the subjects retained *normal* ERG parameters. At least one 30 Hz flicker abnormality occurred in 63% of subjects. The incidence of "sustained abnormality" was 25%, but this might provide only a *lower bound* on the true incidence of abnormal ERG (although since specificity appears low, the number also may not be reliable even as a lower bound).

- No subjects experienced single abnormal ERG from VGB before 3.1 months

Reviewer: Findings do not support the validity of this observation. This result reflects *testing interval*, not necessarily time to onset of abnormality. Most patients weren't tested until after 6 months of VGB, and this patient wasn't tested until 3.1 months. (Of note, VGB has an initial pharmacological effect to increase ERG flicker voltage. This effect could delay apparent onset of abnormal ERG).

- For prospective patients, mean time to detection of ERG abnormality was 15.6 months.

Reviewer: Time of onset of ERG abnormality would, on average, be earlier than time of detection. Most patients were examined every 6 months, so time to onset might be estimated by subtracting half the inter-test interval from the time of detection, yielding about 13 months.

- In the VGB-treated subjects who developed sustained abnormalities, the average times to sustained 30 Hz flicker and sustained cone b-wave abnormalities were 27 and 36 months, respectively.

Reviewer: Findings do not support the validity of this observation. 'Sustained abnormality' is not an adequate measure of time to onset of ERG abnormality, but describes abnormality on the *final two* examinations, and thus depends on *time to the final two examinations*, not necessarily time to onset of the abnormality.

- Visual field abnormalities potentially related to VGB were found in 5 of 63 children (8%).

Reviewer: Findings do not support the validity of this observation. Visual field was mainly tested by confrontation. The sensitivity of confrontation field testing is likely low in this population.

- No VGB-induced reductions in central visual acuity were found.

Reviewer: Findings do not support the validity of this observation. Most subjects were not tested or gave no response at any visit. When testing was conducted, mainly Teller acuity was used, which might not have detected acuity loss that was not relatively severe.

- Since a sizeable number of infants with IS have an age-adjusted abnormal reading at a single visit, to confirm VGB induced retinal injury requires 2 serial abnormal examinations

Reviewer: Findings do not support the validity of this method. While the specificity of the flicker test was not discussed, it appears to be relatively low; the odds of two false positive results in a row is therefore fairly high. *Critically, since serial testing is conducted, the odds of any two tests out of many being false positive is even higher.* Of similar concern, given a risk of false-negative results, to 'confirm' a true retinal injury would sometimes require fully four (or more) tests, not two; a 'true positive' followed by a 'false negative' would then require two more 'true positives' to 'confirm' retinal damage. With 3-month intervals between tests, a year of treatment and continued visual field deterioration would pass before diagnosis.

- Significant correlation of male sex with effect on flicker response was not found
Review findings agree. While it's difficult to explain a negative result, large test variability might have obscured any gender effect.
- Defects did not seem to appear after drug was discontinued.

Reviewer: The data is inadequate to address the question. Almost no patients had more than 1 ERG exam after stopping VGB. At least 10 patients showed lower flicker results after stopping VGB, with some patients changing from 'normal' to 'abnormal' (e.g. patient 14IWL).

- Some subjects normalized parameters while still on drug and remained normal following discontinuation.

Reviewer: This finding may only represent artifactual 'normalization' compared to earlier 'false positive'.

Individual Cases

Reviewer: 30-Hz data flicker data is presented below for 3 representative patients in the Westall study. The data raise concern about test performance and clinical interpretability. Apparent inter-test variability suggests that false-positive and false-negative findings would be common, and that early diagnosis of retinal damage would not be reliable. The third example gives the impression that test results decrease exponentially, as might be expected of VGB damage. Importantly, however, this case does not represent early diagnosis, only potential confirmation of irreversible retinal damage. (Of note, while this last example appears to show steady progression, it might actually represent only a chance pattern).

Subject 1528X

30 Hz flicker decreased from $\approx 120 \mu\text{V}$ to $\approx 65 \mu\text{V}$ after 6 months, a 50% decrease that would seem to indicate significant retinal damage (

Figure 3). However, VGB was continued, and the ERG then decreased further, to $\approx 35 \mu\text{V}$ at 1.5 years, at which time VGB was stopped. *Importantly, stopping VGB after the third exam would seemingly have failed to diagnose VGB early, since about 75% of the flicker voltage was already apparently lost to VGB damage.* At 2 years, however, the test returned to $\approx 100 \mu\text{V}$, and stayed $\approx 100 \mu\text{V}$ at 2.5 years. Even looking at the full set of tests retrospectively, it is not clear if the changes in flicker values represent VGB toxicity or other types of variability.

Figure 3: Subject 1528x ERG Flicker

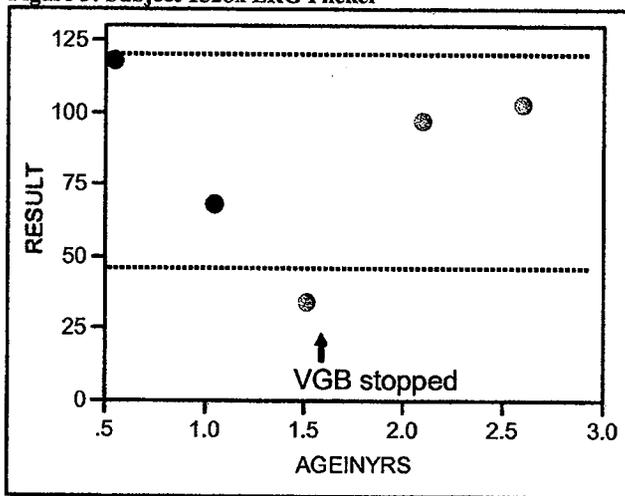


Figure 3: Upper and lower limit of normal are approximately represented by the red lines (normal age-related increase in values not shown). Red circles represent flicker result for left eye, and green for right eye. 'Result' is 30 Hz flicker result, in microvolts, versus patient age in years.

Subject 15AX2

Baseline flicker was below lower limit of normal, but VGB dosing continued. Data points appear scattered, and prevent clear clinical interpretation, even considering all 7 exams.

Figure 4: Subject 15AX2 ERG Flicker

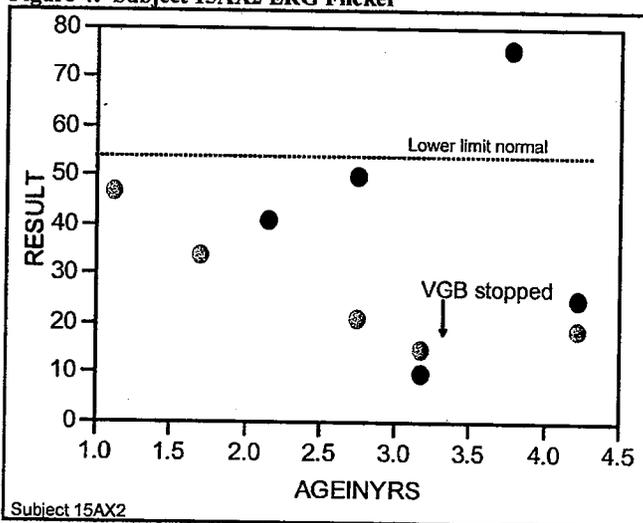


Figure 4: Lower limit of normal is approximately represented by the red line (normal age-related increase in value not shown). Red circles represent flicker result for left eye, and green for right eye. 'Result' is 30 Hz flicker result, in microvolts, versus patient age in years.

Subject 1530G

A series of decreasing test values for this patient might represent VGB damage. VGB was continued, and testing might only have confirmed irreversible retinal damage.

Figure 5: Subject 1530G ERG Flicker

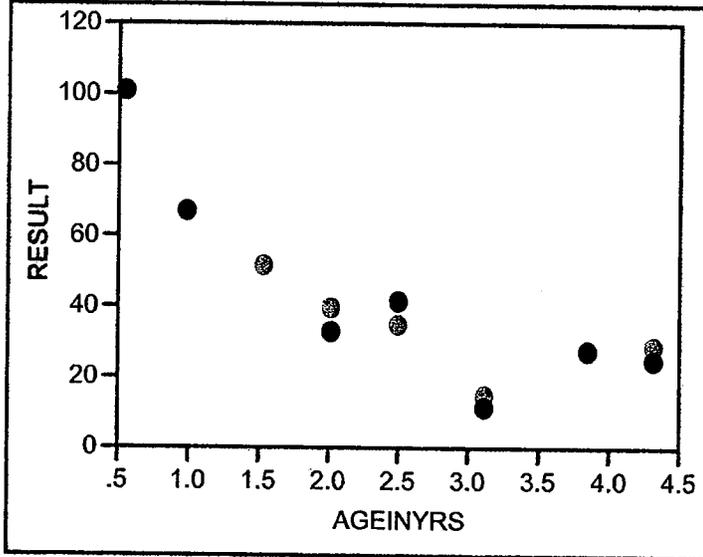


Figure 5: Red circles represent flicker result for left eye, and green for right eye. 'Result' is 30 Hz flicker result, in microvolts, versus patient age in years.

Westall Group Publications

Buncic JR et al., Characteristic retinal atrophy with secondary "inverse" optic atrophy identifies vigabatrin toxicity in children. Ophthalmology 2004;111:1935-42.

This paper concluded that the central as well as the peripheral retina is damaged by VGB:

- The macula is relatively spared, although superficial retinal light reflexes indicating wrinkling of the innermost retina suggest early macular toxicity as well.
- This pattern of atrophy also supports the notion of diffuse, but differential, involvement of peripheral and central retinal cells and the ganglion cell layer.
- Peripheral retinal atrophy occurs initially, with progression to involve the central retina with time.

This paper also detailed 3 cases that offer insight into the clinical monitoring of children on VGB.

- Case 1 suggests that ERG can fail to detect visual field constriction in children. This 10-year old girl took VGB 2.5 g/day for 4 years before first ERG exam. Goldman fields showed constriction to central 20 to 30 degrees in both eyes. ERG was within normal limits.
- Case 2 suggests that clinically disabling visual field defect can develop relatively precipitously after many years of VGB treatment. A 13-year old autistic, non-verbal boy with generalized tonic-clonic seizures had been treated with VGB 1 g/day for 6 years prior to ERG monitoring. First ERG was 'mildly abnormal' (of note, flicker was not recorded because of 'technical difficulties'). No visual difficulties were

observed by the parent at the time. The patient returned to the clinic after 18 months. The parent now noted the patient was bumping into things and seemed not to see where he was walking. ERG was markedly reduced. Visual acuity was preserved to $\geq 20/40$. The macula showed some involvement of both the nerve fiber layer and deeper layers.

- Case 3 illustrates several issues: a) practical difficulty of interpreting ERG findings, b) clinical disability from VGB in children, and c) potential progression of damage after stopping VGB. A 13-month old boy with trisomy 21 and IS since age 9-months had a normal ERG after 5 months of 500 mg/day VGB. At 11 months, ERG showed some reduction from the previous, but was still 'well within normal limits.' However, at 16 months the ERG 30-hz flicker was 'decreased dramatically to become 55% lower than age-expected.' VGB dose was decreased, but at 24 months the patient was noted to stare straight ahead, and to respond more to sound than to visual cues. The parent reported the need to attract the child's attention downward to his food at mealtimes by tapping on his plate. The ERG 30-hz flicker was similar to previous, but cone response had decreased to 42% below normal. The macula showed wrinkling and irregular thickness. VGB was stopped, but 3 months later the ERG showed further reduction in both eyes.

Reviewer Summary and Conclusions, Westall Experience

Large inter-test variability appears to limit the precision with which ERG can characterize or monitor for VGB-induced retinal injury, particularly for mild or moderate defects. Consistent with this, inter-test variability of ERG in normal volunteers suggests that a 50% decrease in flicker amplitude can be needed to detect a true decrease with 95% confidence (Fishman et al, 2003⁴).

As discussed in more detail in Section 7, sensitivity of ERG for even moderate vigabatrin visual damage appears to be low. Some published reports suggest that ERG might be more reliable for detecting severe vigabatrin retinal damage (for example, Harding et al., 2004, also discussed in section 7).. However, testing would then be confirming damage rather than contributing to its prevention.

Inter-test variability is particularly problematic when ERG is used for serial monitoring. False-negative or false-positive results are almost inevitable with repeat testing simply due to probability. Confirmatory testing for any single result is necessary, but delays diagnosis while retinal damage worsens. To speculate, increased frequency of ERG monitoring at intervals less than the proposed 3 months might improve the performance of ERG testing, but this would need to be studied.

The lack of data correlating ERG to visual field remains extremely problematic in clinical interpretation. Case 3 above suggests that decreased ERG flicker to just 55% below

⁴ Fishman GA et al., Short term intervisit variability of ERG amplitudes in normal subjects and patients with retinitis pigmentosa. *Retina* 1997;17:33-7.

normal, essentially the level of first reliable detection of defect, can cause visual disability in children with IS.

b. Boston children's hospital

Retrospective data was collected from 47 children between 3 and 52 months of age treated at Boston's Children's Hospital. Most patients had only a single ERG test.

Descriptive statistics compared patients with 6 months of exposure to those with greater than 6 months of exposure to VGB.

The mean 30 Hz flicker amplitude was 77.6 μV ($\pm 24.5\mu\text{V}$) for those who were tested ≤ 6 months after the first VGB dose compared to 54.7 μV ($\pm 20.4\mu\text{V}$) for subjects tested > 6 months after the first dose of VGB.

Reviewer discussion

Lack of serial exam data limits conclusions from this study. Findings support a positive correlation between exposure and severity of retinal damage.

c. Study 4102

This was a cross-sectional observational study of the prevalence of visual field defect in young children exposed to VGB. Thirty-nine children from 3 centers were enrolled, 3 with IS and the remaining with partial seizures.

Standard perimetry was used in 12 patients, H-stimulus was used to evaluate 35 patients, and ERG was used in 26 patients. On average, the patients received 1,400 mg/day for 2.2 years. Peripheral VFD was found in about 1/3 of patients.

Reviewer discussion

Only a brief description of study findings was provided by the sponsor. H-stimulus is noted by the sponsor as a potential method of monitoring VGB retinal damage, but insufficient data or analysis was provided for evaluation.

d. Study 0201

This was a 1 year open-label, follow-up, long-term maintenance study of vigabatrin as adjunctive therapy in 210 children with uncontrolled complex partial seizures. The study enrolled patients previously in study 0118 and 0221. Visual field exams (kinetic or static), ERGs, and VEPs were performed to characterize VGB effects. The VGB dose was adjusted to achieve the "optimum" dose for each patient. The total daily dose did not exceed 100 mg/kg/day or 6g, whichever was less.

ERG flicker amplitude decreased on average from 83 μV to 69 μV in patients followed longitudinally for 1 year (N=88). Flicker amplitude decreased in more than twice as many eyes as it increased (Table 12).

Table 12: Flicker Amplitude, Study 0201

	Flicker	
	Right eye (n=80)	Left eye (n=81)
Increase	8.8	8.6
Decrease	16.2	22.2

Table 12: Percent of eyes showing >44% change in flicker amplitude [From 'Study 0201a3.pdf]

13/69 with visual field tests had at least possible constriction. 11 of these 13 had progression of ERG abnormalities during the study. 23 of 51 patients with normal fields also showed ERG progression.

Snellen visual acuity was measured at baseline and end of study. The sponsor notes that acuity results could vary based on the subjective nature of the test, skill of examiner, and proper spectacle correction. There were 13 patients with greater than 2-line change in acuity in one or both eyes: 6 patients with a positive change, and 6 with a negative change.

Reviewer discussion

ERG findings support a positive association between VGB exposure and retinal damage, but the sensitivity and specificity of ERG testing didn't appear to be high enough for a useful clinical test (apparently false-positive ERG progression occurred in nearly half the patients).

7. ERG/Visual Field Correlation

ERG is an objective test of retinal function that does not require patient effort. The sponsor proposes ERG as the primary method of monitoring for VGB adverse visual events in young children and adults who are unable to perform perimetry. The sponsor asserts that specific ERG abnormalities, particularly 30 Hz flicker, have been shown to correspond with the VGB-induced VFD. The sponsor cites in particular the following published studies:

- *Comaish IF, Gorman C, Brimlow GM, et al. The effects of vigabatrin on electrophysiology and visual fields in epileptics: A controlled study with a discussion of possible mechanisms. Doc Ophthalmol 2002;104:195-212*

Reviewer: Moderate correlation (r = 0.65) was found with cone maximal response b-wave amplitudes. However, a clinical test based on this strength of correlation would have poor sensitivity and specificity (as illustrated below in the discussion of Miller et al., 1999, which presented more detailed data).

- *Krauss GL, Johnson MA, Miller NR. Vigabatrin associated retinal cone system dysfunction: Electroretinogram and ophthalmologic findings. Neurology 1998;50:614-8.*

Reviewer: This paper does not give adequate information to determine strength of association between ERG findings and visual field defect.

- *Harding GFA, Wild JM, Robertson KA, et al. Electro-oculography, electroretinography, visual evoked potentials and multifocal electroretinography in patients with vigabatrin-attributed visual field constriction. Epilepsia 2000;41:11:1420-31*

Reviewer: 7 of 8 patients in the study had severe field constriction to within 10-15 degrees of fixation. The findings therefore don't address the sensitivity of ERG for detecting VGB before it is severe, which would much of the point of safety monitoring. Of note, the multifocal ERG data from patients with severe field constriction showed damage to the macula.

- *McDonagh J, Stephen, LJ, Dolan FM, et al., Peripheral retinal dysfunction in patients taking vigabatrin. Neurology 2003;61: 1690-1694.*

The sponsor asserts that this study documented that the VFD corresponds with abnormalities of flicker response.

Reviewer: The referenced study does not support a strong correlation between visual field defect and flicker response; most patients with visual field defect had flicker response in the normal range (Figure 6).

Figure 6: Visual Field/ERG Correlation, McDonagh Data

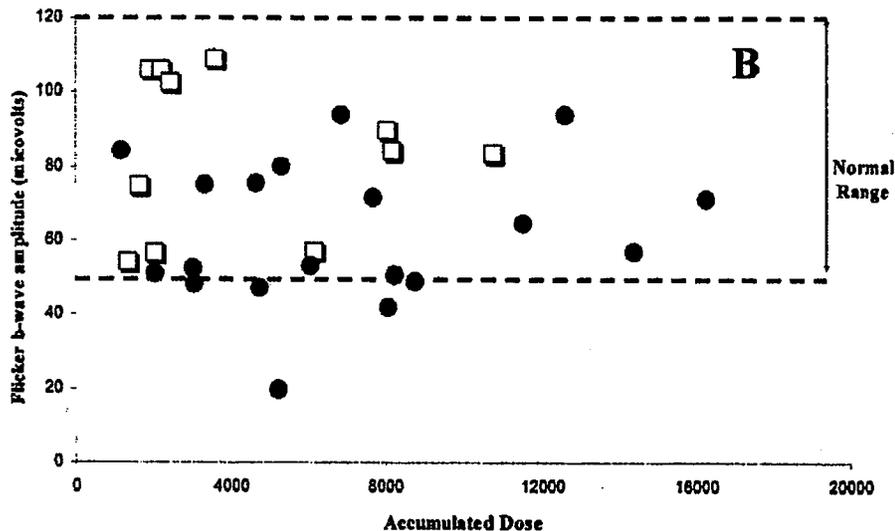


Figure 6: VGB patients with (solid circles) and without (open squares) bilateral visual field defects.

- Miller NR, Johnson MA, Paul SR, et al. Visual dysfunction in patients receiving vigabatrin: Clinical and electrophysiologic findings. *Neurology* 1999;53:9:2082

This study found a correlation between ERG flicker response and degree of visual field constriction (Figure 7), with $r \approx 0.68$.

Reviewer: While this r-value indicates a moderate correlation, it does not appear to be high enough to allow reliable conclusions about visual field based on flicker ERG data. For example, if 40 µV is considered upper limit of normal based on the control patients (Figure 7, triangles), then most VGB patients would be considered abnormal, even though nearly half the patients would have visual field results indistinguishable from normal (>50 mean radial degrees). Lowering the upper limit to 20 or 30 µV doesn't particularly improve the test, since that voltage could correspond to a visual field ranging from severely affected to normal.

Figure 7: Field/ERG Correlation, Miller et al., 1999

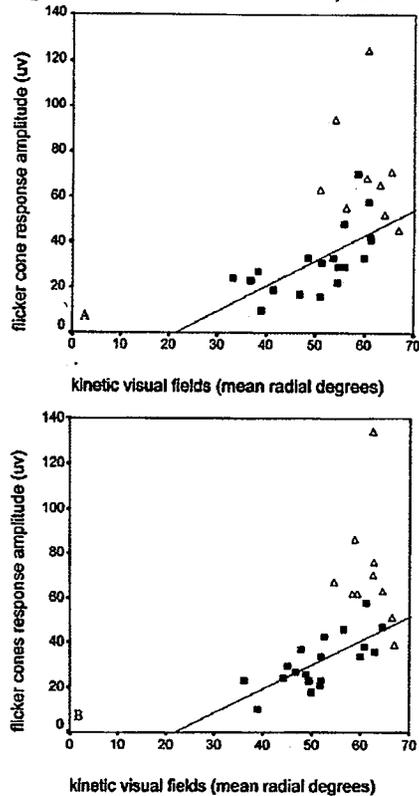


Figure 7: Filled squares are VGB patients, and triangles are controls. Right (top) and left (bottom) eyes shown separately.

- *Ponjavic V, Andreasson S. Multifocal ERG and full-field ERG in patients on longterm vigabatrin medication. Doc Ophthalmol 2001;102:63-72*

The sponsor asserts that this paper reported that full-field ERGs are effective in monitoring the reduction in b-wave amplitude in patients over time. The paper reported that in 12 patients, 100% of patients with field defects had reduced 30 Hz flicker amplitude in at least one eye and that no patients with normal fields had reduced 30 Hz flicker amplitude.

Reviewer: The field defects were severe. The findings therefore do not address how ERG might perform in early detection of VGB visual damage.

- *Brigell MG, Wild JM, Ruckh S. The effect of vigabatrin on visual function data from a long-term open-label add-on trial in patients with uncontrolled partial seizures [abstract]. Neurol 2000;54;S3:A308*

The sponsor asserts that Brigell used a combination of flicker amplitude and latency measurements of cone system and reported a 71% sensitivity of the ERG to monitor for the presence of the peripheral VFD in their patients.

Reviewer: This report is a brief meeting abstract, without adequate detail for interpretation.

- *Parks S, McDonagh J, Dolan F, Dutton GN, Keating D, Brodie M.J. Separating the transient physiological effects and retinotoxic effects of vigabatrin related retinal dysfunction using the wide field multifocal ERG. Invest Ophthalmol Vis Sci 2003;44:2721 [Abstract]*

The sponsor asserts that this report found that 30 Hz flicker amplitude was the most sensitive predictor of peripheral VFD, with a threshold of <0.52 microvolts, the predictive value had a sensitivity of 100% and a specificity of 75%. Adding photopic a-b wave amplitude or the first oscillatory potential, the specificity could be increased to 83%.

Reviewer: This report is a brief meeting abstract, without adequate detail for interpretation.

Reviewer Discussion, ERG Flicker Testing

This review finds little evidence that serial ERG monitoring would allow for reliable early diagnosis of VGB retinal damage. The available data suggest that ERG testing for anything other than severe VGB retinal damage would likely generate a high proportion of false-negative and false-positive results.

8. H-Stimulus

H-stimulus is a VEP method that compares peripheral and central retina. The stimulus consists of a central area from 0-5 degrees, an annulus of neutral density, and an outer stimulus from 30-60 degrees. The child needs to be cooperative and to look at the central stimulus. The sponsor asserts that it has been validated for assessing peripheral VFD in children 3 to 10 years of age with a sensitivity of 75% and a specificity of 87.5%.

The sponsor indicates that this technique is in use in Europe and Canada, and can also be used in adults with cognitive difficulties who cannot provide reliable perimetry data. The sponsor supports these assertions by citing the work of Harding, with two publications based on the same patients (Study 4102 in this submission is also based on the same patients. Only 4 pages of information were submitted for study 4102):

- Harding GFA, Robertson K, Spencer EL, et al. Vigabatrin: Its effects on the electrophysiology of vision. *Doc Ophthalmol* 2002;104:213-29

- Harding GFA, Spencer EL, Wild JM, et al. Field-specific visual-evoked potentials. *Neurology* 2002;58:1261-5

The study examined 39 children with epilepsy treated with VGB. The paper states that a number of the children were cognitively impaired, and that 35/39 could complete the task. The authors note that H-stimulus correctly identified 3 out of 4 children with abnormal visual fields, and 6 out of 7 with normal fields. No information was provided about the severity of the visual field abnormalities.

Reviewer: This study does not contain adequate information to determine if H-stimulus would be useful in detecting early VGB visual damage. Sensitivity and specificity estimated from the small number of subjects still suggests that false-negative and false-positive results may hinder clinical use.

Reviewer Conclusions and Discussion

H-stimulus is discussed only briefly in the submission as a potential method for monitoring for retinal damage. Insufficient data was provided to adequately evaluate the method.

Data was available from only one investigator, on only 4 children with a documented field defect. No information was provided about the severity of the visual field abnormalities, so it was not possible to determine if H-stimulus would be useful for early detection of VGB damage. The method requires patient cooperation, and would not be usable in many VGB patients, particularly those with IS. Also, many of the children started on VGB are under 3 years old and would not be eligible for the test on that basis.

9. Postmarketing Adverse Events Reports

Vigabatrin was initially approved in 1989 outside the United States, in Europe, Australia, Korea, Canada, and other countries. Adverse events occurring both in phase 4 studies and from spontaneous reports are included in Periodic Safety Update Reports (PSUR).

Estimated patient exposure was roughly 50,000-150,000/year between 1992 and 2005, peaking in 1998 and declining thereafter. Exposure data for the first 6 months of 2006 was expressed as 5.4 million treatment days.

The sponsor reports that information to estimate duration of VGB therapy prior to onset of visual field defect was provided in 519 postmarketing reports (54.1%). There were 23 reports of VFD within the first 6 months of the reported drug start date. In 9 of the 23 reports, the VFD onset was reported to be on the same date as the initiation of VGB therapy. Of the remaining cases, the earliest time from drug start date to reported event of VFD was 5 days. There were 13 additional cases that reported time to onset in less than 6 months. The sponsor concludes that insufficient information is known about the cases to adequately characterize the events or determine relationship to VGB.

Review agrees.

The PSURs generally contain a few reports of ‘serious and unlabeled’ events potentially representing visual adverse effects of VGB that are different from visual field constriction, as represented by the following examples:

- Patient 199710789
A 43 year old woman taking VGB for 4 years developed macular degeneration, and diminished vision in left eye.
- Patient 95001315
A 47 year old man developed bilateral optic nerve atrophy proceeded by blurred vision after 21 months of VGB. The macula appeared normal. Visual fields showed concentric, binasal constriction.
- Patient 199710611
A 60 year old man taking VGB 2 g/day for 5 years developed ‘senile macular degeneration’ that the investigator assessed as related to VGB. Other findings included abnormal color vision and bilateral visual field constriction with tessellated fundus in the periphery. The patient experienced no ocular symptoms.

Reviewer discussion.

VGB has rarely been associated in postmarketing adverse events reports with visual field defect within only a few days of initiation. However, it is not possible to determine from the available data the degree to which these reports represent false-positives, a common problem with testing for VGB field defects

There are few reports suggesting *severe* central acuity loss from VGB. To speculate, given the high level of awareness of VGB visual adverse effects, and the high degree to which central acuity loss would be symptomatic, it seems likely that more cases would have been reported if severe acuity loss occurred commonly.

10. Key Characteristics of VGB Visual Damage

a. Visual Acuity

The sponsor argues that central visual function is only rarely, if ever decreased from damage by VGB. The sponsor bases this conclusion in large part on result from study 4020, the Glasgow study, and the Westall Study.

The acuity data from study 4020 appear to be of poor quality. The submission states that “a retrospective quality control of the data revealed potential ambiguities in the recording of visual acuity and refraction.”

The Glasgow acuity data is presented only as summary statistics. While the data suggest that average visual acuity is not affected by VGB, the data does not exclude decreased acuity in a subset of VGB patients. Also, the overall protocol for the Glasgow study is not presented in sufficient detail to determine reliability of findings.

The Westall study was not able to record acuity from most patients, and only suggests that some children taking VGB likely retain at least near-normal visual acuity.

Reviewer discussion

The studies cited by the sponsor to support that visual acuity is not affected by VGB do not address the issue with much precision. Review of the overall safety database suggests that *severe* decrease in visual acuity from VGB is rare if it occurs at all. In contrast, some case series suggest that mild decrease in acuity may occur from VGB. For example, Miller et al.⁵ found 20 of 32 VGB patients to have visual acuity of 20/20 or better, while 12 of 32 had acuity ranging from 20/25 to 20/60 in one or both eyes. Matched control patients, in contrast, had normal acuity. Some degree of deficit in color vision also occurred in the patients of Miller et al.

b. Non-retinal visual system injury

Autopsy data including histology is available from a single patient with VGB field defect. The retina was severely atrophied, but there was no evidence for intramyelinic edema in brain sections.

Reviewer discussion

VGB clearly causes retinal and optic nerve injury. While the optic nerve injury might result solely from loss of retinal ganglion cells, direct toxicity to the optic nerve can not be excluded. Visual evoked potentials generally do not show conduction delay in cases of VGB field defect, but while this suggests that intramyelinic edema is not occurring, it does not rule out other toxic effects of VGB directly on the optic nerve. Damage to higher visual centers has not been identified, but has not been studied in detail.

c. Reversibility

The sponsor argues that little is known about the extent to which VGB-induced VFD improves after discontinuation of VGB, but acknowledges that in most reports loss of function has remained after stopping VGB.

Reviewer discussion

Although measurement error in field testing can be considerable, VGB visual field defects appear to be essentially irreversible. There is no persuasive evidence that clinically meaningful recovery can occur.

d. Latency

The sponsor argues that visual field constriction does not begin immediately upon initiation of VGB-therapy but occurs slowly, with average onset after several years of treatment. The sponsor cites results from study 4020, stating that the earliest time to onset from that study as 12 months. The sponsor also states that Kinirons et al (2005)⁶ found in a longitudinal study of 93 adults that earliest onset occurred at 13 months.

⁵ Miller NR et al., Visual dysfunction in patients receiving vigabatrin. *Neurology* 1999;53:2082

⁶ Kinirons et al., Vigabatrin retinopathy in an Irish cohort: Lack of correlation with dose. *Epilepsia* 2006, 47:311-317.

Reviewer Discussion

This review concludes that there is little reliable data about the risk of early onset of vigabatrin visual damage. In study 4020, average time of VGB treatment before enrollment was 2- to 4 years, such that the study was poorly designed to measure earliest onset of field defect. Kinirons et al. state that the majority of patients in their study had been taking VGB for a number of years before testing, and that little data was available on how quickly constriction develops.

As discussed under individual studies above, some patients appear to develop constriction after less than 2 months of VGB treatment. For example, subject 405003 from the prospective study R003, and subject 006 from study 4020 each appeared to develop field defect after less than 2 months of VGB treatment.

The 'Pooled Cohort study discussed above suggested that the peak incidence of field constriction occurred at just less than 1 year. This is supported by study R003, in which 5 of the 7 field defects were diagnosed before or shortly after 1 year of treatment

The uncertain sensitivity and specificity of ERG testing in children prevents reliable estimate of latency of visual damage, as discussed in detail above under the Toronto Study.

e. Progression with Continued VGB use

The sponsor notes that the prevalence of VFD increases in subjects who continue VGB therapy. While some published reports found no progression of VGB damage with continued use of VGB, others suggested deterioration occurs if VGB is not stopped. The sponsor notes that study 4020 showed deterioration of fields while subjects were on VGB, but not following discontinuation of the drug. However, the sponsor points out that inconclusive or unconfirmed perimetry results hinder interpretation.

Reviewer discussion

Progression of VGB damage appears to occur in both adults and children that continue VGB treatment; normal patients develop field defects, and existing field defects worsen. However, the degree and proportion of patients progressing has not been reliably quantified. For example, study 4020 found that 35% of patients with field defects that remained on VGB progressed, compared to 13% who never took VGB. While most or all of the 'progression' in patients never on VGB was likely attributable to testing variability, the much higher rate of progression in patients continuing VGB indicates that progression likely occurred in subjects remaining on drug.

Notably, field loss appears to develop over a short period of time in some patients, and then to slow or even stop despite continued VGB use. For example, Best and Acheson (2005) identified 16 patients who continued taking VGB for at least 5 years (range 5-12 years) despite having developed field defects. Patients were followed with serial kinetic fields for an additional 18-43 months while continuing VGB. Mean visual field remained fairly

constant, about 37 degrees, over the course of the study, but one of the 16 patients deteriorated. That patient had been treated with 1.5 g/day VGB for 8 years before enrollment, and deteriorated from a 36 degree to a 23 degrees field over 19 months of study. This case suggests that even for patients with seemingly stable field defects, progression to severe defects may occur relatively suddenly, and may not be preventable by visual field monitoring.

The time course of field progression is of critical importance in safety testing. With gradual deterioration, periodic testing might detect early damage, allowing drug to be stopped before severe damage develops. In contrast, if damage occurs rapidly and then remains fairly constant, periodic testing may not effectively catch early damage, and instead may only confirm that severe damage has already occurred. Adequate data on which to base screening recommendations is lacking about the time course of field progression.

f. Progression after Stopping VGB

The sponsor notes that VGB-induced VFD clearly does not progress inexorably after the defect has occurred, and that most reports indicate no progression of VGB field defect once drug is stopped. However, the sponsor cites several publications suggesting progression can occur despite stopping VGB (for example, two cases reported by Malmgren et al.⁷). The sponsor also notes that visual field in one patient in study 4020 (subject 016-067) appeared to progress after stopping VGB. The patient was first examined 2.5 years after discontinuation of VGB, and was found to have lateral field to 36 degrees. On repeat testing 1.5 years later lateral vision was about 15 degrees. The sponsor suggests that this case illustrates that progressive visual defects may occur in some individuals many years after exposure. However, the sponsor indicates that since only a small number of late onset peripheral defects or cases of pre-existing defects have been reported, a causal relationship between VGB therapy and progression of defect due to VGB cannot be established without further study.

Reviewer discussion

Even slow worsening of vision, or worsening in a minority of patients after stopping VGB, would greatly increase the overall risk of the drug to vision. Evidence is clear that in *most* patients vision does not *rapidly* deteriorate after stopping VGB. Critically, however, available data does not reliably address the potential that many patients may slowly worsen, or that rare patients may quickly worsen after stopping VGB.

Meaningful reassurance derives from the fact that in almost 2 decades of marketing, thousands of exposures in trials, and marketing exposure of roughly 350,000 patients, there is little reliable evidence of severe visual deterioration after stopping VGB. Unlike field defect, severe bilateral *acuity* loss is almost invariably symptomatic, and seemingly would have been reported. Importantly, however, this reassurance must be tempered by the fact that severe acuity loss in VGB patients might often be wrongly attributed to glaucoma or

⁷ Malmgren K, Ben-Menachem E, Frisén L. Vigabatrin visual toxicity: Evolution and dose dependence. *Epilepsia* 2001;42:609-15

macular degeneration. Since glaucoma and macular degeneration are common in the general population, careful comparison to expected incidence would be necessary to detect even fairly large increase in risk.

Over several decades after VGB exposure, the issue of progression of VGB damage can't meaningfully be separated from the 'true' occurrence of glaucoma or macular degeneration. Expectation would be that the overall clinical course of otherwise unrelated eye disease would be more severe in combination with pre-existing VGB damage. For example, *central* vision loss from age-related macular degeneration might result in loss of *almost all* vision in VGB patients with pre-existing *peripheral* loss. The prevalence of ARMD increases rapidly with age, from about 2% in the sixth decade, to about 10% in the seventh, and 30% in the eighth.

g. Exposure

The sponsor notes that extreme ranges of dosing and duration of therapy have been shown to be associated with VFD, and that in some ways the adverse event resembles an idiosyncratic drug reaction. Since many individuals do not develop a VFD after years of treatment and many kilograms of drug, it is clear that toxicity is not simply dose-related. However, the sponsor notes that many, but not all studies have found an association between severity, duration of use, total dose, and less clearly, higher daily dose.

The sponsor proposes that if exposure time is short enough, on the order of a few days or weeks, there would be little risk to vision while efficacy of VGB could be established in the patient.

Reviewer discussion

For the exposures studied, a weak positive correlation appears to exist between field damage and time of exposure, cumulative dose, and daily dose. Since a broad range of exposures is associated with VGB damage, the correlation is not likely to be useful clinically at exposures commonly used in epilepsy.

As a special case, the sponsor proposes that very short exposure of only a few days or possibly weeks carries little risk of visual damage. Since VGB hasn't been used in this way, no direct evidence addresses the issue. While the range of VGB exposures associated with visual damage is remarkably large (including postmarketing reports of onset on the first day of treatment), there is no convincing evidence of 'paroxysmal visual loss' from a single or very few doses of VGB. At some minimum exposure, risk of consequential visual damage likely approaches nil; however, the risk at any given exposure is unknown.

h. Gender

The sponsor notes that several studies have found the risk of VGB field defect to be about 1.5-fold higher in males versus females.

Reviewer discussion

Increased risk in males has been found in several studies. However, since studies were not adequately controlled, the possibility remains that the finding was due to undetected bias.

i. Mechanism of retinal injury from VGB

The mechanism of retinal injury from VGB is unknown. VGB inhibits GABA-transaminase, and leads to increases in retinal and vitreal concentrations of GABA in animals. High levels of GABA, however, have not been demonstrated to be retinotoxic. Vigabatrin has been associated with extensive pathological changes in all portions of the retina, including the ganglion cells and other cells in both the inner and outer retina.

11. Functional Correlates of VGB Field Loss

The sponsor notes that most patients with VGB field loss are asymptomatic, and suffer no significant functional impairment, but that in a minority of cases, field defect is sufficiently severe to hinder daily activities. The sponsor concludes that functional impact of the defect is relatively small since central, high acuity vision is spared.

Questionnaires probing for symptoms of visual disability demonstrated no evidence that the presence of VGB field loss conferred any functional impairment, but the sponsor acknowledges that investigators thought the questionnaires not to be validated measurement instruments, and to have poor sensitivity and specificity.

Reviewer discussion

Most patients with VGB field loss are asymptomatic, but little reliable data addresses the proportion with symptoms, or the severity of patient disability. A proportion of seemingly asymptomatic patients may actually be symptomatic from field loss, but not realize that symptoms are of visual origin, instead attributing them to clumsiness or drowsiness. In other cases, field loss may be experienced by the patient as blurry vision or oscillopsia. Patients who are initially asymptomatic frequently become symptomatic after diagnosis of visual field defect, potentially after realizing the true cause of their problems.

Overall visual ability might reasonably be considered as the relatively independent sum of central acuity and extent of peripheral visual field. Central acuity is critical for functions like reading and recognizing faces, while peripheral field is critical for functions associated with mobility and orientation. Studies of the impact of visual field loss in glaucoma patients may be relevant for understanding the impact of field loss from VGB, although visual field loss in glaucoma is often asymmetric, both between eyes and between superior and inferior hemifields, such that remaining field in one eye or hemifield could compensate for loss in the other. Theoretically, disability from VGB might be greater because field loss is bilateral and symmetrical. With such caveats in mind, field loss from glaucoma has been shown to increase the likelihood of bumping into objects, and to decrease walking speed. Importantly, however, even bilateral glaucoma is not usually associated with needing help from others for self-care (e.g. eating, bathing), doing household chores, shopping, or doing

necessary business (Freeman et al., 2008⁸). Figure 8 suggests that overall visual function, as measured by an instrument querying about difficulty with tasks such as reading, driving, walking, and preparing meals, is on average maintained even with severe binocular field loss. *Importantly, however, a significant minority of glaucoma patients report difficulty with visual tasks even with 50% or more of visual field preserved.*

Figure 8: Activities of Daily Vision Scale Versus Binocular Visual Field in Glaucoma

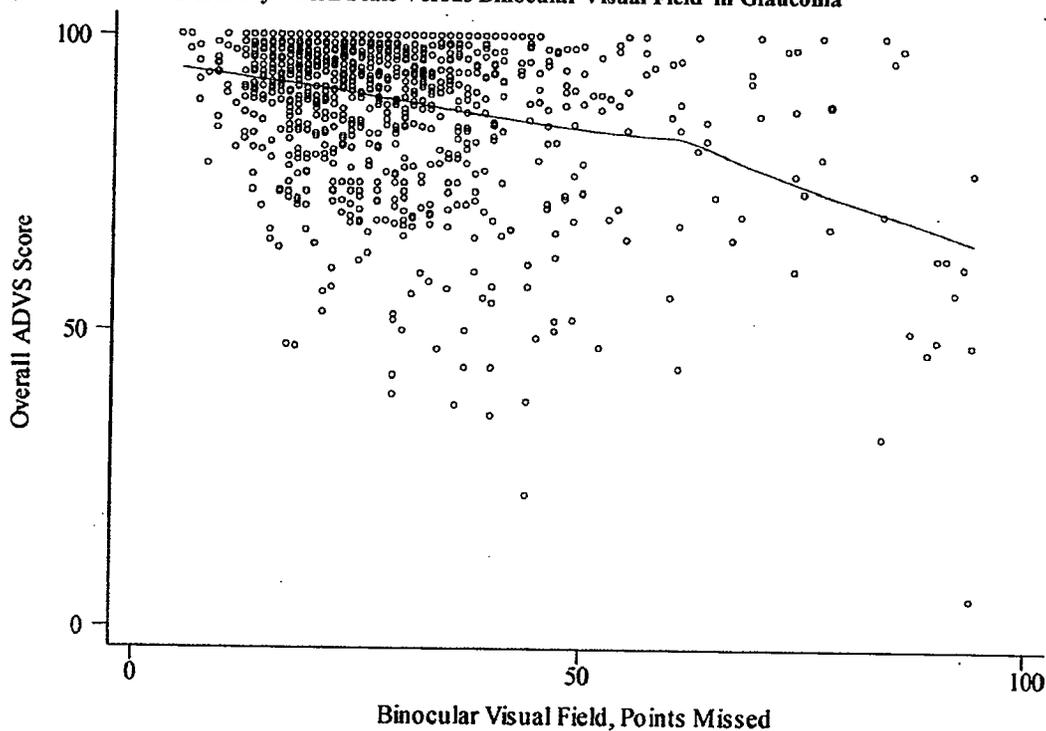


Figure 8: Scatter plot of overall Activities of Daily Vision Scale score by binocular visual field score, represented by 96 points to 60 degrees in the periphery. From Freeman et al., 2008

The relationship between visual loss and clinical disability depends on how well adaptive behaviors can be used to compensate for the visual loss. Impaired visual function can limit a person's ability to perform a specific activity, but it does not necessarily limit that person's ability to achieve the goal of that activity. Therefore, the overall negative impact of visual field loss for a given patient might be less than limitations in specific activities would at first suggest. Of concern, some patients with epilepsy, particularly patients with IS and mental retardation, might be less able to compensate for visual field loss than glaucoma patients. Little data is available to address this issue, but case reports from the Toronto group suggest that visual disability from vigabatrin in IS patients can be profound⁹.

⁸ Freeman EE et al., Glaucoma and Quality of Life. Ophthalmology 2008;115:233-238.

⁹ Buncic et al., Characteristic retinal atrophy with secondary 'inverse' optic atrophy identifies vigabatrin toxicity in children. Ophthalmology 2004;111:1935-1942.

Particularly as patients with VGB field loss age, the risk of falling may be expected to increase compared to persons with full visual fields. In the elderly, mobility problems are also associated with loss of independence, depression, and overall decrease in health.

As a final note, while for legal purposes (e.g. the U.S. Social Security Administration) an eye that has a visual field limitation to 20 degrees is considered as having visual acuity of 20/200 and of meeting the definition of legal blindness, there is no clinical basis for such a correlation.

12. Pregnancy

The sponsor indicates that it still remains unclear whether prenatal VGB exposure carries a risk for ophthalmic dysfunction. Ophthalmic abnormalities have been reported in the offspring of mothers using VGB during pregnancy, including strabismus, optic nerve pallor, nystagmus, and visual inattention.

A single published report describes ophthalmic exam results of two children exposed prenatally to VGB (Sorri et al., 2005¹⁰). These children showed no clear ophthalmic abnormalities, although perimetry and field-specific VEP were borderline.

Vigabatrin is excreted into breast milk in low concentrations. Based on vigabatrin breast milk concentrations from one patient, it was estimated that 0.3% of a daily maternal dose of 2 g daily would have been excreted into breast milk.

Reviewer discussion

Pre-natal exposure to VGB has not been clearly associated with visual damage, but the issue has not been studied in any detail.

13. Ophthalmic Safety Monitoring Plan in Adults

The sponsor asserts that either static or kinetic perimetry is sensitive and specific enough to be used to establish baseline and monitor peripheral vision in patients taking VGB. The following is the sponsor's ophthalmic safety monitoring plan for adults:

Patients should have baseline evaluation of vision by a testing method appropriate for their cognitive state. For the great majority of patients, that would mean some variety of perimetry examination such as static or kinetic perimetry. Appropriate methods have been published for perimetry as well as techniques suitable for cognitively impaired patients and will be in materials made available by Ovation Pharmaceuticals to vision specialists, neurologists and all others involved in caring for people with epilepsy.

¹⁰ Sorri et al., Ophthalmologic and neurologic findings in two children exposed to vigabatrin in utero. *Epilepsy Res* 2005;65:117-20.

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¹⁰ Sorri et al., Ophthalmologic and neurologic findings in two children exposed to vigabatrin in utero. *Epilepsy Res* 2005;65:117-20.

study R003 suggest that monitoring every 3 months might be able to detect moderate, but not early VGB damage; 3 of 7 defects were apparently not identified until fields had constricted to within about 20 or 25 degrees of fixation. Testing every 6 months, as proposed by the sponsor, might presumably worsen the performance of safety testing compared to study R003.

The time course of field progression is of critical importance in safety testing. With gradual deterioration, periodic testing might detect early damage, allowing drug to be stopped before severe damage develops. In contrast, if damage occurs rapidly and then remains fairly constant, periodic testing may not effectively catch early damage, and instead may only confirm that severe damage has already occurred. Susceptibility to VGB visual damage varies widely among patients. Adequate data on which to base screening recommendations is lacking. While frequent testing might improve the performance of safety monitoring, this would need to be demonstrated.

Perimetry is a difficult test for patients to perform, with a large learning effect. Anecdotal, successful perimetry is significantly more difficult in epilepsy patients, and 20% of patients may not be monitorable at all with perimetry. Wild et al.¹¹ in a discussion of perimetric monitoring for VGB field loss note that “the results of perimetry can often be inconclusive and frequently require one or more confirmatory repeat examinations, even though the results of the subsequent tests can remain equivocal.”

This raises the additional problem of obtaining reliable perimetry *when initiating* therapy with VGB. The first field exam that a patient performs often does not accurately reflect the extent of the visual field, or yields uninterpretable results. If the baseline results do not accurately reflect the intact field, detection of VGB damage over time would also not be accurate.

14. Ophthalmic Safety Monitoring Plan in Children

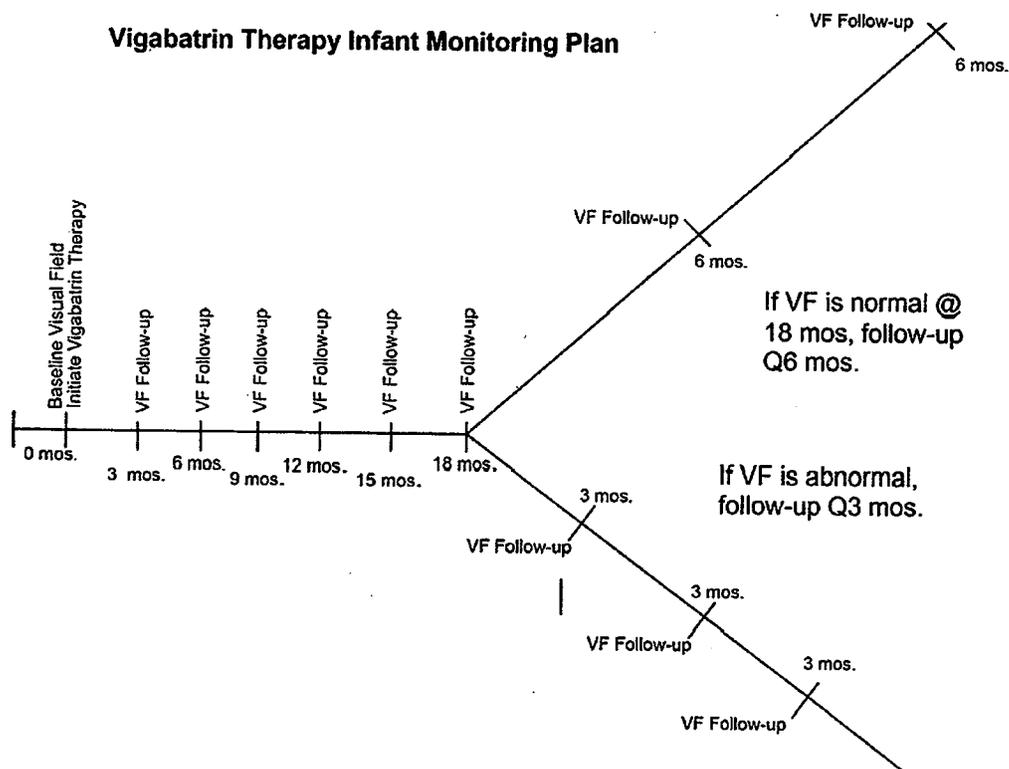
The following is the safety monitoring plan submitted by the sponsor for infants and young children:

Infants.

A baseline ERG evaluation with methods suitable for age should be performed. That baseline examination may occur up to 2 weeks before VGB therapy to a maximum of 3 months after initiation of therapy, although examination close to the onset of therapy is best. The evaluation should then be repeated every 3 months for the first 18 months, and then repeated every 6 months thereafter unless an abnormality is discovered. If abnormal, a repeat exam in 3 months and repeat exams at 3-month intervals if still abnormal are recommended. No testing is necessary in some clinical situations, such as in patients in whom vision is absent or when other

¹¹ Wild, JM. Detecting Vigabatrin Toxicity by Imaging of the Retinal Nerve Fiber layer. Invest. Opth. Visual Sci 2006;47:917-924.

clinical factors eliminate the need for visual testing. Examples of such cases would be in cortically blind children or infants in whom other conditions reduce the likelihood of a visual defect having an impact on function. Because of the potential relationship between the incidence of peripheral VFD and the total lifetime dose of VGB, patients should be given regular visual examinations throughout the entire course of therapy. If a peripheral VFD or retinal abnormality is identified in a patient, it is important to perform confirmatory testing in a timely fashion. If a defect is confirmed, both patient/caregiver and clinician should review both the benefits of therapy and the risk of visual injury to make a timely decision on continuation of therapy.



Reviewer Discussion, Ophthalmic Safety Monitoring in Children

The sponsor focuses on ERG 30 Hz flicker as the safety test of choice for VGB visual monitoring in subjects unable to perform perimetry. This review finds that monitoring with ERG flicker has not been established as an effective method for monitoring VGB retinal damage. The Westall data appear to show large inter-test variability, suggesting that sensitivity and specificity are low, and that ERG would not be able to reliably diagnose

VGB retinal damage until at best severe (Section 6a). The correlation between ERG and field loss is weak, (section 7), such that once abnormality is detected it might correspond to a large range of severity.

Studies on older children and adults who could perform perimetry suggest that ERG often fails to identify field defects. In study R003, ERG was able to detect zero of 3 mild defects, and only 1 of 3 moderate defects. In the Toronto study, a 10 year old girl with field constriction to within 30° of fixation had a normal ERG.

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this page is the manifestation of the electronic signature.**

/s/

Ronald Farkas
7/18/2009 08:57:17 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA: 20-427
Drug: Vigabatrin (SABRIL)
Route: Oral
Indication: Refractory complex partial seizures
Sponsor: Ovation
Review Date: 3/17/09
Reviewer: Sally Usdin Yasuda, Safety Team Leader
Neurology Drug Products, HFD-120

1 Background

Vigabatrin is an irreversible inhibitor of gamma-aminobutyric acid transaminase. In the current submission the Sponsor has provided a safety update for the NDA for which the Sponsor is seeking approval for treatment of refractory complex partial seizures in adults. The proposed initial dose is 500 mg BID and the proposed usually effective dose is 3 g/day (1.5 g BID). The NDA was submitted to FDA in 1994, and the application was found Not Approvable in 1995 due to deficiencies in the presentation of safety data, according to the background provided by Dr. Jerry Boehm in his review. Vigabatrin received an approvable letter in 1997 after addressing identified deficiencies. However, the Sponsor subsequently withdrew the application prior to approval in the US, due to the finding of permanent visual field defects. Ovation filed the present submission on 12/28/07. Vigabatrin is approved for use in over 50 countries and has been approved for use in the United Kingdom since 1989.

Dr. Boehm has reviewed the safety data except for visual field defects that are reviewed by Dr. Farkas and intramyelinic edema (IME)/MRI abnormalities that are reviewed by Dr. Phillip Sheridan separately. This memorandum summarizes the primary concerns from the safety review, conducted by Dr. Boehm, of the Sabril NDA (20-427) for complex partial seizures (CPS).

2 Summary of Findings from the Safety Review

2.1 Integrated Review of Safety

The current submission summarizes pooled safety data from 15 controlled and uncontrolled trials that included 2,148 subjects from studies in adults with CPS, children with CPS, infantine spasms (IS), and safety studies evaluating visual field defects, and these data were from studies not reported in previous regulatory submissions. The sponsor also submitted data analyses of pooled data from 80 epilepsy trials, including over 4000 vigabatrin exposed subjects dating back to the original NDA, at the request of the Division. The prior data (n=3,440) combined with the current data (n=2,148), results in the pooled integrated data (combined n=4,855). **According to Dr. Boehm's review, the Sponsor reported in the 5/1/08 submission that 3,476 epilepsy subjects were exposed for**

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at least 6 months (1,112 subjects at a dose between 3 to < 4 g/day) and 2,758 were exposed for at least 1 year (587 exposed to between 3 to < 4 g/day).

2.1.1 Deaths

According to Dr. Boehm's review there were 63 deaths in the integrated data pool of epilepsy study subjects. The most commonly reported causes of death were seizures (n=22), SUDEP (n=18), and respiratory events (n=4). Deaths due to hepatic failure were reported and occurred primarily outside of the clinical trials database; these deaths will be discussed later under *Hepatic Injury* in Section 2.1.7.

2.1.2 Serious Adverse Events

Dr. Boehm has presented serious adverse events (SAEs) among vigabatrin subjects from the integrated data pool of epilepsy study subjects (n=4737). The most common SAEs were visual field defect (6.8%), convulsions (2.8%), and status epilepticus (1.6%). In a pooled comparative analysis of SAEs using 12 controlled trials, SAEs of status epilepticus, depression, confusional states, bronchitis, pneumonia, and fatigue occurred more frequently among vigabatrin subjects than placebo subjects. In postmarketing reports, the most commonly reported SAEs were visual field defect and convulsions. Visual field defects were reviewed in detail by Dr. Ron Farkas and will not be further discussed here.

Dr. Boehm has also summarized less frequent but potentially concerning SAEs. These included rash maculopapular that was not well documented with respect to diagnosis for the rash or how the rash was treated; leukocytoclastic vasculitis, not documented with supporting objective data, which occurred following administration of vigabatrin for 23 days and resolved 4 days after discontinuation of vigabatrin; and 1 case of Stevens Johnson syndrome. The Stevens Johnson case (Subject 0201/1398-0009), as Dr. Boehm noted, was in a 12 y.o. patient and occurred in April 1997 after 3 months of treatment with vigabatrin in the open label long-term follow up study 0201. The patient entered this study after participating in the Phase 3 controlled study 0221 and receiving vigabatrin for 117 days. The patient was also taking lamotrigine and carbamazepine at the time of the event. However, the patient had been taking Lamictal for more than 1 year (since March 1996) at the time of discontinuation and had taken carbamazepine for longer than that (since some time in 1995) according to the documentation of concomitant medications. Approximately 3 months after discontinuation of vigabatrin, the patient was hospitalized for conjunctivitis and stomatitis and erythema and those events resolved within 1 week. At that time the patient was taking Depakote that was started in April 1997 just after the first event. It is difficult to determine whether the adverse event in April 1997 was due to vigabatrin.

Two subjects had anemia SAEs. One of those had a history of anemia requiring iron replacement and had an AE of anemia while being treated with vigabatrin. A second subject had acute anemia due to epistaxis. Dr. Boehm points out that neither of the cases had sufficiently detailed supporting data. There was also a SAE case of decreased platelet count. All 3 cases resulted in discontinuation. There were no SAEs of aplastic anemia.

Other SAES included a case of drug hypersensitivity that included findings suspicious for angioedema (lips, tongue, and gum swelling with generalized itchy rash) in a patient with a history of "drug allergies". This began after the first and second doses of study drug, after which the subject was discontinued from the study, a Phase 4 observational study. The reaction was treated with Solumedrol, Benadryl and prednisone and resolved. An additional case of tongue edema provided insufficient clinical details to evaluate the event. Angioedema is included as a SAE in the postmarketing AE section of the label.

There was one SAE of hepatic failure and hepatic necrosis (in a patient who had experienced status epilepticus) included as a death. This was unlikely to be due to vigabatrin.

2.1.3 Dropouts and Other Significant Adverse Events

The most common AEs leading to discontinuation among vigabatrin subjects in the integrated data pool of epilepsy subjects were depression (1.5%) and convulsion (1.4%). Vigabatrin subjects discontinued from controlled trials more frequently than placebo subjects, with depression, headache, agitation, confusional state, and status epilepticus leading to discontinuation more commonly among vigabatrin subjects than control subjects.

2.1.4 Common Adverse Events

Dr. Boehm was noted that, in general, the proportion of subjects reporting AEs was higher in the prior data compared to the current data. On further review by Ovation, the sponsor felt this was mostly due to higher vigabatrin doses in prior data studies and underreporting of AE risks in study 4020 that was included in the current data. In the integrated data pool, adverse events occurring most commonly (>5%) included headache, somnolence, fatigue, dizziness, nystagmus, tremor, coordination abnormal, memory impairment, depression, disorientation, diplopia, weight increased, and vision blurred. In placebo controlled trials, these occurred to a greater extent in vigabatrin treated subjects than in placebo treated subjects. In a pooled comparative analysis of 12 trials, peripheral edema was observed in 4.1% and occurred to a greater extent in vigabatrin treated subjects than in placebo; peripheral edema will be further discussed in Section 2.1.7. In some cases, some evidence for a dose response relationship could be observed from fixed dose randomized placebo controlled studies, although as Dr. Boehm states, the small number of outcomes precludes drawing firm conclusions about dose response.

2.1.5 Laboratory findings

There were several laboratory changes of concern as presented by Dr. Boehm, and these will be summarized below.

Hemoglobin/Hematocrit: Decreases in hemoglobin and hematocrit were observed from baseline to end of study in U.S. controlled epilepsy studies. The observed decrease demonstrated a dose-response relationship. Mean changes in hemoglobin and hematocrit were observed in the adult population and in the pediatric non-IS population.

For the U.S. controlled epilepsy studies, these changes, as presented in on p. 68 of Dr. Boehm's review are shown in the table below.

Hematocrit and Hemoglobin Change from Baseline to End of Study by Dose, US Controlled Epilepsy Studies

		US Controlled Epilepsy Studies (024, 025)				
Parameter		Placebo	1g VGB	3g VGB	6g VGB	All VGB
Hematocrit	Change from baseline	0.53	0.58	-0.24	-1.39	-0.29
Hemoglobin	Change from baseline	0.02	-0.12	-0.44	-0.91	-0.46

Source: 5/31/97 Submission, table B-47

Vigabatrin subjects also had higher risks for low hemoglobin and hematocrit result outliers. Three vigabatrin subjects in the integrated database experienced anemia SAEs and 3 from the integrated database discontinued for anemia AEs. Dr. Boehm notes that for anemia adverse events there were no follow-up relevant lab tests. Only 2 vigabatrin subjects had unexplained declines in hemoglobin below 8 g/dL or hematocrit below 24%.

Dr. Boehm has recommended that any ongoing or planned vigabatrin clinical trials should incorporate monitoring of relevant hematologic parameters and that 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. *I agree with Dr. Boehm's recommendation.*

The sponsor has identified anemia under "Other Adverse Events ($\geq 1\%$) Observed During Clinical Trials" in section 6.2 of the proposed labeling. Dr. Boehm has added a section describing the laboratory findings and clinical events under Warnings and Precautions. *I agree with Dr. Boehm's recommendation.*

Liver Function Assessments: Dr. Boehm has noted a reduction of transaminases ALT (SGPT) and AST (SGOT) that appears to be dose related. The mean changes, as provided on p. 68 of Dr. Boehm's review are shown in the table below, from U.S. Controlled epilepsy studies 024 and 025. Similar changes in transaminases were also observed in the pediatric non-IS population. In terms of outlier analysis, Dr. Boehm notes that in the North American Controlled trials, 94% (263/280) of subjects had a 60-100% maximum decrease in ALT compared to baseline, and 4% had an ALT result of 0. In placebo subjects, 78% had a 0-40% maximum decrease in ALT compared to baseline. The decreases in ALT occurred within the first 3 weeks of therapy, with the maximum decrease within 4-8 weeks. The onset of the drop in AST was 4-8 weeks after starting therapy and 40% reached their maximum decrease during this period.

Mean Change from Baseline for AST and ALT, Studies 024 and 025

Parameter	Placebo (n=135)	VGB 1g/d (n=45)	VGB 3g/d (n=135)	VGB 6g/d (n=41)	All VGB (n=221)
AST	-0.18 \pm 4.34	-1.51 \pm 5.53	-3.65 \pm 6.05	-3.88 \pm 4.35	-3.26 \pm 5.71
ALT	-0.07 \pm 8.12	-11.82 \pm 9.30	-16.23 \pm 10.10	-19.12 \pm 12.88	-15.87 \pm 10.72

Source: 5/31/97 Submission, table B-42, p.SB-V2-P273.

The decrease in AST/ALT is likely due to an interaction directly with these transaminases. This inhibitory interaction has been demonstrated *in vitro* (measuring these enzyme activities in human serum in the presence or absence of vigabatrin).¹ The relevance of this is that ALT/AST will not be reliable as early markers for liver disease or drug-induced hepatotoxicity.

The Sponsor was asked to identify the number of vigabatrin clinical trial subjects with evidence of hepatic injury as defined by elevation of AST or ALT to 3X ULN and elevation of total bilirubin to 2X ULN.

According to Dr. Boehm's review, the sponsor reported that no vigabatrin subjects in the development program met these criteria. In addition, transaminase and total bilirubin high outlier results were uncommon among the subjects enrolled in the pool of vigabatrin controlled clinical trials, as shown in the table below extracted from Dr. Boehm's review (n=number of subjects with specified abnormality; N=number of subjects normal at baseline).

However, as Dr. Boehm points out and as discussed above, these results need to be considered with respect to the interference with transaminase laboratory determinations. Please refer to discussion of hepatic injury in Section 2.1.7, below.

	Vigabatrin (N=952) n / N (%) ^a
ALT (SGPT) (U/L)^a	
>1.5x ULN	4 / 892 (0.45)
>3x ULN	1 / 892 (0.11)
>5x ULN	0 / 892 (0.00)
>10x ULN	0 / 892 (0.00)
>20x ULN	0 / 892 (0.00)
AST (SGOT) (U/L)^a	
>1.5x ULN	2 / 778 (0.26)
>3x ULN	2 / 778 (0.26)
>5x ULN	1 / 778 (0.13)
>10x ULN	0 / 778 (0.00)
>20x ULN	0 / 778 (0.00)
Total Bilirubin (mg/dL)^b	
>1.5x ULN	1 / 927 (0.11)
>2x ULN	0 / 927 (0.00)
Either AST or ALT > 3x ULN with Total Bilirubin > 1.5x ULN	0 / 916 (0.00)

2.1.6 Vital Signs and ECG

Heart Rate, Systolic and Diastolic Blood Pressure, and Respirations

Through the original NDA and NDA Amendment Dr. Boehm does not find a clinically relevant relationship between vigabatrin and mean vital signs changes (pulse, systolic and diastolic blood pressure, respiration) in mean changes. In the current submission, in 1 small controlled trial (Study 0222) there was a larger mean decrease in systolic and diastolic blood pressure in vigabatrin patients (n=9) vs gabapentin patients. In controlled trial 0223 there was not a dose-dependent change in systolic or diastolic blood pressure or pulse. In the pediatric non-IS controlled studies, there did not appear to be consistent differences between vigabatrin and placebo for systolic and diastolic blood pressure, heart rate, and respiration. There did not seem to be a consistent signal in the few outliers identified in the outlier analyses.

Weight Gain

The NDA and NDA Amendment did not evaluate mean changes in weight. In the current submission, in 1 small controlled trial (Study 0222) there was a larger increase in weight (mean change of 5.63 lbs for vigabatrin; n=8) vs gabapentin (mean change of -1 lb; n=9). In controlled trial 0223 there was a dose-response for weight increase that was up to an

¹ Richens A, McEwan JR, Deybach JC, Mumford JP. Evidence for both *in vivo* and *in vitro* interaction between vigabatrin and alanine transaminase. Br J Clin Pharmacol 1997; 43:163-168.

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average of 3.8 lbs for the 6g/day group. In the pediatric non-IS controlled studies, there appears to be a vigabatrin associated increase in weight, with the greatest changes in the pediatric population occurring in the ≥ 12 y.o. group. In this age group in Study 0118 there was a mean increase of up to 9.7 lb (n=11) on 100 mg/kg/day vs -1.9 lb (n=10) for placebo. In Study 0221 this age group gained an average of 3.3 lbs for vigabatrin (n=15) compared to 1.2 lbs for placebo subjects (n=12).

In terms of outlier analysis, the NDA review showed that 47% of patients on vigabatrin vs only 15.8% of placebo patients in the US epilepsy controlled trials had a weight increase of 7-15%. In the current submission, 31 subjects (0.64%, 31/4,855) discontinued from trials included in the Integrated Population for weight increased and 1 subject (0.02%, 1/4,855) discontinued for weight decreased. Dr. Boehm also notes that in the Integrated database, 10.2% of vigabatrin subjects had a weight increased AE.

The Sponsor was asked to further examine the relationship between weight gain and vigabatrin, and examined weight gain in 1843 vigabatrin subjects (excluding data from IS studies and from infants in non-IS studies, and excluding studies that did not include at least 1 baseline and 1 post-baseline weight measurement). In that analysis, 26.3% (484/1843) vigabatrin subjects gained $\geq 7\%$ weight compared to baseline. An analysis of 9 randomized controlled trials showed similar results as shown below in the Table from Dr. Boehm's review.

Weight change by sex, from 9 randomized controlled vigabatrin trials

% of Subjects that gained $\geq 7\%$ compared to baseline			
Sex	Vigabatrin	Placebo	RR
Male	17.1% (38/215)	8.5% (11/130)	2.0
Female	17.1% (39/228)	7.6% (11/145)	2.3
Mean weight change from baseline (kg)			
	Vigabatrin	Placebo	Vigabatrin-Placebo
Male	3.0	1.8	1.2
Female	3.9	1.5	2.4

Source 5/23/08 submission, Tables 3.3, 3.4, p.11

An analysis that stratified subjects into age groups of < 18 years, 18-45 years, and 46-64 years showed that the relative risk for weight gain of $\geq 7\%$ weight compared to baseline was greatest in the 18-45 year group but that the mean weight gain relative to placebo was similar in all three groups.

The Sponsor has only included weight gain in a list of the most commonly occurring adverse events. Dr. Boehm proposes language for Warnings and Precautions. *I agree with his recommendation. In addition, changes in lipids and glucose are not routinely available in this database, and as Dr. Boehm points out, long term consequences of vigabatrin-related weight gain in terms of cardiac and metabolic risk are not known. This type of metabolic data should be included in future studies of reasonable duration.*

ECGs

The non-clinical and clinical studies conducted during the vigabatrin development program preceded the recently developed guidelines regarding evaluation of QT prolongation. However, according to Dr. Boehm's review, Ovation reported no significant adverse cardiac findings in nonclinical studies related to this concern. The safety review did not identify significant adverse cardiovascular findings.

Dr. Boehm has recommended a thorough QT study in humans. Since his review, the Sponsor has submitted the results of Study OV-1033 (A Double-Blind, Double-Dummy, Randomized, Comparative, Positive and Placebo Controlled, Crossover Design Trial to Assess the Effects of Vigabatrin on Cardiac Repolarization Following a Therapeutic and Supratherapeutic Dose in Healthy Volunteers). Vigabatrin was administered orally in single doses of 3.0 and 6.0 g daily. The study report was reviewed by the Interdisciplinary Review Team for QT studies (QT-IRT) in January 2009. According to the QT-IRT, assay sensitivity was demonstrated with moxifloxacin. The QT-IRT did not find significant QT prolongation following administration of vigabatrin, with the largest upper bound of the 2-sided 90% CI for the mean difference between vigabatrin and placebo being less than 10 msec, the threshold for regulatory concern. The peak concentrations for 6g Sabril were approximately 2x higher than peak concentrations following a single 3 g dose. Exposure-response analysis did not indicate an increase in QT prolongation with an increase in exposure. The QT-IRT has recommended the following text for the label in Section 12.1, Pharmacodynamics:

Effects on Electrocardiogram

There is no indication of a QT/QTc prolonging effect of SABRIL in single doses up to 3.0 g. In a randomized, placebo-controlled, crossover study, 58 healthy subjects were administered a single oral dose of SABRIL (3 g and 6 g) and placebo. Peak concentrations for 6.0 g SABRIL were approximately 2-fold higher than the peak concentrations following the 3.0 g single oral dose.

2.1.7 Adverse Events of Special Interest

Depression and Suicide

Dr. Boehm finds that there is evidence to support an increased risk for depression with vigabatrin, although the number of SAEs was relatively small. He also finds an increased risk for depression AEs leading to discontinuation among vigabatrin subjects compared to subjects randomized to other treatments. Dr. Boehm reports that there was 1 completed suicide among 4,855 subjects in epilepsy trials included in the integrated database. Depression will be included among the most commonly reported adverse reactions in clinical studies. The class labeling language for antiepileptic drugs and suicidality will be used for Sabril.

Edema

As reported by Dr. Boehm, vigabatrin use was associated with the development of edema. In the Integrated database, there were 3% of patients with AE of edema peripheral, 0.4% with edema, 0.1% with generalized edema, 0.1% with localized edema,

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0.1% with facial edema, < 0.1% with pitting edema, and < 0.1% with gravitational edema. None were SAEs and only 5 edema peripheral and 2 edema events led to discontinuation. The risk of edema was higher in vigabatrin subjects vs placebo subjects in pooled control clinical trial data.

Dr. Boehm reports that in a separate analysis, 50/215 vigabatrin subjects with an edema related AE also had a weight gain AE, although only 23 of those occurred within a month of the edema related AE. The mechanism for the edema AEs is unknown and did not appear to be related to cardiac, renal or hepatic AEs or associated with increased creatinine, low serum albumin, or proteinuria.

Dr. Boehm has proposed labeling language for edema with vigabatrin to be added to Warnings and Precautions. *I agree with his recommendation.*

Peripheral Neuropathy

Dr. Boehm has outlined considerations of peripheral neuropathy that begin with the original NDA review. According to Dr. Boehm's summary, the reviewer of the original NDA noted that treatment emergent risks for paresthesia and hyporeflexia adverse events were 3x higher among vigabatrin subjects compared to placebo subjects. In studies 024 and 025, hyporeflexia was reported as a treatment emergent reaction in 5% of vigabatrin-treated subjects and in 1% of placebo-treated subjects, as was paresthesia. According to the Sponsor's expert, Dr. Cornblath who reviewed the data in 1998, in North American controlled trials, 11/457 (2.4%) of subjects developed symptoms or signs of a distal, large-fiber sensory polyneuropathy. This included 0/188 subjects in the placebo arms 4/280 in vigabatrin arms of placebo-controlled trials. The Sponsor has since provided no new information, noting that the reviewed studies were not designed to systematically evaluate peripheral neuropathy. Dr. Boehm has recommend language to be added to the Warnings and Precautions section of the label regarding peripheral edema. *I agree with his recommendation.*

Hepatic Injury

Dr. Boehm has reviewed hepatic injury cases as well as the previous evaluation of these findings in the previous submissions and reviews. He has discussed these findings and his considerations in detail in pp. 57-61 of his review. In brief, there were 4 hepatic related deaths in the clinical trial database. However, all were confounded with other factors that were more likely to have caused the deaths. This included a case of hepatic failure with hepatic necrosis with multisystem organ failure in a patient who experienced status epilepticus. In the post-market period there have been several reports of hepatic injury resulting in death or transplant. In 3 of these the patients were exposed to vigabatrin for less than 1 year, although in some cases these were also confounded by exposure to other medications associated with hepatotoxicity (such as valproic acid, carbamazepine, phenytoin or acetaminophen). I agree with Dr. Boehm that the data are not sufficient to allow the conclusion that vigabatrin causes liver injury. However, it is not possible to completely rule out the role of vigabatrin in these cases. In addition, as discussed above in Section 2.1.5, the decrease in transaminases observed after administration of vigabatrin due to laboratory interference, results in inability to use

transaminases as an early marker of hepatic toxicity. *I agree with Dr. Boehm that the data merit close monitoring and I agree with his recommendation that the Sponsor should closely follow up any spontaneous reports of liver injury and should submit any serious livery injury cases as 15 day reports. Dr. Boehm has recommended labeling language for Warnings and Precautions that addresses the decreases in ALT and AST and that identifies the difficulty with use of these markers to detect early hepatic injury. I agree with his recommendation.*

Growth

The Division asked Ovation to summarize data that would allow an assessment of growth in vigabatrin treated children. There were 4 studies in CPS and 3 in IS that recorded baseline and final height and weight. **According to Dr. Boehm's review, the data suggest consistently greater mean increases in weight for pediatric CPS subjects exposed to vigabatrin compared to placebo (approximately 2x greater changes from baseline).** Differences in height are based on small numbers and it is difficult to interpret those results. Dr. Boehm agreed with the Sponsor that the short duration for controlled phases of the IS studies precludes meaningful analysis of the data in that population. Please refer to additional discussions about weight gain in Section 2.1.6 above.

2.1.8 Other findings and considerations

Human Carcinogenicity: Dr. Boehm reports that Ovation found an increased ratio of observed to expected cancer diagnosis in the vigabatrin development program, with the biggest increase for brain cancers. The Sponsor believes this disparity is due to differences in the vigabatrin clinical trial population and the general population from which the SEER data is derived, and supports this with data from the literature. Due to the relative short vigabatrin exposure prior to brain cancer diagnosis, Dr. Boehm questions whether vigabatrin was causally involved in these events.

Human Reproduction and Pregnancy Data: There were 300 reports of pregnancies with vigabatrin exposure through 9/2006, of which 238 reported outcome information and 61 were abnormal. Dr. Boehm has provided more detail in his review. Spontaneous abortions were also reported, as well as pregnancies that ended in therapeutic abortion. The sponsor has included information about their pregnancy registry in the labeling. The standard language that the Agency is requesting for all AEDs containing a statement that informs physicians to advise pregnant patients who are taking anticonvulsants to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry should be included as well.

Demographics: According to information available from the NDA Amendment review, and in the Safety Update review, most subject were Caucasian, with roughly equal numbers of males and females exposed. For the overall safety population the population in the controlled clinical studies and in long-term studies was primarily Caucasian in both US and non-US studies. In the US controlled studies 10% were Black and 82% Caucasian. In uncontrolled (non-US) studies, race was 91% unknown.

2.1.9 Labeling and Post-Marketing Risk Management Plan

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Dr. Boehm has recommended some changes to the Sponsor's proposed labeling and that labeling is being reviewed by the Division. Vision loss and suicidality will be included in the REMS.

3 Conclusions

Dr. Boehm has not identified any issues in his review of the safety data that would prevent approval of Sabril. In addition to the recommended labeling changes suggested by Dr. Boehm, I have the following recommendations:

1. Any ongoing or planned vigabatrin clinical trials should incorporate monitoring of relevant hematologic parameters and should incorporate hematologic testing during post-treatment washout in order to assess rate of recovery from reduction of hemoglobin and hematocrit.
2. Since the long term consequences of vigabatrin-related weight gain in terms of cardiac and metabolic risk are not known, this type of metabolic data (such as lipids and glucose) should be included in future studies of reasonable duration.
3. The Sponsor should closely follow up any spontaneous reports of liver injury and should submit any serious livery injury cases as 15 day reports.

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this page is the manifestation of the electronic signature.**

/s/

Sally Yasuda
3/17/2009 08:09:00 AM
INTERDISCIPLINARY

CLINICAL SAFETY REVIEW

Application Type NDA Amendment
Submission Number 020-427
Submission Code N 000

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Established Name Vigabatrin
(Proposed) Trade Name Sabril
Therapeutic Class Antiepileptic
Applicant Ovation

Priority Designation S

Formulation Oral
Dosing Regimen BID
Indication Refractory CPS
Intended Population Adults

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The Executive Summary-Safety Review

This review considers the overall safety of vigabatrin, excluding visual field defects and Intramyelinic edema (IME)/MRI abnormalities. Data on visual field defects are reviewed by Dr. Ronald Farkas, and IME/MRI abnormalities are reviewed by Dr. Phillip Sheridan, in separate memos.

Vigabatrin is an orally administered irreversible inhibitor of gamma-aminobutyric acid transaminase. Ovation's current submission is a safety update for the NDA seeking approval for vigabatrin for the treatment of refractory complex partial seizures in adults. Ovation submitted a separate NDA seeking approval for the use of vigabatrin in the treatment of Infantile Spasms (IS). The safety data specific to that submission are reviewed in a separate document.

Vigabatrin has a long and complicated regulatory history including numerous regulatory submissions, three advisory committee meetings, and a sponsor change. FDA put the development program on hold in the 1980s due to the finding of intramyelinic edema IME in several animal species. After resuming development, the sponsor submitted the vigabatrin NDA to FDA in 1994. The Division completed its review in 1995 and the application was found not approvable, due mainly to deficiencies in the presentation of safety data. The sponsor submitted an amendment to the NDA that addressed the identified deficiencies and vigabatrin received an approvable letter in 1997. The sponsor subsequently withdrew the application, prior to vigabatrin approval in the US, due to the finding of permanent visual field defects in a notable percentage of treated patients. Ovation acquired the the rights to vigabatrin from Aventis and submitted the amendment to the NDA that is the focus of this review.

Vigabatrin is currently approved for use in over 50 countries. Vigabatrin was first approved in the United Kingdom in 1989. Vigabatrin is approved in most countries in the European Union as well as Canada and Mexico.

There are numerous FDA approved treatments for epilepsy. No approved epilepsy treatment is completely efficacious. Many epilepsy drug treatments are associated with substantial and in some cases life threatening toxicities.

Vigabatrin related IME was a major preclinical safety finding. IME, manifested as microvacuolization in the brain, has been identified in mice, rats, dogs, and less consistently in monkeys. These findings led to a clinical hold for the development program and 3 advisory committee meetings. Another preclinical finding of note was retinal degeneration observed in albino rats but not in pigmented species.

The current vigabatrin submission summarizes pooled safety data from 15 controlled and uncontrolled trials including 2,148 subjects from studies in adults with CPS, children with CPS, IS, and safety studies evaluating visual field defects. The data included in these analyses come from studies that were not reported in previous regulatory submissions. In addition to presenting pooled analyses (Overall population), Ovation presented analyses of safety data from these 15 studies that stratified patients into the following subpopulations: adult subjects, pediatric (non IS) subjects and the IS subjects. At the request of the Division, Ovation also submitted Integrated

data analyses of pooled data from 80 epilepsy trials, including over 4,000 vigabatrin exposed subjects dating back to the original NDA. The Division requested these analyses to allow estimation of adverse event risks based on the available data and to allow examination of adverse event risks over time and across submissions.

Considering only the data in the current submission, the number of patients exposed to vigabatrin in phase II/III combined controlled and uncontrolled trials exceeds ICH guidelines and investigators exposed adequate numbers of subjects to the intended recommended doses. The current amendment submission includes safety data for 2,148 subjects exposed to vigabatrin in the combined controlled and uncontrolled trials. Ovation reported that for the studies included in the current submission 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.

Division reviewers have identified 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 results have been generally acceptable. Narrative summaries of serious adverse events or AEs leading to discontinuation were generally of poor quality and often containing insufficient information to completely characterize the event being described.

The most commonly reported causes of death in the Integrated data pool of epilepsy study subjects were seizures (n=22), SUDEP (n=18), and respiratory events (n=4). In a comparative mortality analysis of 12 pooled controlled trials data, there were 4 deaths among vigabatrin subjects (n=952) and none among placebo subjects (n=393). The reported causes of death generally were those expected in the studied populations.

The most common SAEs among vigabatrin subjects in the Integrated data pool of epilepsy study subjects were visual field defect (6.8%, 324/4737), convulsions (2.8%, 132/4737) and status epilepticus (1.6%, 77/4737). The overall SAE risk was higher for vigabatrin subjects compared to placebo subjects in analyses of controlled trials data. In an analysis of pooled controlled trial data, vigabatrin subjects had a higher SAE incidence for status epilepticus (vigabatrin 2.9/100PY, placebo 2.0/100PY), depression (vigabatrin 2.2/100PY, placebo 2.0/100PY), confusional state (vigabatrin 1.8/100PY, placebo 0), pneumonia (vigabatrin 1.3/100PY, placebo 0), and fatigue (vigabatrin 1.1/100PY, placebo 0).

The most common AEs leading to discontinuation among vigabatrin subjects in the Integrated data pool of epilepsy study subjects were depression (1.5%, 71/4855), and convulsion (1.4%, 68/4855). Vigabatrin subjects discontinued from controlled trials for AEs more frequently than placebo subjects. In a pool of controlled trials, depression (vigabatrin 3.2/100PY, placebo 1/100PY) headache (vigabatrin 3.0/100PY, placebo 2.0/100PY), agitation (vigabatrin 1.5/100PY, placebo 0), confusional state (vigabatrin 1.3/100PY, placebo 0), and status epilepticus

(vigabatrin 1.1/100PY, placebo 0) led to discontinuation more commonly among vigabatrin subjects than control subjects.

Common AEs that occurred more frequently among vigabatrin subjects and in some cases that exhibited evidence of a dose response relationship included fatigue, somnolence, sedation, irritability, gait disturbance, dizziness, headache, nystagmus, tremor, coordination abnormal, parasthesia, hypoesthesia, confusional state, amnesia, memory impairment, disturbance in attention, depression, disorientation, diplopia, weight increased, edema peripheral, tremor, vision blurred, and diplopia.

Vigabatrin use was associated with development of edema. 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. Edema adverse events were not classified as SAEs and infrequently led to discontinuation. 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.

Evidence supports an increased risk for depression with vigabatrin but there is insufficient evidence to support an increased risk of suicidal behavior. Data from 12 pooled controlled studies document an increased risk for depression 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.

Vigabatrin was associated with increased risk of peripheral neuropathy signs and symptoms. In the original NDA, risks for parathesia and hyporeflexia adverse events were 3 times higher among vigabatrin subjects compared to placebo subjects. Vigabatrin studies were not designed to systematically evaluate potential cases of peripheral neuropathy and did not include nerve conduction studies, quantitative sensory testing, or nerve biopsy.

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. Confounding factors such as concomitant medications, and prolonged duration of vigabatrin use prior to liver injury, make it difficult to assess the role of vigabatrin in these events. There were no cases of transaminase elevations $>3x$ ULN with total bilirubin $>2.0\text{mg/dL}$ in the vigabatrin development program, and there was no increased risk of transaminase outliers among vigabatrin subjects in an analysis of pooled controlled trial data. These laboratory results must be interpreted in light of the understanding that vigabatrin causes *decreases* in serum transaminases (see below).

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.

Lab data suggest that vigabatrin subjects experienced declines in hemoglobin and hematocrit that were not seen in subjects that received placebo. Despite these laboratory findings, vigabatrin subjects did not appear to experience high frequencies of concerning clinical events. 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.

Vigabatrin causes reductions in serum transaminases (ALT>AST), presumably through its effect as a transaminase inhibitor. In one analysis, 94% of vigabatrin treated study 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 hinder the ability to monitor patients for hepatotoxicity.

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 $\geq 7\%$ of baseline body weight. In the Integrated database, 10.2% (415/4077) of vigabatrin subjects had a weight increased AE. The long term impact of vigabatrin associated weight gain on cardiac disease or blood pressure outcomes is not known.

Due to the small number of analyzed ECGs, lack of specified timing in relation to dose, and lack of pre-specified measurement methodology, Ovation's analyses of ECGs collected during vigabatrin clinical trials are insufficient to assess the effect of vigabatrin on cardiac repolarization. Preclinical data did not appear to suggest an effect of vigabatrin on ion channels or repolarization.

Recommendations

Any ongoing or planned 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 Integrated Review of Safety

Background

Vigabatrin has a long and involved regulatory history. Vigabatrin's first sponsor (Marion Merrill Dow) filed the original IND in February of 1980. In 1983, the Division suspended clinical investigations due to the finding of intramyelinic edema (IME) in rats, dogs, and possibly monkeys. IME manifested histologically as microvacuolization, most notably in the cerebellum, reticular formation, and optic tracts. In 1984, following an advisory committee meeting on IME, the Division required the sponsor to collect additional information about IME prior to resuming clinical testing. In 1985 the sponsor provided data related to IME and following another advisory committee meeting the Division decided that prior to resumption of clinical testing, the sponsor would have to identify a non-invasive test capable of detecting IME at an early stage in humans. In late 1989, following yet another advisory committee meeting, the Division allowed clinical testing to resume with the sponsor monitoring subjects for IME using visual evoked potentials and MRI. In 1989, vigabatrin was approved for marketing in the United Kingdom. Clinical testing resumed in the United States in 1990.

The sponsor submitted the vigabatrin NDA to the FDA on 4/29/94 and the Division deemed that application Not Approvable on 5/28/95, primarily for quality related issues with the non US studies safety database. 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 response to the issues raised in the Not Approvable letter, 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. In another development, the January 1997 issue of the BMJ published 3 post marketing case reports from the UK of patients treated with vigabatrin that developed bilateral concentric visual field loss.

On 5/31/97, the sponsor (now Hoechst Marion Roussel) filed an Amendment to the NDA that responded to the shortcomings identified by the Division in the Not Approvable letter. To address the Division's concerns about non-US studies lack of CRFs, 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).

Upon completion of the NDA Amendment review, the Division issued an Approvable letter for vigabatrin and identified several safety issues requiring additional exploration. The approvable letter requested a separate review of safety data for pediatric patients treated with vigabatrin, additional information regarding a variety of topics in the proposed labeling, and updated information regarding visual field defects. The sponsor provided another safety update in 1/98 and responded to the requests in the approvable letter on 4/24/98.

Due to the finding of visual field defects in patients treated with vigabatrin, the sponsor withdrew the application prior to the Division's final regulatory decision. The sponsor subsequently met with the Division on several occasions to discuss visual field defect findings with vigabatrin and explore avenues for approval but that sponsor (at this time Aventis) decided to abandon the application.

Ovation acquired the US rights to vigabatrin and on December 23, 2005 filed an Amendment to the NDA application for FDA approval for vigabatrin for treatment of refractory complex partial seizures in adults. The Division deemed the submission an incomplete response for reasons related to deficiencies in the format and content. Ovation attempted to address these deficiencies in a 10/10/06 submission. Ovation filed their NDA for vigabatrin for the treatment of infantile spasms on 10/17/06. These submissions were also deemed incomplete and Ovation submitted responses in March of 2007. Shortly thereafter, the Division became aware of publications describing MRI findings suggestive for intramyelinic edema in children treated with vigabatrin. The Division met with Ovation and informed them that additional information about these findings would be required prior to accepting the vigabatrin applications. Ovation conducted additional analyses and re-filed their submissions for both refractory CPS in adults and IS on 12/28/07.

7.1 Methods and Findings

7.1.1 Deaths

Prior Submissions

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

Through the 12/31/95 cutoff date for the NDA Amendment, the sponsor identified 11 deaths from the completed US and non US primary safety data clinical trials. The sponsor also identified 9 deaths from the secondary safety data clinical trials and 8 deaths from the non-CRF safety database (from trials where CRFs were not available). In addition, the sponsor identified 32 deaths from clinical trials that were ongoing at the time of the amendment cutoff date. The sponsor re-categorized these 32 deaths (ex. to completed primary study category or post

marketing trial category, etc.) in subsequent submissions, after the trials were completed (Source, Amendment review 10/28/97, pp. 14-18; Safety Update Table 9-21).

For the 11 deaths in vigabatrin treated subjects from completed US and non-US primary data studies in the NDA amendment, 7 were from US clinical trials and 4 from non-US primary studies. The crude mortality rate for vigabatrin treated subjects in the US studies was 1.11/100 PY (7/630PY; 1.3%, 7/537) and for the non-US primary studies was 0.9/100PY (4/449PY; 0.3%, 4/1,189). For the US studies, the reported causes of death were seizures (n=3), drowning, coronary artery disease, trauma, and suicide. The causes of death for the non-US primary studies were pneumonia, infection, fall, and motorcycle accident (Source, Amendment review 10/28/97, pp. 14-16, Appended exposure table). In controlled US trials, one death (0.5%, 1/222, suicide) occurred among vigabatrin subjects and none (0/135) among placebo subjects. No deaths were reported from non-US primary controlled trials.

The sponsor identified 9 vigabatrin subject deaths from completed studies included in the secondary data group and 8 vigabatrin subject deaths from the non-CRF data group. The reported causes of death for the secondary and non CRF databases included sudden/unwitnessed (n=3), suicide (n=3), coronary artery disease (n=2), aspiration/seizure, status epilepticus, seizure, lung cancer, colon cancer, congestive heart failure, trauma, progression of underlying disease, and unknown.

In addition to the clinical trial deaths, the NDA Amendment included deaths identified from post marketing reports and from compassionate use programs. For the most part, the causes of death reported from these non-clinical trial data sources (cutoff date 12/31/95) were similar to causes reported above, although there were 6 deaths due to hepatic failure. In 4 of these cases the patient was treated with vigabatrin for 1-6 years prior to the development of hepatic failure. In one of the remaining cases, liver failure occurred in the setting of multi-organ failure, following cardiac arrest. The remaining case summary did not identify any strong confounding factors but included only limited clinical details. I summarize those cases in an appendix to this review (Source Amendment Review 10/28/97, pp. 18-19).

Safety Update (1/1/96-3/15/97)

The sponsor identified a total of 22 deaths from completed US and non US primary trials in this Safety Update (Safety Update table 9-24). The crude mortality risk for this group was 1.3% (22/1,667). The reported causes of death were seizure (n=8), status epilepticus (n=2), intracranial hemorrhage (n=2), drowning (n=2), cardiac arrest (n=2), SUDEP, aspiration, lung cancer, myocardial infarction/ventricular fibrillation, myocardial infarction/ GI bleed, and valvular heart failure. (Safety Update table 9-24).

The sponsor identified 22 additional deaths from sources other than primary data trials (completed and ongoing Japanese trials, post marketing trials, and miscellaneous sources-Safety Update Table 9-24). The reported causes of death were drowning (n=6), accident/trauma (n=3), suicide (n=2), seizure/aspiration, seizure/fall/suffocation, status epilepticus/pneumonia, heart failure, oligodendroglioma, sepsis/cardiac arrest, SIDS, CMV infection, bronchopneumonia,

pneumonia/respiratory failure, and fulminant hepatitis. The hepatitis death occurred in a 3 year old female patient being treated with vigabatrin and phenobarbitone and liver histology was reportedly consistent with a toxic etiology and the report stated that other causes of hepatic injury had been excluded (no specific test results reported).

Current Submission

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

Ovation reported 16 deaths from completed trials in the Overall Safety Population (0.74%, 16/2,148). Four deaths were related to epilepsy/seizure; 3 related to myocardial infarction; 3 related to respiratory causes (pneumonia and respiratory arrest; pneumonia and urinary tract infection; and pulmonary hemorrhage secondary to pulmonary angiomas respectively); 3 cancer related (pulmonary carcinoma with pneumonia and multiple organ failure; carcinoma; and adenocarcinoma respectively), 1 related to hepatic necrosis with multisystem organ failure; 1 cause not reported; and 1 sudden death. The narratives for the myocardial infarction deaths suggested that these were sudden and or unwitnessed events and contained insufficient information to support the diagnosis of myocardial infarction. The death due to hepatic necrosis with multisystem organ failure occurred in a 17 year old female who had been treated with vigabatrin for 20 months and developed status epilepticus the evening after undergoing an intracranial monitoring procedure in preparation for possible lobectomy for seizures. She was treated with antiepileptics, mechanical ventilation, pressors and broad spectrum antibiotics. The subject died and a post-mortem report described the cause of death as extensive hepatic necrosis with multisystem organ failure. Ovation provided narrative summaries for the Overall Safety Population deaths identified in the 12/28/07 submission and I summarize information from those narratives in an appendix to this review.

Pediatric Subpopulation (non IS, age 3-<16)

Ovation reported no deaths among the 444 pediatric patients that were part of the Overall Safety Population (12/28/07 Submission, p.151).

IS Subpopulation

Ovation identified four deaths among the IS patients that were part of the Overall Safety population. The reported causes of death were pneumonia, pulmonary hemorrhage, cardiac arrest, and sudden death.

Integrated Data

Ovation's Integrated Data summary of deaths includes only those deaths from epilepsy clinical trials. Ovation's presentation consisted of a table that listed the total number of deaths and the number of deaths by cause. The table includes the following 3 columns: prior data, current data, and combined data. I provide that table below.

The causes of deaths listed for the Prior Data in the Integrated analysis table below cannot be compared to causes listed in previous submissions because the events have been re-coded using MedDRA. The previous submissions did not use the same coding dictionary to categorize adverse event verbatim terms that was used for the Current data. In order to provide the Integrated analyses, Ovation had to re-code the adverse event verbatim terms in the previous submissions so that the events could be categorized in a uniform manner. Ovation explained that they re-coded the adverse event verbatim terms from previous submissions using MedDRA version 8.0 (Amendment p.33).

The 42 deaths identified from Prior Data include deaths from the NDA Amendment and 1998 Safety Update. Ovation includes 18 deaths from completed primary and secondary data sources in the NDA Amendment (two deaths noted above were not included in this analysis because one was from a clinical pharmacology study and another from a tardive dyskinesia study, Response to Reviewer Questions 2/11/08). Ovation also includes the 22 clinical trial deaths reported in the 1998 Safety Update. The final 2 deaths in the Prior Data column were reported as from an ongoing study in the 1998 Safety Update and are included now by Ovation in their final accounting of deaths (Response to Reviewer Questions 2/11/08).

The Current data deaths are the 16 deaths reported by Ovation in the current Amendment Submission.

The Combined Data total includes the Prior data deaths (n=42, as described above), the Current Data deaths (n=16), and 5 additional deaths identified by Ovation that were reported from ongoing studies in the Safety Update but not reported elsewhere (see footnote of table for explanation).

Table 67. Subject Deaths Integrated Data

Adverse Event Related To Subject Death	Prior Data (N=3441) n (%)	Current Data (N=2148) ^a n (%)	Combined Data (N=4855) ^a n (%)
Total	42 (1.22) ^a	16 (0.74)	63 (1.30)
Seizure (all)	15(0.44)	4 (0.19)	22 (0.45)
SUDEP	16 (0.47)	2 (0.09)	18 (0.37)
Respiratory events	0	4 (0.19)	4 (0.08)
Aspiration	3 (0.09)	0	3 (0.06)
Cancer	0	3 (0.14)	3 (0.06)
Cardiovascular events	0	3 (0.14)	3 (0.06)
Coronary artery atherosclerosis	3 (0.09)	0	3 (0.06)
Drowning	2 (0.06)	0	2 (0.04)
Hypoxia	2 (0.06)	0	2 (0.04)
Myocardial infarction*	1 (0.03)	0	2 (0.04)
Trauma*	1 (0.03)	0	2 (0.04)
Acute Myocardial infarction	1 (0.03)	0	1 (0.02)
Brain hypoxia	1 (0.03)	0	1 (0.02)
Bronchopneumonia	1 (0.03)	0	1 (0.02)

Cardiac arrest	1 (0.03)	0	1 (0.02)
Cardiac valve disease	1 (0.03)	0	1 (0.02)
Cardiogenic shock	1 (0.03)	0	1 (0.02)
Cerebral hemorrhage	1 (0.03)	0	1 (0.02)
Completed Suicide	1 (0.03)	0 (0.00)	1 (0.02)
Confusional state	1 (0.03)	0	1 (0.02)
Congestive cardiomyopathy	1 (0.03)	0	1 (0.02)
Dyspnea	1 (0.03)	0	1 (0.02)
Gastric hemorrhage	1 (0.03)	0	1 (0.02)
Gastric ulcer	1 (0.03)	0	1 (0.02)
Hemorrhage intracranial	1 (0.03)	0	1 (0.02)
Hepatic events	0	1 (0.05)	1 (0.02)
Hepatic neoplasm	1 (0.03)	0	1 (0.02)
Injury Asphyxiation	1 (0.03)	0 (0.00)	1 (0.02)
Lung cancer metastatic	1 (0.03)	0	1 (0.02)
Lung neoplasm malignant	1 (0.03)	0	1 (0.02)
Malignant glioma	1 (0.03)	0	1 (0.02)
Multiple organ failure	0 (0.00)	1 (0.05)	1 (0.02)
Pulmonary oedema	1 (0.03)	0	1 (0.02)
Subdural hematoma	1 (0.03)	0	1 (0.02)
Sudden death	1 (0.03)	0	1 (0.02)
Tachycardia	1 (0.03)	0	1 (0.02)
Ventricular fibrillation	1 (0.03)	0 (0.00)	1 (0.02)
Ventricular tachycardia	1 (0.03)	0	1 (0.02)
Unknown	0 (0.00)	1 (0.05)	1 (0.02)

*The following 5 subject deaths were reported in 1998 SU as deaths in "ongoing" studies, and therefore not reported in rest of this current SU. However, for completeness and accuracy in accounting for all the deaths in the combined analysis, the following 5 deaths are included under the "combined" total data but not reported elsewhere in the current SU: Subject 1349-0007 from study 0101 cause of death was Unwitnessed Death: Possible seizure and pulmonary edema. Subject 1344-0002 from study 0101 cause of death was Unwitnessed Death: Cerebral hypoxia due to a seizure. Subject 1507-1001 from study 242 cause of death was Head injury secondary to motor vehicle accident. Subject 1541-0003 from study 242 cause of death was Unwitnessed Death: Seizure disorder. Subject 1545-0004 in study 242 cause of death was Unwitnessed Death: Myocardial Infarction. These 5 causes of death are not present in Table 66, however 5 is added to the existing prior and current data totals. 42 deaths in prior + 16 deaths in current + 5 deaths reported as deaths in ongoing studies from 1998 SU = 63 total deaths in the combined population of 4837. Preferred terms flagged with * indicate counts which include these additional deaths.

Additional Analyses

The Division asked Ovation to submit a comparative analysis of mortality based on the data from pooled controlled trials. Ovation pooled data from 12 phase II/III epilepsy controlled trials that used a double blind, parallel group, dose, placebo or active control design. Ovation provided a table of the studies included in their analysis and that table is included as an appendix to this review (Table 5). The studies differed in terms of the durations (range 5 days to 52 weeks) and numbers of subjects enrolled (range 18- 457). The analysis included 948 vigabatrin treated subjects, 229 carbamazepine treated subjects, 9 gabapentin treated subjects and 384 placebo subjects. The results of the analysis are provided below (Source: 2/11/08 and 3/14/08 submissions).

Mortality by Treatment Group for Pool of Phase 2-3 Studies					
Treatment Group	Total Number of	Total Number of	Crude	Patient Years	Mortality/100

	Patients ^a	Deaths	Mortality ^b	Exposure	Patient years ^c
Vigabatrin	952	4	0.004	446.004	0.897
Carbamazepine	229	1	0.004	166.084	0.602
Valproate	113	0	0	68.657	0
Gabapentin	9	0	0	1.725	0
Placebo	393	0	0	101.897	0

^a Includes only patients who received study drug; therefore these numbers may vary from Table 5, which includes all randomized patients.
^b Crude mortality = number of deaths/total number of subjects
^c Mortality/100 patient years= number of deaths/patient years exposure x 100

The causes of death for the vigabatrin group were suicide, valvular cardiac failure, myocardial infarction/GI bleed, and possible seizure/pulmonary edema.

Ovation's controlled trial mortality analysis found a higher mortality rate in the vigabatrin treated subjects compared to the active control and placebo subjects. There did not appear to be a clustering of similar causes of death among the vigabatrin subjects. Due to the small number of deaths and the relatively low exposure, this analysis does not provide robust evidence of increased mortality risk with vigabatrin.

Post Marketing Reports

The post marketing reports of deaths from the prior submissions were discussed above.

In the current submission, Ovation summarized deaths in patients identified from foreign post marketing reports received during the period of 3/97 through 6/07. Ovation identified 17 reports that described 18 patient deaths. Twelve of the identified deaths were in patients aged less than 12 years. For these pediatric deaths, the included patients ranged in age from 9 days to 11 years and 3 were males and 4 were females (5 unknown sex). Four reports included insufficient detail to characterize the causes of death. Two patients were found dead in bed (one noted to be taking cisapride). The reported causes of death for the remaining subjects were SSPE, sepsis/pneumonia, congenital heart malformation, underlying metabolic disorder, recurrent pulmonary infections, and respiratory insufficiency/septicemia. For the six deaths in patients 12 years or older, the age range was 12-47 years and 4 patients were male and 2 patients were females. The reported causes of death include suicide (2), malignant hyperthermia, liver damage, bilateral pulmonary embolism, and one patient was found dead in bed.

Discussion

Ovation summarized the deaths occurring during the safety update period and provided a cumulative count of deaths by cause of death (Integrated data) for the epilepsy studies in the development program. I provided a summary of mortality data from earlier submissions that was included in previous Division safety reviews. Ovation's quantitative comparative assessment of mortality was limited by the small number of deaths and the limited exposure. A qualitative assessment of mortality is severely limited in some cases by the lack of clinical detail presented in the death narratives. The causes of death reported by Ovation are generally those expected in a population of patients with seizure disorders. There were deaths due to hepatic failure and these are discussed in more detail in section 7.1.5.6.