

Review and Evaluation of Safety Data

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Safety Review

Application Information

NDA 20-427

Hoechst Marion Roussel

Drug Name

Generic: Vigabatrin

Proposed Trade Name: Sabril

Drug Characteristics

Pharmacological Category: GABA transaminase inhibitor

Submissions Reviewed

Final Safety Update, 1/20/98

Response to Approvable Letter, 4/24/98

Updated Safety Information, 7/29/98

Safety Reviewer

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Introduction

Since completion of the review of the NDA amendment for vigabatrin, the sponsor has provided 3 separate submissions related to a variety of safety topics. A brief description of each submission is provided in the following paragraphs.

Description of the Submissions

Final Safety Update

The final safety update was submitted 1/20/98 in both electronic format and as 43 volumes on paper. This submission includes an updated integrated safety presentation that the sponsor compiled by combining data from the amendment, cutoff date 12/31/95, with data from the interim safety update, cutoff dates 1/1/96 through 3/15/97. Following the integration of these data, the sponsor provided updates of exposure and demographics and calculated updated estimates of risk for various events. In addition, this submission includes presentations updating special safety topics of concern as well as efficacy data for the use of Sabril® for infantile spasms.

Response to the Approvable Letter

On 4/24/98, the sponsor submitted their response to the approveable letter. The document is an electronic submission, which includes the responses to specific requests for additional information that were made in the approveable letter. Specifically, the sponsor's response addresses pediatric safety, information about data sources used in the NDA amendment, urinalysis and coagulation lab study data, and clinical descriptions for several events that were more frequent in vigabatrin exposed subjects in controlled clinical trials. The response also provides proposed product labeling for topics such as vacuolization, SUDEP, status epilepticus, ophthalmologic events, peripheral neuropathy, cognitive/neuropsychiatric events, liver failure and anemia. Lastly, the sponsor submitted proposals to include information about the effect of vigabatrin on tests for aminoaciduria, and a statement about reports of myoclonus reports from post-marketing surveillance.

Updated Safety Information, Ophthalmologic Events

On 7/29/98, the sponsor submitted updated information addressing ophthalmologic events. It contains proposed labeling for ophthalmologic events, published case reports of eye related events, an expert review of perimetry data from vigabatrin exposed patients, a visual field defect prevalence study, results of a UK PEM study and summary tables and Medwatch forms for visual events in vigabatrin patients.

Material from these 3 submissions have been reviewed by myself as well as Dr. James Sherry, neurology medical officer and Dr. Armando Oliva, neurology medical officer and neuro-

ophthalmologist. Dr. Sherry has focused on the MRI, EP and peripheral neuropathy issues. Dr. Oliva has reviewed the perimetry report and ophthalmology data included in the 7/29/98 submission.

The following document contains my review of the submitted material. Since information on specific topics (i.e. ophthalmological events) often appears in more than one submission, the review was arranged in an effort to present related information together. Using this approach means that each topic may include information from separate submissions. In order to maintain clarity about the source of the information, I will include references to the source document at the beginning of each section.

1. Sabril® Final Safety Update

The information for the final safety update was included in the 1/20/98 submission. The sponsor's presentations in the final safety update provided summaries of the data from 14 clinical trials that were ongoing at the time of the amendment cutoff date. The sponsor reviewed the data from these 14 trials as a separate group, and then, following the integration of these data with the information presented in the NDA amendment. Two of the 14 studies were clinical pharmacology studies, one looking at the combined use of Sabril® and phenytoin and the second looking at the effect of a single dose of Sabril® on glucose in diabetic subjects. Two controlled trials were conducted in epilepsy patients, one comparing Sabril® to phenytoin and the other to carbamazepine. Two controlled trials were conducted for other indications (infantile spasms [REDACTED])

The remaining studies were open label in epilepsy subjects or subjects with infantile spasms. In addition, the sponsor included information about serious adverse events from 12 studies that were ongoing at the time of the cutoff date for the final safety update. Sponsor's table 9-1 summarizes the studies included in the final safety update (see appendix).

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In the NDA amendment, data from the Sabril® development program were presented in various groupings (ex. primary, secondary, etc.). The classification was based upon data quality, which was determined by the processes used to capture study information and CRF availability. The sponsor applied these same criteria to the studies included in the safety update. Thirteen of the 14 studies included in the safety update were considered primary. The one exception, study 71754-3-W-006, a clinical pharmacology study, did not meet the criteria for primary data because investigators retrospectively completed the case report forms. The sponsors included the data from this study in several presentations of integrated data and felt comfortable doing so because of the small number of subjects enrolled (n=20). These data were not included in the table that updated adverse events (S9-V1-P185).

1.1 Exposure

1.1.1 Completed Clinical Trials

The sponsor reported that 1773 subjects were exposed to Sabril® in the 14 clinical trials included in the safety update (compared to the 1726 subjects exposed in US and primary non-US studies included in the NDA amendment). Thirty-three subjects were exposed in clinical pharmacology trials, 338 in controlled trials, and 1329 in uncontrolled trials. Seventy-three subjects were exposed in trials for other indications (infantile spasms [REDACTED])

Because some patients participated in multiple studies, the counts in the exposure tables cannot be summed to arrive at the number of unique individuals exposed to Sabril®.

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1.1.2 Exposure in Ongoing Trials

Six hundred seventy subjects were being exposed to blinded treatment and 518 were being exposed in ongoing long term follow-up studies at the time of the final safety update cutoff date.

1.1.3 Post Marketing

The sponsor provided an updated worldwide post-marketing exposure estimate for 1989 through 3/15/97 using annual sales figures for Sabril® tablets and sachets. To calculate exposure, the sponsor chose an average dose of [REDACTED]. This led to an estimate of 350,000 patient years exposure. Compared to the NDA amendment, this represents an increase of 100,000 patient years exposure. Assuming an average duration of therapy of 2 years, the sponsor estimated that [REDACTED] individuals have been exposed to Sabril® in the post-marketing setting.

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The appendix includes sponsor's table 9-16, which provides a breakdown of exposure by types of trials for the entire development program.

1.2 Demographics, Completed Trials in the Safety Update

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

1.3 Mortality

1.3.1 Safety Update

The sponsor reported 23 deaths in Sabril® patients since the NDA amendment cutoff date. Sixteen (0.9%, 16/1773) were from US and primary non-US studies (compared to 11 deaths, 0.6%, 11/1726 from US and primary non-US studies in the NDA amendment). The remaining deaths in the safety update were from Japanese trials (3), spontaneous post marketing reports (3) and from an independent IND (1). The circumstances surrounding these deaths were described in the interim safety update and were reviewed with the NDA amendment. Seizure was commonly listed as a cause of death in this group. Other causes listed were cardiovascular events, cerebrovascular events, respiratory events and drowning. For 7 of the deaths, the event was not witnessed and in many of these cases the cause of death was attributed to seizure. The safety update identified one hepatic failure death from a spontaneous report (previously reviewed with the interim safety update). There were no deaths due to renal failure, Stevens Johnson syndrome, aplastic anemia or rhabdomyolysis in the safety update.

Ten of the 1667 (0.6%) exposed in completed US and primary non-US epilepsy studies died within 30 days of their last dose of Sabril®. This percentage results from pooling controlled and uncontrolled studies with different observation periods. The sponsor did not provide an estimate of person time exposure for this data grouping to allow calculation of mortality rates.

1.3.2 Integrated summary

There have been 145 deaths in Sabril® patients through 3/15/97(S9-V2-P9). The reported causes of death in descending order of frequency include seizures, cardiovascular events, cerebrovascular events, infectious diseases, suicide, respiratory events, cancer, drowning, hepatic events, and trauma. The sponsor presented the percentage of deaths for epilepsy subjects, using data from US, primary non-US, and secondary non-US studies. Using this grouping the sponsor reported 40 deaths within 30 days of last exposure to Sabril® in 3339 subjects (1.1%). The sponsor did not provide the person time exposure for this data grouping to allow calculation of a mortality rate.

1.4 SUDEP Update

The sponsor's consultant, [REDACTED], reviewed the available information for epilepsy patients who died. He focused on the deaths from the trials that had reliable exposure information. The sponsor identified 41 deaths in epilepsy patients from trials with reliable exposure information. Using the same criteria employed in the amendment, the consultant determined that 13 of these deaths were sudden and unexplained. He calculated an updated SUDEP rate of 3.4 per 1000 patient years (13 per 3806 patient years). This rate is comparable to the SUDEP rate provided by the sponsor in the NDA amendment (2.8/1000 patient years). It is also comparable to the rates observed with lamotrigine (3.5/1000 patient years) and gabapentin (3.8 per 1000 patient years). The classification of sudden deaths for the most part appeared reasonable. There may have been 1 or 2 deaths classified as non-SUDEP that could be included as SUDEP. Without exposure data files, I was unable to assess the accuracy of the exposure estimate.

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1.5 Overall dropout profile

1.5.1 Safety Update

In the epilepsy trials included in the safety update, 42% (708/1667) of enrollees withdrew prior to completion of the studies. The common reasons for discontinuation were loss of efficacy (18%, 304/1667) and adverse event (14%, 225/1667). The percentage of enrolled subjects discontinuing was similar whether looking at the controlled epilepsy trials (40%, 136/338) or the uncontrolled trials (43%, 572/1329). Because the presentation lacked person time data, dropout rates could not be calculated. The dropout percentages presented in the safety update are comparable to the discontinuation (45%), dropout due to lack of efficacy (23%) and dropout due to adverse event (17%) percentages for the US epilepsy studies described in the NDA. The percentage of enrolled individuals discontinuing was lower (18%, 13/73) in the trials for indications other than epilepsy. In these studies, the most common reasons leading to withdrawal were loss to follow up (7%, 5/73) and loss of efficacy (6%, 4/73).

1.6 Discontinuations due to AEs

1.6.1 Safety Update

The sponsor reports that 234 patients (13%) discontinued from trials included in the safety update for adverse events (S9-V2-p.75). The sponsor did not provide a detailed summary of the events leading to discontinuation for this group and the remainder of their presentation focused on the events leading to discontinuation for the integrated data.

1.6.2 Integrated Summary

During the development program, 533 Sabril® subjects discontinued from clinical trials for AEs (13.8%, 533/4018). Four hundred eighty seven Sabril® subjects (14.6%, 487/3339) withdrew from US and non-US epilepsy studies for AEs. Sixteen percent withdrew from US studies for AE's compared to 13.2% from non-US studies. Following the integration of data for epilepsy studies (table 9-31, S9-V2-P79), there were no material changes in the order of the most commonly reported system categories leading to discontinuation. When looking at individual events, the most common AE's leading to discontinuation following integration of the data from epilepsy studies were depression (1.9%, 65/3339), drowsiness (1.5%, 51/3339), convulsions (1.4%, 47/3339), and fatigue (1.3%, 43/3339). The sponsor did not include any additional comparator data to allow an updated assessment of drug relatedness for these events. In reviewing the listings for discontinuations due to AEs (appendix E3-listing 1-3), there was one discontinuation for renal failure (1192-0002 VGPR0098 a 32 YO male who developed status epilepticus, rhabdomyolysis and renal failure which resolved) that was previously identified. There were no newly identified discontinuations for hepatic failure, renal failure, rhabdomyolysis,

Stevens Johnson syndrome, or aplastic anemia in vigabatrin exposed patients in the safety update data.

1.7 Serious Adverse Events

As in the NDA amendment, the sponsor did not present the serious AE data in single presentation in the safety update, but rather as a series of separate presentations. The following sections include reviews of the sponsor's presentations for events that would be included in a serious AE section.

1.7.1 Hospitalizations

During the safety update period, there were 280 Sabril® subjects who were hospitalized for adverse events. The integrated total of hospitalizations for AE's was 993. The updated hospitalization risk for US and primary and secondary non-US epilepsy studies is 13.9% (465/3339). The risk of hospitalization was higher in US epilepsy studies (20.2%, 285/1409) compared to non-US epilepsy studies (9.2%, 185/1975). CNS and psychiatric events most commonly led to hospitalization in both the US and non-US epilepsy studies. The events most commonly leading to hospitalization in US studies were convulsions grand mal (4%, 56/1409), convulsions (3.5%, 49/1409) and for non-US studies the order was reversed; convulsions (2.2%, 44/1975), and convulsions grand mal (1.4%, 27/1975).

In appendix E4 Summary 2, the sponsor provided a summary of the events leading to hospitalization during controlled trials by the treatment the subject received. Therefore comparisons can be made between Sabril® and placebo or active comparators. According to this table, 969 subjects received Sabril® and 491 received placebo in controlled epilepsy trials. Seven and a half percent of subjects exposed to Sabril® in controlled epilepsy trials were hospitalized compared to 2.2% of placebo exposed. The biggest difference between the groups was the hospitalization risk for convulsions. Three percent (29/969) of Sabril® exposed subjects were hospitalized for this event compared to 0.4% (2/491) of placebo exposed. The risk of hospitalization for convulsions in subjects receiving valproate or carbamazepine, was 0.9% (1/113, and 2/229 respectively). Five Sabril® (0.5%) and no control subjects were hospitalized for confusion. Within the Psychiatric category, there were 5 subjects hospitalized for psychosis (0.5%), 1 for schizophrenic reaction, 5 for depression and 1 for depression psychotic among those exposed to Sabril®. In the control groups, one patient (valproate) was hospitalized for any of the above reasons (psychosis). After reviewing the hospitalization listings (appendix E4, listings 1-6), I found no newly identified hospitalizations for hepatic failure, renal failure, Stevens Johnson syndrome, aplastic anemia or rhabdomyolysis.

1.7.2 Overdose

The sponsor has made few changes in its presentation of overdose compared to the NDA amendment and interim safety update. In the entire development program, there have been 38 OD events in 36 Sabril® subjects. Fifteen were reportedly suicide attempts, 7 were accidental overdoses and 16 were unknown. Reports for 28 events included information on the dose ingested (range: 3-90g, most between 7.5 and 30g). For 24 events, Sabril® was the single suspect drug. Twenty-three events led to hospitalization. Five patients required intubation and mechanical ventilation. No deaths were reported, although 7 of the 38 events lacked outcome information. The symptoms reported were coma/unconsciousness (12), drowsiness/somnolence (4), apnea/irregular breathing (3), bradycardia (3), vomiting (3), confusion (3), vertigo (2), agitation (2), and increased seizure activity or status epilepticus (2). Ataxia, semicomatose, delirium, concentration impaired, abnormal behavior, speech disorder, auditory hallucinations, psychosis, hypotension, hypothermia, headache, slowed thinking, irritability, tremor, oliguria, pupillary

hippus, withdrawn, syncope, dehydration, and pulmonary infiltrates were reported for one patient each.

1.7.3 *Status Epilepticus*

The sponsor updated the total number of patients experiencing at least one episode of status epilepticus while on Sabril® (n=191). For the US and non-US epilepsy studies the risk for status was 3.1% (102/3339). There was no updated comparison of risk for status between Sabril® and placebo populations. For the controlled trials with active comparators included in the safety update, the risk for status for Sabril® was 0.9% (3/338), for valproate was 0.9% (1/113), and for carbamazepine was 0 (0/229). Throughout the development program, 41 episodes of status have occurred upon discontinuation or dose reduction/interruption or with alteration of the dose of a concomitant AED.

1.7.4 *Pregnancy*

The sponsor updated the number of pregnancies and adverse outcomes occurring on Sabril®. There have been no substantial changes in the number or types of adverse pregnancy outcomes reported.

There is little available information regarding lactation and Sabril®. The sponsor reported that in a sample of one, Sabril® was detected in breast milk, in lower concentrations than plasma. The sponsor also reported that an infant was born drowsy to a mother taking Sabril® and remained that way until the child stopped breast-feeding.

1.7.5 *Cancer*

In the studies included in the final safety update, 12 subjects were diagnosed with cancer. For the entire database, 33 Sabril® exposed individuals were diagnosed with cancer. The most commonly recorded site of cancers was the CNS (14/33). These cancers were predominantly reported in secondary studies and spontaneous reports. None were diagnosed in subjects from US studies. Three subjects were diagnosed with brain tumors in primary non-US studies. In one of these subjects, an astrocytoma was identified on the baseline CT and the subject was withdrawn from the study. One of the remaining patients was diagnosed with a glioma after 8 months of exposure and the second had a left temporal tumor of unknown histology following 12.6 months exposure. From the secondary studies, there were 4 patients diagnosed with brain tumors. One subject appeared to have metastatic disease (colon and liver tumors also mentioned). The remaining 3 subjects were diagnosed with astrocytomas following 8.5-28.7 months of exposure. Seven patients were diagnosed with brain tumors from ongoing studies (1), compassionate use (3), and post-marketing use (3). The reported types included glioma, astrocytoma, and unknown. Although brain cancers were the most commonly diagnosed cancers, they were relatively uncommon in the US and primary non-US studies and the exposure time prior to diagnosis was relatively short in most cases.

1.7.6 *Disability*

The sponsor identified 12 patients who developed at least 1 disability in the safety update. The events leading to disability included visual field defect (6), arthrosis (2), CVA (2), intracranial hemorrhage (1), macular degeneration (1), pneumothorax (1) and broken bone (1).

In the entire database, there were 41 events that were permanently disabling or that resulted in significant disability or incapacity. Fifteen of these were eye related. None of the eye related events occurred in completed US or non-US studies. One report of macular degeneration came from an ongoing study and the 14 remaining eye related disability cases were identified from

spontaneous reports. Of the eye reports, 9 mentioned restrictions of visual field. The next most common disability was behavioral event (9) including aggression and psychosis.

1.7.8 Life Threatening Events

The sponsor integrated the life threatening events from the safety update with the information from the NDA amendment. Forty-seven individuals had 1 or more life threatening events through 3/15/97. The two most commonly reported life threatening events were increase in seizures (12) and suicide attempt (9).

1.7.9 Events Requiring Medical Intervention

The sponsor did not identify any events for this category in the studies included in the safety update.

1.7.10 Medically Serious Events

When concerns arose about visual AEs and the potential for intramyelinic edema (IME), the sponsor categorized the vision and MRI abnormality reports as medically serious to speed reporting. There were 21 vision related medically serious reports from 1/1/96 through 3/15/97. Twenty reports included visual field defects and 5 mentioned optic atrophy. In addition, there were 3 reports of abnormal MRI's (cases previously reviewed with the interim safety update).

Through the safety update cutoff date, there have been a total of 42 reports mentioning visual field defects, 18 reports of optic atrophy, 2 reports of optic neuritis, 1 report of optic vasculitis, and 1 report of myodesopsia. From completed US and non-US studies, there have been 10 reports of visual field defects, 3 of optic atrophy, and 1 of optic vasculitis. In compassionate use the sponsor identified 1 patient with optic atrophy and 2 with optic atrophy plus visual field defects. From spontaneous reports there have been 36 medically serious ophthalmologic adverse events. Most of these were visual field defects.

1.8 Adverse events regardless of severity

1.8.1 Safety Update

The sponsor's safety update focused on AE's for the newly completed US and primary non-US studies by type of study (controlled, uncontrolled). In addition, they provided overall AE percentages following the integration of the safety update data with the data from the NDA amendment. My aim in reviewing the safety update was to describe the AE experience from these 14 studies and to identify any inconsistencies with previous submissions. In order to achieve this goal, I reviewed the sponsor's summary of adverse events. I noted the frequency for commonly occurring events for the controlled trials and reviewed information for the comparator drugs. I then compared the frequency of events in the safety update to the frequencies reported in the NDA amendment. In addition, I reviewed sponsor's table 9-15, which compared the percentages of individuals reporting adverse events in the amendment to the safety update for the epilepsy trials. I created a summary table for events reported in at least 1%, and that differed in frequency by at least a factor of 2 when comparing the NDA amendment to the safety update. In a separate table, I listed the events in the safety update occurring in at least 1% of those enrolled and that were not reported in the epilepsy studies in the NDA amendment. These 2 comparisons focus on changes from previously reported percentages for Sabril® exposed individuals and do not include control groups, which would be required to comment on relatedness to drug.

1.8.2 Epilepsy studies

The controlled epilepsy trials in the safety update used active comparator groups (valproate, carbamazepine). The percentage of subjects reporting AEs was 83% (280/338) for Sabril®, 66% (75/113) for valproate and 85% (194/229) for carbamazepine. Notably, valproate was less

frequently associated with CNS and psychiatric AE's than Sabril® and carbamazepine had an increased risk of skin AEs. The following table compares the commonly reported adverse events for Sabril®, valproate, and carbamazepine.

A comparison of selected adverse events from the newly completed controlled trials included in the final safety update

Event	Sabril®	Valproate	Carbamazepine
Drowsiness	23% (78/338)	16% (18/113)	28% (64/229)
Fatigue	18% (60/338)	13% (15/113)	21% (49/229)
Dizziness	12% (42/338)	6% (7/113)	13% (29/229)
Weight increase	10% (34/338)	10% (11/113)	5% (11/229)

Compared to the data presented in the NDA amendment (Table F1: Incidence of Adverse events by preferred terms for US and Primary Non US placebo controlled epilepsy trials), the percentage of Sabril® subjects reporting these events has not substantially changed.

For both the US and non-US uncontrolled trials, the most commonly reported body systems for AE's were CNS, GI, and Psychiatric. Drowsiness, headache, infection viral and fatigue were commonly reported events in these trials. There were no new cases of hepatic failure, renal failure, Stevens Johnson syndrome, aplastic anemia, or rhabdomyolysis.

1.8.3 Other indications

Drowsiness (22%, 16/73), bronchitis (12%, 9/73), and agitation (11%, 8/73) were the 3 most commonly reported adverse events in trials for indications other than epilepsy. There were no recorded cases of Stevens Johnson Syndrome, renal failure, hepatic failure, aplastic anemia, agranulocytosis or rhabdomyolysis in subjects receiving Sabril® for other indications.

1.8.4 AE's by subgroups

The risk of adverse events in the safety update was compared across several different demographic subgroups. Such an analysis is performed when one is interested in detecting evidence of effect modification. Unfortunately, the risk stratified by these demographic variables in a similar but unexposed group was not presented; therefore we cannot determine if effect modification occurs for these events. * The sponsor presented the following gender differences in which the percentage of individuals reporting an event was at least double when comparing sexes:

Adverse events by gender in vigabatrin patients

	Males	Females
Aggressive reaction	2.8% (24/861)	0.9% (8/901)
Allopecia	0.6% (5/861)	2.3% (21/901)
Neuropathy	0.9% (8/861)	2.1% (19/901)
Hypoesthesia	1.6% (14/861)	4.2% (38/901)

The sponsor also presented AE's stratified by age groups. Because they used 6 categories for a relatively small number of patients and there were few subjects in the youngest and oldest categories, comparisons between strata are not very meaningful. In addition, there was no presentation for a similar, unexposed (control) group.

* The rates of these events may vary as a function of any of these demographic variables in a similar unexposed population. Therefore we cannot presume that the observed differences in reporting are the result of effect modification associated with drug. Any differences between groups could be related to factors other than exposure to drug (patient population, study design, etc.).

1.8.5 Integrated summary of adverse events

The sponsor combined data on adverse events for epilepsy studies from the final safety update with AE data from epilepsy studies included in the NDA amendment. One must consider that there is substantial variability in the design and duration of the studies pooled in this analysis. This analysis, which uses persons in the denominator to calculate risk, pools results from controlled and uncontrolled trials. Following this pooling, there were no changes in the 3 most commonly reported body systems for adverse events compared to the AE presentation in the NDA amendment (CNS, Psychiatric, GI). The addition of the data from the 14 studies in the safety update had little effect on the ranking of adverse events by percentage of exposed subjects reporting an event.

In the following table, I list the events reported by at least 1% of those enrolled, and that differed in risk by at least a factor of 2 when comparing the amendment to the safety update.

This analysis serves to demonstrate differences between exposed groups in the NDA amendment and the safety update. Without an unexposed comparator group, this information is insufficient for exploring the question of drug relatedness.

The frequency of selected adverse events from epilepsy studies included in the NDA amendment compared to the epilepsy studies included in the safety update

Event	NDA Amendment (n=1208)	Safety Update (n=1667)
Hyperkinesia	2.1% (25)	0.4% (7)
Hyporeflexia	1.8% (22)	0.7% (12)
Hyperreflexia	1.5% (18)	0.6% (10)
Nervousness	2.9% (35)	1.3% (22)
Psychosis	0.7% (9)	1.6% (26)
Euphoria	1% (12)	0.3% (5)
Dry Mouth	1.2% (15)	0.6% (10)
Stomatitis Aphthous	0.5% (6)	1.1% (18)
Ther response incr	0.5% (6)	1.1% (18)
Rigors	1.1% (13)	0.4% (6)
Bronchitis	1.3% (22)	0.3% (5)
Erythema	1% (12)	0.4% (6)
Weight decreased	0.5% (6)	1.1% (19)
Retinal disorder	1.1% (13)	0.3% (5)
Dysmenorrhea	3.3% (40)	1.4% (24)
Vaginitis	1.6% (19)	0.8% (13)
Ear disorders	1.2% (14)	2.6% (44)
GGT increased	1.6% (19)	0.4% (7)

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Highlighted events have increased frequency in the safety update compared to the amendment.

The following table includes the frequencies for the adverse events reported by at least 1% of those enrolled in trials included in the safety update, but not reported in the amendment.

Adverse events reported in epilepsy trials included in the safety update at a frequency of at least 1% and not reported in epilepsy trials in the amendment

Event	Frequency
Convulsions aggravated	3.1% (52)
Fracture pathological	1.1% (18)
Photopsia	1.1% (19)

The explanation for why these events occur in the safety update appears to be related the use of a different coding dictionary for these studies.

I reviewed sponsor's table 9-15 and appendix D1 summary 1, and appendix D1 listing 11 to identify any infrequent but potentially important adverse events. There were no events coded as Stevens Johnson Syndrome, aplastic anemia, agranulocytosis, liver failure, or rhabdomyolysis. Three Sabril® exposed subjects were noted to have skin exfoliation listed as an adverse event (verbatim terms described localized scaling of skin). One Sabril® exposed patient developed an event coded as acute renal failure (VGPR0098-1192-0002-verbatim pending kidney failure) and one developed a renal calculus (VGPR-0098-1262-0007). Neither of these patients was listed with the hospitalizations.

Comments

This safety update includes data from 14 studies in which 1773 subjects were exposed to Sabril®. Following integration the sponsor states that 3,339 subjects have been exposed to Sabril® in epilepsy trials. To update the post marketing exposure the sponsor used worldwide sales figures to estimate that individuals have been exposed to Sabril® and estimates 350,000 person years of use. The demographics of the subjects included in the safety update and the amendment were similar. There were 10 (0.6%, 10/1667) deaths within 30 days of last exposure to Sabril® in the 14 trials in the final safety update. The sponsor identified 145 deaths within 30 days of last exposure to Sabril® from all sources (clinical trials, spontaneous reports, etc.). The ranking of the most common causes of death as presented in the amendment remains unchanged following the integration of the safety update data. The updated SUDEP rate (3.4/1000PY) is minimally changed from the estimate provided in the amendment and remains within the range reported for other approved AEDs. Following integration of safety update data, there were no material changes in the reasons for discontinuations, hospitalizations, overdoses, pregnancy data, cancers, events resulting in disability, or other serious events. There are few changes in the frequency of AEs regardless of severity.

b(4)

2. Pediatric Safety

In the approveable letter, the division requested a separate review of safety in pediatric patients. The sponsor provided pediatric safety information in the NDA and amendment as part of the overall presentations of safety. In this presentation, the pediatric experience has been extracted and presented separately from the adult data. This information was provided in the 4/24/98 submission.

2.1 Exposure

2.1.1 Studies Enrolling Pediatric Subjects

Pediatric patients were defined as subjects ≤16 years of age. There are 6 completed non-US studies that enrolled only pediatric subjects, all for the infantile spasm indication. In addition, 1 US and 34 non-US protocols enrolled both pediatric and adult patients.

2.1.2 Patient Enumeration

The sponsor identified 489 pediatric patients exposed to Sabril® in the development program. The subjects were enrolled in the following types of studies:

Clinical Pharmacology, n=1

Controlled epilepsy studies, n=46 (39 primary, 7 secondary)

Uncontrolled epilepsy studies, n=340 (175 primary, 173 secondary)

Ataxia and tremor studies, n=5 (all primary)

Infantile spasm, n=107 (all primary)

A total of 321 pediatric subjects were exposed in completed US and primary non-US studies. Another 13 pediatric patients were involved in an ongoing study at the time of the cutoff date.

2.1.3 Pediatric Dose/Duration Exposure Data

Table 30 Sra-V19-P8-(see appendix) provides the extent of Sabril® use at each of the following 4 dose ranges: ≤40mg/kg/day, >40-60mg/kg/day, >60-80mg/kg/day, and >80mg/kg/day. There were 220 pediatric patients exposed in US and primary non US studies, excluding infantile spasms indication. A total of 60 patients have been exposed for at least 1 year. For the infantile spasms indication (3 studies), the maintenance dose was 150mg/kg/day. Subjects were titrated rapidly to this dose and the sponsor did not include a summary dose/duration table for these subjects.

2.2 Demographics

The sponsor summarized the demographics for a subset of pediatric patients (those receiving Sabril® as their first randomized treatment) from US and primary non-US completed clinical studies in table 32 Sra-V19-P12. That information is included in the following table.

Demographic data for vigabatrin pediatric patients

	US N=13 n (%)	Non US N=139 n (%)
Gender		
Male	5 (39%)	54 (39%)
Female	8 (61%)	61 (44%)
Unknown	0	24 (17%)
Age (yrs)		
Mean ±SD	13.2±2.71	7.3±6.82
Range	8, 16	0, 16
<2	0	60 (43%)
2-<12	4 (31%)	24 (17%)
12-16	9 (69%)	55 (40%)
Race		
Caucasian	11 (85%)	33 (24%)
Black	1 (8%)	0
Other	1 (8%)	2 (1%)
Unknown	0	104 (75%)
Weight (kg)		
Mean±SD	47.9±13.28	30.1±23.8
Range	27.22, 68.04	4.67, 82
<10	0	52(37%)
10-<35	2(15%)	33(24%)
35-<60	8(62%)	29(21%)
60-<90	3 (23%)	25(18%)

With the exception of race, the group was relatively evenly distributed across these demographic strata.

2.3 Pediatric Mortality

The sponsor reported 25 pediatric deaths from all sources. The deaths by source of information were:

- 1 from non-US completed study
- 4 from miscellaneous sources
- 6 from non-US compassionate use
- 14 from spontaneous reports/literature
- 29 from the PEM study

The circumstances surrounding these deaths have previously been reviewed with the amendment and interim safety update information. The listed causes of death included cardiac arrest, infections, respiratory events, epilepsy, SIDS, cancer, hepatic failure, renal failure, microcephaly, and anemia (Sra-V19-P21).

2.4 Overall Dropout profile

Fifteen percent (46/321) of US and primary non-US pediatric patients discontinued from Sabril® trials. The most common reason for dropout was loss of efficacy (6%, 20/321), followed by adverse event (4%, 14/321). Of the 214 pediatric subjects exposed to Sabril® in epilepsy studies, 13% (28/214) discontinued. Reasons for dropout included loss of efficacy 5% (10/214), and AE 5% (10/214). In infantile spasms studies, 16% (16/101) dropped out. Reasons for discontinuation included loss of efficacy 10% (10/101), AE 3% (3/101). In ataxia/tremor trials 20% (1/5) dropped out and the reason given was adverse event.

2.5 Discontinuations due to Adverse Events

The sponsor identified 43 pediatric subjects who discontinued trials due to adverse events. Thirty-two discontinued from the following study groups: primary non-US (23), and secondary non-US (9) studies. The most frequently reported events leading to discontinuation were convulsion (6), hyperkinesia (6), and aggressive reaction (4).

2.6 Serious Adverse Events

As with the previous submissions, the sponsor did not present an overall review of serious adverse events but rather a collection of separate reviews. The following sections discuss the sponsor's presentations of these events.

2.6.1 Hospitalizations

The sponsor states that there have been 141 pediatric hospitalizations for adverse events from all sources. Four hospitalizations were from US studies and 16 from primary non-US studies. The remaining hospitalizations were from secondary non-US studies (10), ongoing studies (30), Japanese studies (2), non-US compassionate use, spontaneous reports, literature reports, and miscellaneous sources (79). I reviewed the sponsor's summary of AE's leading to hospitalization for the US and non-US studies. Of the 489 pediatric patients enrolled, 30 were hospitalized. The most common events leading to hospitalization, as with the adults, were convulsions, convulsions grand mal, and convulsions aggravated. No subjects from these trials were hospitalized for dermatologic events, hepatic events, agranulocytosis, aplastic anemia, rhabdomyolysis, or renal failure. Of the hospitalizations from other sources (spontaneous reports, literature reports, etc.), 7 were for hepatic events (hepatic insufficiency, hepatic coma etc.), 3 for rashes, and one for aplastic anemia.

2.6.2 Overdose

The sponsor reports information on 6 pediatric overdoses. Three were accidental, one was a suicide attempt and two were for unknown reasons. The dose ingested ranged from 6-20g and Sabril® was the single suspect drug in 4 events. In the remaining two events, lamotrigine and carbamazepine were also involved. The symptoms reported included coma/unconsciousness (2), ataxia, auditory hallucinations, vomiting, dehydration, abnormal behavior and speech disorder (1 each). Three patients were hospitalized, and 3 were treated with charcoal/gastric lavage. Five of the 6 events had outcome information and these reportedly resolved without sequelae.

2.6.3 Status Epilepticus

Thirty-five pediatric patients taking Sabril® experienced status epilepticus. Ten were from US and primary non-US studies. None of these events resulted in death. The risk for status in children

taking Sabril® for epilepsy (3.4%, 13/382) was similar to the risk described for adults (3.1%, 102/3339) in the final safety update.

2.6.4 Cancer

A child from a non-US primary study was diagnosed with a left temporal tumor (histology not reported). A second pediatric patient, identified by a spontaneous report, was diagnosed with an astrocytoma and non-Hodgkin's lymphoblastic lymphoma. The UK PEM study identified a child exposed to Sabril® who was diagnosed with brain cancer.

2.6.5 Disability

During clinical trials, no pediatric patients developed disability (events that are permanently disabling or resulting in persistent or significant disability or incapacity). Nine pediatric patients exposed outside of clinical trials (8 post-marketing, 1 compassionate use) experienced events that led to disability. Included in this group were ophthalmologic events (visual field defect, optic neuritis, and decreased visual acuity), behavioral changes, choreoathetosis, MRI changes, and autoimmune thrombocytopenia with cerebral hemorrhage.

2.6.6 Life Threatening Events

Ten pediatric patients taking Sabril® experienced life-threatening events. Two were from US studies, one from a Japanese study and the remainder from spontaneous reports. The reported events included increase in seizure frequency or status, near drowning, delayed recovery following anesthesia, respiratory depression, hematemesis, leukopenia, neutropenia, anemia, and autoimmune thrombocytopenia with cerebral hemorrhage.

2.6.7 Medically Serious Events

This category included ophthalmologic complaints and MRI abnormalities. Two pediatric patients were included in this presentation, both from spontaneous reports. These children experienced visual field defect with optic atrophy and optic neuritis with optic atrophy.

2.7 Adverse Events Regardless of Severity

The sponsor's presentation consisted of AE information stratified by age, gender, and dose. There was no presentation of comparison group (placebo or active drug) data to allow assessment of relationship to drug. This is due to the fact that only 49 patients were exposed in pediatric controlled epilepsy trials. The most commonly reported adverse events (those in $\geq 2\%$) in the pediatric patients are listed in the following table (source Sra-V19-P283):

AE's occurring in more than 2% of the pediatric patients exposed to Sabril®

Drowsiness	14.3%
Fever	8.4%
Hyperkinesia	7.2%
Agitation	5.9%
Fatigue	5%
Convulsions	4.7%
Trauma injury	4.7%
Weight increase	4.7%
Bronchitis	3.7%
Vomiting	3.4%
Convulsion grand mal	3.4%
Headache	3.1%
Throat irritation	3.1%
Ataxia	2.8%

URI	2.8%
Appetite increased	2.8%
Otitis Media	2.8%
Insomnia	2.5%
Constipation	2.5%
Rhinitis	2.5%
Hypertonia	2.5%
Gait Abnormal	2.2%

I reviewed the sponsor's table of all AE's by patient to identify events occurring less frequently but of potential clinical significance. There were no events suggestive of hepatic failure, rhabdomyolysis, Stevens Johnson Syndrome, aplastic anemia, agranulocytosis, or renal failure listed for pediatric subjects receiving Sabril® in clinical trials.

2.7.1 AE's by Age Group

As with the overall AE presentation, there is no comparator group data for the different age strata to allow for assessment of effect modification. The percentage of enrolled subjects reporting AE's by age group were 60% (59/98) for the <2yr old group; 50% (66/132) for the age 2-12yr old group; and 73%(66/91) for the age 12-16yr group.

The most commonly reported body systems for the <2yr old group were: CNS 37% (36/98); Respiratory 21% (21/98); Psychiatric 13% (13/98); and GI 13%(13/98).

For the 2-12yr old age group, the most commonly reported AE's were in the following groups: CNS 31% (41/132), Metabolic 11% (15/132), and Psychiatric 11% (14/132). In the 12-16yr old group, the most commonly reported body systems for AE's were: CNS 55%(50/91), GI 18%(16/91), Psychiatric 12% (11/91) Metabolic 12% (11/91) and Body as a whole 12% (11/91).

The most frequently reported AE's by age are included in the following table.

The most common adverse events in pediatric patients by age groups

<2 years old	2-12 years old	12-16 years old
Drowsiness (17%, 16/98)	Drowsiness (10%, 13/132)	Drowsiness (18%, 16/91)
Bronchitis (10%, 10/98)	Hyperkinesia (10%, 13/132)	Fatigue (13%, 12/91)
Agitation (8%, 8/98)	Agitation (6%, 8/132)	Headache (10%, 9/91)

2.7.2 AE's by Gender

As with the previous presentations, there are no comparator data in this presentation. Considering only those exposed to Sabril®, AE reporting by gender was similar for the <2yr old group, demonstrated a slight male predominance in 2-12yr old group, and a slight female predominance in the 12-16yr old group.

2.7.3 AE's by Dose

Because of the dose titration that occurred in these studies, individual patients could be included in more than 1 dose category. The sponsor counted patients reporting a specific AE and categorized the event by the dose the subject was taking at the time of the event. They used the total number of individuals exposed to the dose range, regardless of duration, as the denominator to calculate risk for events. Since patients could have reported an event at more than one dose, and patients contributed to more than one dose category, there is the potential for considerable overlap in these calculations. In addition, events occurring at or near the time of titration could be misclassified with respect to the dose at which the event occurred. Using the sponsor's approach, the overall AE risk was lowest for the 60-80mg/kg group (13%), and similar among the remaining dose groups (26-44%). None of the events exhibited stepwise increases with dose.

There was little evidence of dose response but time and misclassification with respect to dose potentially confound this analysis.

Comments

In this section of the response to the approvable letter the sponsor provided a summary of the pediatric experience for Sabril®. The sponsor reported that over 400 pediatric subjects have been exposed in clinical trials. Sixty pediatric patients have been observed for more than 1 year. Looking only at the US and primary non-US data, considered the highest quality throughout prior reviews, 321 subjects have been exposed, most in uncontrolled epilepsy studies. In the sponsor's review, there did not appear to be any safety signals of concern that are specific for the pediatric population. Within the clinical trial data, there was insufficient experience to allow meaningful comparison between Sabril® exposed and control groups. There were no material differences in the commonly reported events when compared to adult trials. As with adult patients, the spontaneous report data for pediatric patients includes several events of concern. Ophthalmologic events, including visual field defects, were identified in pediatric patients. There were 7 reported serious hepatic events including hepatic function abnormal, hepatic necrosis, and acute liver failure. In addition, the sole known case of aplastic anemia in a Sabril® patient occurred in a pediatric patient. The lack of details makes it difficult to determine the exact relationship between Sabril® and many of these events. We have no estimate of post marketing pediatric usage to allow calculation of pediatric event reporting rates.

In limited use, the sponsor has not detected any safety issues that appear unique to the pediatric population. The database is relatively small and has limited power to detect infrequent events.

3. Response to Specific Requests for information included in the approveable letter

Within the approveable letter, the division included specific requests for information that was omitted in previous submissions. In addition the sponsor was asked to group information differently or asked to provide information to help clarify certain topics. The following sections discuss the sponsor's response to these requests. The sponsor provided this material in the 4/24/98 submission.

3.1 Clinical Descriptions of selected events

In reviewing the controlled trial data in the NDA amendment, there were several adverse events that were reported in a higher percentage of Sabril® exposed than placebo exposed subjects. We were interested in reviewing these events in greater detail. In many cases we were uncertain of what the sponsor was reporting based on the provided preferred term (ex. Did UTI mean dysuria, cystitis, pyelonephritis? Was the event associated with nephrolithiasis?) To better understand these events, we asked the sponsor to provide clinical descriptions for the events listed as dyspnea, dependent edema, dysmenorrhea, and urinary tract infection.

3.1.1 *Dyspnea*

In the North American controlled trials, 6 subjects reported 8 episodes of dyspnea. Two of the 6 individuals had a history of dyspnea prior to beginning the trial (etiology not provided). Seven of the 8 episodes were considered mild by the investigator. No subjects required hospitalization or withdrew, and the sponsor reported that all of the individuals recovered. One episode required intervention, in that case an investigator lowered the dose of a concomitant AED. One of the patients was given a diagnosis for this symptom (hyperventilation syndrome).

3.1.2 *Dependent Edema*

Seven subjects had 9 episodes of dependent edema in the North American controlled trials. Investigators described 6 episodes as mild and 3 as moderate. One event was treated with elevation of the extremities and another with medication (diuretic). None of the events led to hospitalization or discontinuation from the trial. The sponsor reported that the event resolved for all subjects but one (ankle swelling in this case attributed to weight gain, which persisted).

3.1.3 *Dysmenorrhea*

Fifteen subjects had 42 episodes of dysmenorrhea in the North American controlled trials. None of the 15 required hospitalization and none discontinued from the trial for this event. All but one patient was treated with NSAIDs and/or OTC analgesics. Investigators felt the event was mild for 10 individuals, moderate for 2, mild to severe for 1 and severe for 2. Of the 15 individuals with dysmenorrhea, 6 had this complaint prior to entering the study. Of the 3 with severe dysmenorrhea, all had a prior history of dysmenorrhea and one had a diagnosis of ovarian cystic disease prior to the trial.

3.1.4 *Urinary Tract Infection*

Thirteen subjects (11 female, 2 male), had 16 UTIs in North American controlled trials. Investigators described 8 of the events as mild and 8 as moderate. Culture results were available for one of the episodes. All 16 events were treated with antibiotics, and all but one resolved (this case was still being treated at the end of the study). None of the events resulted in hospitalization but one did lead to discontinuation from the study (073-007, 61 YO female patient with UTI and urinary retention). None of the cases were diagnosed as pyelonephritis and none were associated with nephrolithiasis.

3.2 **Dose/Duration Information**

The division requested information from the sponsor regarding combined dose and duration of exposure to vigabatrin, especially for the higher dose groups. While the sponsor did provide separate tables for dose and duration, they did not provide a description of combined dose and duration data in the NDA amendment. Therefore we were unsure about exposure for different dose levels. In the response to the approveable letter, the sponsor provided a table that listed the length of exposure for individuals in 3 dose group categories (4-5g/day, 5-<6g/day, and ≥6g/day) for the US and primary non-US studies, excluding infantile spasms. Because of the dose titration that occurred in these studies, subjects may be included in more than one cell and cells cannot be added to arrive at the total number of individuals exposed. The sponsor states that 3209 individuals were exposed to Sabril® in the included studies. Of those exposed, 2027 were treated for 6 months with 436 in the 4-<5g/day group, 160 in the 5-<6g/day group, and 155 in the ≥6g/day group. The sponsor states that 1673 were treated for 1 year with 215 in the 4-<5g/day group, 69 in the 5-<6g/day group and 106 in the ≥6g/day group. The entire table is included in the appendix (Table 1 Sra-V1-P25).

3.3 **Use of Individual Case Summaries (ICS)**

The division requested information about the extent of reliance upon data from the Individual Case Summaries (ICS) in preparing the amendment. The medical officer reviewing the NDA recognized that in some instances the sponsor included patient data from an ICS as opposed to the case report form (CRF). This was considered inadequate since these summaries were completed retrospectively, by abstracting data from CRFs and medical records. One important concern was that the use of the ICS could result in incomplete reporting in situations where all data from CRFs were not included. Again in the amendment, the sponsor reported that some of the data included in presentations were from ICS's, although they did not quantify the amount. In the response to the approveable letter, the sponsor provided a response to our request regarding information about

the use of ICS data. They affirmed that supplementary information from the ICS was used only when considered necessary to complete a presentation for a patient. They provided examples such as when information about AE's, termination from the study, or dosing information was not included in the CRF. To provide some perspective, they reported that of the 8,826 AE's reported in the NDA amendment, 350 (4%) were from ICS sources and would not have been reported if the ICS wasn't used.

3.4 Urinalysis lab data

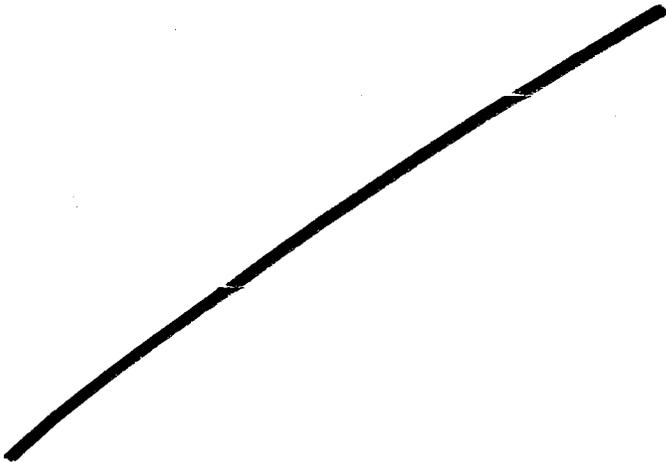
In their presentation of lab data in both the NDA and the NDA amendment, the sponsor provided discussions of urine pH and specific gravity data but omitted microscopic and protein results. In the response to the approveable letter, the sponsor included these analyses. They provided data from studies 021, 024, and 025, the North American controlled trials. Their analyses demonstrated no substantial differences in the number of individuals with outliers for RBC, WBC, or protein when comparing Sabril® exposed to placebo exposed individuals in these studies.

3.5 Coagulation lab data

Despite collecting blood coagulation labs (PT), the sponsor did not provide a summary of these data in the NDA or the NDA amendment. In the response to the approveable letter, the sponsor included analyses of PT lab data from study 021, 024, and 025. When looking at the number of individuals with outliers at various levels (i.e. PT>13.5, PT>15, and PT>20) there was no material difference in the percentage of Sabril® and placebo exposed meeting these outlier criteria.

3.6 Labeling Information

When the proposed labeling was reviewed as part of the amendment submission, the division made specific requests for data in order to improve the description of selected events. This section reviews the sponsor's response to these requests. I reviewed these responses by comparing the sponsor's presentation to data previously submitted in the NDA, NDA amendment, and final safety update.



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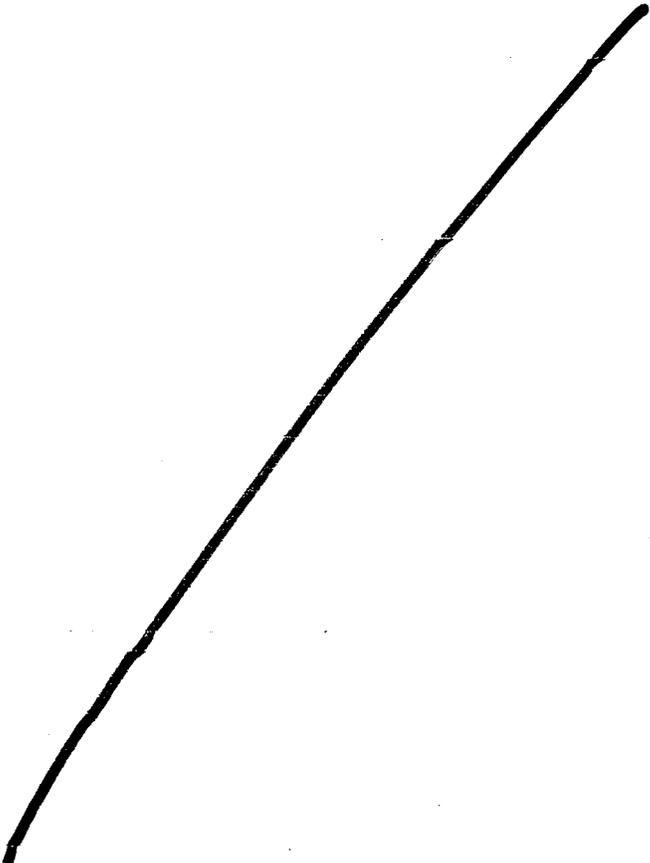
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 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)



b(4)

Comments

In the response to the approveable letter, the sponsor provided information addressing the specific requests made by the division. The dose/duration table clarified the exposure experience for subjects enrolled in vigabatrin trials. The sponsor addressed the use of Individual Case Summaries and indicated that accounted for <5% of the AEs reported in trials. Summaries of urinalysis and coagulation lab data did not reveal any new concerns. The sponsor's clinical descriptions for several events suggest that while these events occurred more frequently in vigabatrin exposed patients, they were generally mild and in most cases did not require therapeutic interventions. Within the proposed labeling, the sponsor provided the information requested in the response to the approveable letter. Following the regrouping of the cognitive/neuropsychiatric adverse events, the category containing confusion still appears to be

too broad to be clinically useful. The sponsor appears to have done an acceptable job in describing time to event and dose response for these events.

The following sections contain reviews of submitted information addressing specific topics of concern. During the development program and review process, several safety concerns have been identified. The sponsor has provided updates throughout these 3 submissions related to vacuolization (MRI, EP and autopsy data), peripheral neuropathy, hepatic toxicity, pancreatitis, and ophthalmologic events. In the following sections, I review the information for hepatic toxicity, pancreatitis, and ophthalmologic events. The remaining topics are being reviewed by Dr. Sherry and will appear in a separate memo.

4.0 Hepatic Failure

4.1 New Cases in the Final Safety Update

In the safety update (submitted 1/20/98), the sponsor identified two reports of hepatic AEs that were not included in the amendment. One case was identified from the published literature and one from a post marketing trial from India. Both of these events were included in the non-integrated safety update and were reviewed under the non-integrated safety update section in the NDA amendment review. The sponsor has not identified any new cases of hepatic failure occurring during the safety update period.

4.2 Proposed Labeling

In the approveable letter, the division requested that the sponsor provide clinical descriptions of the liver failure cases and that they provide an estimate of the rate hepatic failure resulting in death or transplant that could be compared to the background rate. The sponsor's responses to these requests were included in the 4/24/98 submission.

The sponsor disagreed with a comparison of the fulminant hepatic failure for vigabatrin with an untreated, non-epileptic population and feel that such a comparison is inappropriate and inconsistent _____ for other anti-epileptic agents. Ideally we would compare rates for similar populations, but unfortunately those comparative data are not available. The use of a general population hepatic failure risk comparison would not be unique to this anti epileptic drug. Felbatol labeling compares, in general terms, the hepatic failure risk for exposed patients to that in the general population. Using the sponsor's calculations, they estimate a rate of liver failure resulting in death or transplant of 2.6 per 100,000 patient years (9/350,000PY), which is 3.4 times the general population rate (not adjusting for under-reporting).

b(4)

b(4)

Comments

The sponsor has not provided any new cases of hepatic failure. They have provided an estimate of the rate of hepatic failure _____ In addition they feel

5. New Pancreatitis Cases

The sponsor identified 2 cases of pancreatitis in subjects from clinical trials. The first case occurred in a female with cholecystitis who subsequently underwent cholecystectomy. The second case occurred in a female hospitalized for sepsis (episode resolved on Sabril®). Two additional cases were also identified from spontaneous reports. The first case was confounded by the use of valproate and the second case had no available supporting information.

6. Ophthalmologic Information

The sponsor included information pertaining to ophthalmologic abnormalities in subjects treated with vigabatrin in all three of the reviewed submissions. The presentations included new information from vigabatrin clinical trials, reviews of reports by ophthalmologic consultants, opinions from a panel of consultants convened to review this issue, and epidemiologic studies. These presentations are reviewed in the following sections. Since the development of this information occurred and was reported over time, some of the studies build upon or refer to previous studies or reviews. Therefore, the information is presented in chronological order, by the submission in which it appeared.

6.1 Ophthalmologic Information presented in the final safety update (1/20/98)

In the Final safety update submission the sponsor presented ophthalmologic data collected from several sources. They included information from vigabatrin trials (protocols VI-PE-0192 and its extension VI-PE-0294 and from protocol VGPR0098), consultant reviews of eye findings, the opinions of an expert panel, and the results of epidemiologic studies.

6.1.1 Vigabatrin trial data

Study VI-PE-0192 was a randomized, parallel, double-blind, placebo controlled trial in pediatric subjects (ages 4-16) that included baseline and end study visual acuity testing, funduscopy, and visual field testing (confrontational). Subjects randomized to Sabril® (n=28) were treated for 17 weeks. No retinal or visual field abnormalities were identified in the treated or control subjects. Following the controlled phase, 44 subjects entered an open label extension, which lasted approximately 28 weeks. Forty-one of these individuals had end study exams. Again, the sponsor reported that no retinal or visual field abnormalities were detected in those subjects with end study exams. The longest duration of therapy for any of these subjects (including both RCT and EXT) was 11.4 months.

One subject from this study did develop visual field abnormalities after completing the extension. This 17-year-old female (14-0090) received vigabatrin for 280 days during the RCT and EXT. Her baseline eye exam for the RCT was essentially normal. During the extension trial she began having difficulty reading overheads at school. An ophthalmology exam documented that her visual acuity was 20/25 OU and her fundoscopic exam was normal. She was diagnosed with monofixation syndrome (using mainly right eye when viewing in binocular conditions). Upon completing the extension, her visual acuity was 25/25, visual fields were normal, and funduscopy was not done. VEPs showed a prolonged P100 latency with stimulation of the left eye. After completing the trials, she continued on commercially available vigabatrin. Within a few weeks, she developed headaches, left retrobulbar pain, and blurred vision. Ophthalmologic exam

demonstrated visual field constriction. Complaints continued over the next few months and she developed an acute episode of visual loss associated with pain in the left eye. The sponsor reported that she had visual field reduction of temporal and nasal fields of both eyes. She apparently continued on vigabatrin and experienced worsening visual acuity (20/50 OD, 20/60 OS) and according to the consultant, a bitemporal hemianopsia. One of the consultants suggested MRI or CT scanning to evaluate this problem (unsure if it was done) but did not comment on possible relatedness to vigabatrin. A second consultant raised the possibility of occipital seizure, but felt that the association of visual loss with vigabatrin was unlikely. No further follow up was provided.

Study VGPR0098 is an ongoing, open label, flexible dose trial in adults in which over 1000 patients have been exposed. One hundred forty-six of these individuals had prior exposure during previous vigabatrin studies. These 146 subjects were selected to undergo eye exams. Exams were not performed on 17 of the 146 subjects because they either dropped out prior to exam (15) or their exam was not completed by the data cutoff date for inclusion in this report (2). The 129 subjects who were tested underwent visual acuity, external eye, fundoscopy, and slit lamp exams. Visual field testing was not performed. The sponsor's consultant reviewed the testing results and considered the abnormalities detected on exams of the 129 subjects who participated to be compatible with pre-existing organic disease. One of the 146 subjects (VGST-1218-0001) developed an ocular adverse event after the eye exam. In this case, the subject developed bilateral visual field defects, detected initially when asymptomatic (during a contact lens evaluation). The defect was described as a nasal hemi-ring scotoma on the right and a more complete ring like defect on the left. She had been taking vigabatrin for almost 7 years prior to detection of this problem. According to the sponsor's summary, historical ophthalmologic exams were normal, suggesting that this finding developed on vigabatrin. Follow up exam 5 months and 6 months after detection noted persistence of this finding. It is not clear from the summary when Sabril® was discontinued. No other retinal or visual adverse events were identified in the patients examined from this protocol. No comment was made regarding the patient described above.

Comments

Ophthalmologic exams conducted during vigabatrin study VI-PE-0192 did not detect any cases of visual field defect in a small number of vigabatrin exposed children (n=28). The exposure period was relatively short in this trial (17 weeks) and visual fields were tested by confrontation, which may have been insensitive to small changes. One patient from this cohort did develop visual changes including loss of acuity and visual field defects shortly after completion of the extension. The exact relationship of this event to vigabatrin is unknown. Of the 129 subjects examined from study VGPR0098, one developed visual field defects that apparently occurred while on vigabatrin. The abnormality has persisted during follow up. Visual field testing was not performed as part of the ophthalmologic examinations of these subjects therefore, the prevalence of VFD cannot be estimated for this group.

6.1.2 Review of Medically Serious Ocular Adverse Events

As part of the safety update presentation, the sponsor's ophthalmologic consultant's reviewed the eye-related events included in the category of medically serious events (see above). The consultants reviewed 14 cases of visual field defects and 3 cases of retinal abnormalities. The consultants found no conclusive evidence of a relationship between visual field defects or retinal abnormalities and vigabatrin treatment. They attributed many of the findings to non-organic causes. In general, the reports contained few details. I have summarized the cases in a table located in the appendix.

6.1.3 Advisory Panel Statement

In the final safety update submission, the sponsor provided statements from an advisory panel of ophthalmologists, and neurologists. The sponsor convened this panel in October of 1997 to discuss the reports of visual field changes in those taking Sabril®. Within the body of the safety update, the sponsor provided the executive summary of the panel. In the appendix, the sponsor provided a more detailed account of the panel's findings, which included references to information supporting their conclusions. The sponsor did not provide a description of all of the information that the experts reviewed to arrive at their conclusions. The three documents included in the endnotes of the appendix were 1) an HMR retrospective epidemiology report that is reviewed below, 2) a case series that appeared in BMJ, and 3) a pilot prevalence study that is described below. Additional references were cited in the panel's findings but were not listed with the endnotes. The panel's executive summary has been provided in the following paragraphs. From the more detailed presentation in the appendix of the safety update, I identified the panel's references for their conclusions (cited in parentheses).

-Symptomatic visual field defects have been reported rarely in patients treated with antiepilepsy drugs, including vigabatrin (based on the number of reports of VFDs in the sponsor's database through 6/30/97, package inserts for other AEDs listing VFD as an AE, and from the HMR epidemiology study). A causal relationship with vigabatrin remains to be established. There is some indication in a small group of vigabatrin treated cases, mainly with symptomatic loss, of a unique and specific pattern of bilateral concentric VFC (two references were cited but only one of them was listed with endnotes- a BMJ case series).

-Routine ophthalmologic screening of all patients taking vigabatrin cannot be justified. However, for patients with epilepsy, including those treated with vigabatrin, confrontation testing of the visual field, with specific questioning for symptoms potentially related to VFD should be performed at baseline and during routine follow up of the patient. Patients should be asked to report any visual problems. If new symptoms suggestive of VFD occur, the patient should be referred to an ophthalmologist.

-In patients developing VFD, where the diagnosis is supported by automated perimetry, decisions on vigabatrin treatment should be based upon an assessment of the benefit risk for that individual patient. Similarly, in new patients being evaluated for treatment, in whom visual field evaluation is not possible (e.g., young infants), an individual benefit risk assessment should be the basis for treatment with vigabatrin.

-The benefit risk ratio remains favorable to vigabatrin, particularly in infantile spasms. Use of vigabatrin needs to be evaluated in the context of its overall benefit risk in comparison to the benefit risk of other AEDs.

In the consensus statement, but not included in the executive summary, was the following comment: The occurrence of VFD in untreated epilepsy or epilepsy treated with other drugs, and its possible relationship to severity type and duration of epilepsy and possibly other factors needs to be established.

6.1.4 Epidemiologic studies

Within the final safety update, the sponsor included two epidemiologic studies. The first study examined VFD data using a UK database and the second study was a pilot prevalence study of VFDs in patients taking AEDs other than vigabatrin.

6.1.4.1 UK General Practitioner Database Study

The sponsor's epidemiology team used a UK general practitioner database to conduct a retrospective study examining the association between visual field defects, epilepsy, and AEDs. Patients in the database on the start date of the study with a diagnosis of epilepsy and without a recorded history of VFD were eligible for inclusion. Newly diagnosed cases of epilepsy identified during the study period and without history of VFD, were also included. The outcome of interest was incident cases of VFD.

For the incident cases of VFD (those with VFD first identified during the observation period), the investigators used the day that the VFD was identified as the index day. To determine AED exposure, they identified all of the AEDs that these patients took in the 120 days prior to the index day and calculated the total exposure for each drug. For patients who did not develop VFD during the study (non-cases) they randomly selected a day during their observation period as an index day and then collected exposure information in the same manner as described for the cases.

The investigators also collected demographic information and medical history for each of the patients in the cohort to be used in selected analyses. The investigators calculated overall and drug specific incidence rates and used logistic regression models to compare risk for VFD among the AEDs and to control for potential confounding variables (severity and duration of epilepsy, previous brain surgery, etc.).

The investigators sent questionnaires to the practitioners caring for the VFD patients to collect specific neurologic and ophthalmologic information. This information was forwarded to 2 ophthalmologists who reviewed the data and classified the cases as probable/possible cases (VFD-1) or probable cases (VFD-2). These cases were used in the subsequent analyses.

The investigators identified 16,447 patients with no prior history of VFD in the database. Of these 16,447 patients 54 had a VFD code entered into the database during the observation period. Upon review by the ophthalmologists, 51 were considered probable/possible (VFD-1) and 22 probable (VFD-2) cases of VFD.

Of the 16,447 patients, 11,939 had taken at least 1 AED within 120 days of their index date and 4,508 had no AED exposure. The following table lists the number of patients and the exposure by AED using the investigator's approach.

AED	Exposure by AED	
	Number Exposed	Patient Years Exposure
Overall	11,939	51,219
Vigabatrin	285	968
Carbamazepine	4,233	15,248
Phenytoin	4,830	18,492
Valproate	3,194	11,538
Others	3,799	13,922

Thirty-eight of the probable/possible (VFD-1) cases and 18 of the probable cases (VFD-2) had exposure to AEDs, using the study definition. The sponsor calculated AED specific rates for these cases. The results are included in the following table. There is overlap since some of the cases had exposure to more than 1 AED.

AED	Incidence rates for VFD by AED rates in cases per 10000 patient years	
	Patient Years	VFD 1
		VFD-2

Overall	51,219	7.4 (38)	3.5 (18)
Vigabatrin	968	31.0 (3)	10.3 (1)
Carbamazepine	15,248	12.5 (19)	5.2 (8)
Phenytoin	18,492	6.5 (12)	3.8 (7)
Valproate	11,538	6.9 (8)	0
Others	13,922	5.7 (8)	2.9 (4)

Using multiple logistic regression analysis, controlling for potential confounders and duration of treatment with each AED, the investigators described a relative risk of 1.7 (95% CI .21-14.1) for VFD-2 (based on 1 vigabatrin case) and a relative risk of 2.8 (CI .81-9.7) for VFD-1 for vigabatrin exposed individuals. In addition the investigators described a trend towards increased risk of VFD with duration of AED use in the new cases of epilepsy (n=1802) diagnosed during the observation period.

Comments

In this study, the investigators used a database to explore the relationship between VFD and AEDs. A substantial part of the analysis involved calculation of drug specific VFD incidence rates. The absolute rates are likely unreliable. The calculation of person time, by using a randomly selected day for non-cases to calculate exposure, underestimates the total exposure and therefore results in inflated event estimates for the cohort.

Another deficiency of this study is its inability to identify asymptomatic individuals with VFD. Subjects in this study were neither tested prior to selection, nor routinely tested during the observation period. Therefore we cannot know if the cases identified during the observation period were truly incident cases or if these individuals had asymptomatic, undetected VFDs prior to this time. Additionally, we have no way of knowing the number of asymptomatic incident cases that were not identified.

Asymptomatic periods could potentially complicate the identification of the relevant AED exposure for the cases. If the patient had an asymptomatic period prior to diagnosis of VFD, using the diagnosis day to determine exposure might not identify the AED related to the development of the VFD. In other words, using this methodology, the VFD could be misclassified to the AED that the patient was taking at the time of diagnosis rather than the AED that the patient was taking when the event began. Therefore, the drug specific comparisons may not be valid.

The results of this study suggest that VFDs were diagnosed in epilepsy subjects exposed to AEDs other than vigabatrin. Although this suggests that VFDs may not be unique to vigabatrin subjects, we are unable to determine from this study if vigabatrin patients are at increased risk of these events or if they experience different VFDs of more severe VFDs than patients taking other AEDs.

6.1.4.2 Pilot prevalence study

A cross-sectional pilot study of 15 patients exposed to AEDs other than vigabatrin found that 3 had VFDs upon initial examination. With repeat testing, none were considered to have VFDs. This study raises concern about reproducibility of VF testing. This study does not support the sponsor's position that VFDs are common in epilepsy patients on AEDs other than Sabril®.

6.2 Ophthalmologic data presented in the response to the approveable letter (4/24/98)

The majority of the ophthalmologic data included in the response to the approveable letter came in the form of updated counts included in proposed labeling. At the time of this submission, the sponsor was in the process of compiling new information regarding VFDs. The sponsor notified

the division of preliminary data suggesting a substantial prevalence of asymptomatic VFDs and that that these data would be provided in a separate submission. For the information included in this submission, the sponsor provided counts for various types of eye related events and they recommended that this section be moved from the *Warnings* section to the *Precautions* section.

6.3 Ophthalmologic data presented in the Updated Safety Information submission (7/29/98)
On 7/29/98, the sponsor submitted 2 volumes presenting new information about ophthalmologic events in Sabril® exposed patients and proposed labeling to address these findings. Specifically, the submission included the proposed labeling addressing ophthalmologic events, references for statements made in the proposed labeling, case reports from the literature, tables summarizing eye findings, a review of perimetry data from spontaneous reports and extension trials, a prevalence analysis for visual field defects (VFDs), and results from the UK PEM study. In addition, the submission contained the Medwatch forms for the spontaneous reports of all eye-related events.

6.3.1 *Wild report*

In an effort to classify the type, severity and etiology of VFDs in individuals exposed to Sabril®, the sponsor had their perimetry consultant, John Wild Ph.D., review perimetry test results. The sponsor sent their consultant the available background medical information and perimetry testing results for 73 Sabril® exposed individuals. These data came from 2 sources. The first group contained the 27 spontaneous reports of VFDs that included perimetry-test results (roughly 14% of all spontaneous VFD reports). The second group included the abnormal visual field test results of 46 asymptomatic volunteers from Finnish and Japanese Sabril® extension trials, who underwent testing as part of an effort to estimate VFD prevalence among Sabril® patients (see Epidemiology report below).

The VFDs were detected using different perimetry testing methodologies. In 39 cases, the field had been examined with kinetic perimetry (Goldman or Topcon bowl perimeters). In 19 cases, the field was measured with static perimeter (15 Humphrey, 3 Octopus). Six were examined with both kinetic and static perimetry. Six cases were examined using suprathreshold perimetry and the remaining 3 by automated kinetic perimetry.

Dr. Wild developed a classification scheme that addressed interpretability of the results, the likely etiology of the VFD, and the severity of the findings. Criteria used to assess interpretability of test results were not specified. Assessments about likely underlying causes were made based upon the available medical information for a given patient included in the event report. Severity of the abnormality was graded as mild, moderate or severe and was based upon criteria developed by the consultant, which considered the degree of abnormality of the test result. If a report contained more than one test result for a patient, the consultant used the most recent result. If results from both static and kinetic methodologies were available, he based the classification on the kinetic results.

Upon review, cases were given the following grades:

- 0-Normal
- 1-mild VFD with no underlying explanation
- 2-medium VFD with no underlying explanation
- 3-severe VFD with no underlying explanation
- 4-VFD with known cause (i.e. glaucoma).
- 5-Uninterpretable/inconclusive

The following table is a summary of the results of the sponsor's classification of VFDs. It was compiled using the consultant's summary table (Validation of case reports of vigabatrin associated visual field loss pp. 11-17). For some cases, the rating differed for each eye. For the cases where one eye had an unknown cause and the other eye had an identified cause or a normal or uninterpretable result, the case was listed as "VFD, no likely cause identified".

Classification	VFD classification results by report source	
	Spontaneous Reports	Extension Trials
Uninterpretable	7	2
No VFD	2	3
VFD with likely cause	3	2
VFD, undecided regarding cause	-	4
VFD no likely cause identified	15	35
Total reviewed	27	46

The consultant considered the cases of VFD with no likely cause to be associated with vigabatrin. For these cases, most were classified as moderate or severe. For the moderate cases, 13 individuals had a reduction that was considered most profound nasally. For the severe cases, 20 individuals had reductions that were most profound nasally.

For the cases considered as associated with vigabatrin, the consultant identified an overall pattern of bilateral concentric reduction in sensitivity more marked nasally than temporally. He states that the presence of a binasal visual field defect is a rare finding. He felt that the finding was present with both kinetic and static perimetry. He could not identify the site of the lesion from perimetry data alone. Based on the other available medical data (VEPs, MRIs, etc.), he felt the lesion resulting in these findings would most likely be located in the retina.

This report will be reviewed by an FDA neuro-ophthalmologist (Dr. Oliva) for comment on the methods, results and conclusions.

6.3.2 Prevalence study

The sponsor's epidemiology team analyzed data from Wild's report to estimate the frequency of unique VFDs and to look for risk groups. The group reviewed only the data from the extension studies mentioned above. Spontaneous report data was not included. The extension trials included patients from ongoing studies in Finland and Japan. The investigators did not comment on why these studies were chosen.

Of the 219 Finnish and Japanese subjects who took Sabril® during open label phases of the included studies, 136 (62%, Finnish n=34, Japanese n=102) underwent testing in the fall of 1997 (9 years after the start of the first of these studies). Each of these individuals had a single visual field evaluation. Results were interpreted locally and the reports with identified VFDs were forwarded to the sponsor's consultant for further evaluation. Two subjects from a Japanese trial who were identified with VFDs by local evaluation had results that the expert considered uninterpretable. They were excluded from the frequency analysis. In determining the overall prevalence, the cases categorized by the consultant as possible VFD or VFD without likely cause were counted as VFD cases. The investigators estimated that the prevalence of VFD was 28% (38/134 CI 20-36%). For the Finnish studies 35% (12/34) of those tested had a VFD and for the Japanese studies 26% (26/100) of those tested had VFD. Using the consultant's categorization of severity, 45% (17) were considered severe, 37% (14) were moderate, 8% (3) were mild. The investigators reported that the 134 individuals were exposed for 649 patient years and calculated an incidence rate of 5.9 per 100 person years.

In looking for risk groups, the investigators reported that 37% of all males (22) v. 21% (16) of all females developed the unique VFD. This gender pattern was consistent when stratifying by country. The investigators compared mean age, duration of use, cumulative dose, duration of epilepsy, weight, and BMI for individuals with VFD to individuals without VFD. They reported that there did not appear to be any differences in these parameters for individuals with VFD compared to those without VFD. The investigators noted that these patients were asymptomatic at the time of diagnosis and that the time of exact onset of VFD was not known. Comparisons of duration of use, cumulative dose and duration of epilepsy were made relative to the time of diagnosis, and not the time of onset of VFD.

The investigators provided a graph that included the percentage of those tested that were positive stratified by duration of treatment in 1-year intervals. Six subjects (all negative) were tested within the first 2 years of treatment. One hundred nine individuals were tested during years 3-5 of treatment and 30 were found to have VFDs. Nineteen individuals were tested after 5 years of treatment and 8 cases were identified from this group.

Comments

This investigators intended to provide a point estimate of the prevalence of VFD in vigabatrin subjects using data from Finnish and Japanese extension trials. Their prevalence estimate may be inaccurate because only a subset of those enrolled in the extensions underwent testing (62%) and the negative VFD tests have yet to be evaluated to assure that there were no false negatives. They found a higher percentage of males (37%) than females (21%) with VFDs.

Beyond the prevalence and gender descriptions given above, few questions can be answered by these data. Without pre-drug/baseline results, the incidence of VFD on Sabril® cannot be calculated. Since all patients were asymptomatic at the time of testing and it is not known at what point the VFDs initially appeared, we are unable to validly assess time-dependent parameters.

This study serves to document that VFDs can be detected in asymptomatic individuals taking vigabatrin but the relationship between this finding and drug exposure has not been explored. Interpretations of these findings can only be made in light of the background prevalence of this type of VFD in non-exposed epilepsy patients or epilepsy patients taking other AEDs. In a study by Johnson and Keltner, the prevalence of binocular VFD in a normal population was 1.1%.¹ Unfortunately, we do not have VFD prevalence data in epilepsy patients. If VFDs are not present in comparable non-Sabril® exposed populations, then this is worrisome finding. If the finding is present in the background or if the occurrence is not known (i.e. never been studied) then value of these findings is unclear.

6.3.3 Results from a UK PEM study

The sponsor included a UK PEM report that described the visual field defects in patients taking one of three anti-epileptic drugs (vigabatrin, lamotrigine, and gabapentin). The cohort sizes followed for these drugs were: vigabatrin-10,178, lamotrigine-11,316, and gabapentin-3100. No cases of visual field defect were reported for the gabapentin cohort. For the lamotrigine cohort, 2 cases of visual field defect were reported. Upon further review, one of the cases was described as hysterical visual impairment and the second was diagnosed by subjective symptoms that resolved when the drug was stopped. In the vigabatrin cohort, 3 cases of VFD were reported and 2 additional cases were identified from reports of visual disturbance that were reclassified as VFD

¹Johnson C Keltner J, Incidence of Visual field Loss in 20,000 Eyes and its Relationship to Driving Performance. Arch Ophthalmol, vol 101, March 1983 pp 371-375.

after follow up. For the 5 vigabatrin cases, all involved bilateral defects. The age range of the individuals with VFD was 26-65 and the duration of exposure varied from <1 month to 30 months. One of the cases reportedly resolved, 2 were persistent on follow up despite discontinuation of vigabatrin and the outcome was unknown for the remaining 2 cases.

6.3.4 Proposed labeling

Within the sponsor's proposed labeling for ophthalmologic events, they state that between 9/89 and 3/98, from both clinical trials and spontaneous reporting, there have been 239 patients (56% males, 44% females) who experienced visual field defects, retinal abnormalities and or optic atrophy/neuritis/vasculitis/ during treatment with Sabril®. The following listing provides the number of reports by source for visual adverse events.

- 19 from US clinical trials
- 23 from non US clinical trials
- 3 compassionate use
- 37 Japanese clinical trials
- 5 UK PEM study
- 152 from spontaneous reports

Of the 239 reports, 192 included information regarding visual field defects (57% male, 43% female). The sponsor comments that few of the reports have information from baseline exams. One hundred twenty-nine of the VFD reports had information about symptoms (68 symptomatic, 61 asymptomatic). For the asymptomatic events, 40 were identified by screening patients during clinical trials and 28 were from spontaneous reports. Forty-eight of the symptomatic events were from spontaneous reports (UK Australia, France). For patients with eye related events, the age range was 9-73 years old. Most of the patients received between 2-3g of vigabatrin/day. The duration of therapy prior to diagnosis ranged from <1 month to over 9 years (mean 39 months), and most (75%) were reported during the first 4 years of therapy. The sponsor also reported that

for reports with follow up information, in most cases the VFD did not resolve upon discontinuation of vigabatrin. The sponsor described a specific pattern of defect that was a bilateral concentric reduction in sensitivity more marked nasally than temporally.

There are 55 reports of retinal abnormalities (including retinopathy, maculopathy, abnormal ERG or EOG, retinal pigmentation, retinal macular drusen, retinal macular atrophy, or degeneration). Retinal event reports did not show a gender difference, and generally lacked baseline-exam information. The age range was 2.5-64 years old. Most of the patients with retinal adverse events were taking 2-3g of vigabatrin /day. The duration of therapy ranged from 1 month to 8 years (mean 32 months), most events occurred within 4 years of beginning therapy with vigabatrin. Several cases of pigmentation, retinal/macular drusen resolved with continued therapy. For those with follow up information, the majority of ERG/EOG abnormalities resolved following discontinuation. For the reports of other retinal abnormalities with follow up information, the events did not resolve even if Sabril® was discontinued.

The sponsor acknowledged 35 reports of optic atrophy, neuritis, and vasculitis. There was equal gender distribution for these events. The age range was 7 months to 71 years and the dose at the time of the event ranged from .25 to 4g/day. The mean duration at the time of diagnosis was 33 months and most were reported within the first 2 years of therapy.

In a UK PEM study, 5 cases of bilateral peripheral VFDs were identified in 10,178 patients. The events occurred in 3 females and 2 males. The age range was 26-65 years and the events were

identified within 1-30 months of treatment. For the event occurring after 1 month of therapy, the VFD resolved within 1 month of discontinuation of Sabril®. In 2 cases, the event did not resolve with discontinuation at the time of the report. The outcome of the other 2 cases is not known. No similar cases of bilateral VFD were identified in PEM studies for lamotrigene or gabapentin.

The sponsor also proposes to include information from a follow up study for patients who were identified with eye related complaints in North American trials. [REDACTED]

b(4)

Lastly, the sponsor includes recommendations for monitoring. They state that visual field testing should be performed at baseline and during routine follow up (initially at [REDACTED] intervals). They suggest that patients should be instructed to report any new visual field problems. [REDACTED]

b(4)

7. Discussion

Within these three submissions have been data addressing many different safety topics. The integrated safety information included in the final safety update provided updated data but did not result in any major changes in the understanding of the safety profile of vigabatrin. The pediatric profile summarized the safety experience in patients under 16 years old. The sponsor did not identify any safety issues that appear to be unique to this group, although there is very little comparative data and relatively little exposure.

In the response to the approveable letter, the sponsor addressed the requests of the division. Aside from clarification of events, there was little new discovered from this submission and no major changes in the understanding of the safety of this drug.

The sponsor provided data for ophthalmologic events, specifically visual field defects, which have resulted in new concerns about the safety of vigabatrin. Prior to the final safety update, there was some indication of an excess of eye related complaints in vigabatrin exposed individuals in controlled trials, but there was no specific pattern noted from the data. Spontaneous reports of visual field defects, retinal events and optic neuritis were identified but their significance was not understood. The sponsor's ophthalmologic consultants found no conclusive evidence of vigabatrin related eye toxicity after reviewing these data as part of the NDA amendment.

Since the NDA amendment, new information has been submitted. The sponsor included new ophthalmologic information from clinical trials in the safety update. The sponsor did identify two cases of VFD in vigabatrin exposed patients, both after the protocol specified testing period. Unfortunately these data did not allow estimation of prevalence or risk for these events. The sponsor's retrospective epidemiology study also provided little useful information about the risk for VFD and their small pilot study did not find any true positive VFD test results in patients exposed to AEDs other than vigabatrin.

Within the latest submission, the sponsor provided the most concerning information about vigabatrin and VFDs. After reviewing visual field testing results, the sponsor's perimetry consultant suggests that there may be a pattern of VFD unique to vigabatrin exposed patients. Unfortunately, we do not have comparative data to assess this conclusion. Using the data from the perimetry consultant, the sponsor's epidemiologists report a prevalence of asymptomatic bilateral VFD of 28% in patients enrolled in Japanese and Finnish extension trials. There is evidence that bilateral visual field defects are substantially less prevalent in normal individuals but without information from a comparable non-vigabatrin exposed population, the significance of this

finding is not clear. Further concern that risk of VFD may be different for vigabatrin exposed patients comes from a UK PEM study. Investigators discovered 5 cases of VFDs in vigabatrin users and no similar cases in cohorts exposed to lamotrigine or gabapentin.

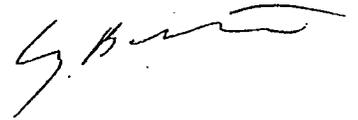
The evidence suggests a signal of concern. Without additional comparative data we have no frame of reference in which to evaluate these findings. The most basic questions that have yet to be answered include the following: Are VFDs seen in the background in epilepsy patients? Are VFDs seen in epilepsy patients with chronic exposure to other AEDs? Are vigabatrin patients at increased risk compared to these other groups? Do vigabatrin patients develop a unique pattern of VFD? What is the evidence of irreversibility for these events? Without further information describing the relationship between visual field defects and vigabatrin, we cannot provide a complete evaluation its safety.



Gerard Boehm MD,MPH

CC: Leber, Katz, Burkhardt, Sherry, Oliva

9-28-98
my comments are in a separate memo.
I also review the consult from
DPE on visual field defects
with other AEDS in that
memo



Appendix

Medically serious Ocular Adverse Events Included in the Safety Update

VGST 1218-0001	39YO Female with R nasal hemi-ring scotoma, L more complete ring-like defect.
VGZ 9700-0079	44YO Male with concentric visual field defect.
VGZ 9600-7165	41YO Male exposed to vigabatrin for 4 years, developed constriction of visual fields of both eyes. MRI- No pathological findings. VER poorly reproducible, delayed in left and right eyes.
VGZ 9700-0046	30 YO Male Right eye almost concentric peripheral visual field deficit and 2 scotomas on the nasal side. Left eye peripheral visual field deficit less pronounced predominantly in the nasal sector. MRI-2 small non-specific hyperintensities in the white matter on the right side, one in the semiovalate, the other in the pars centralis.
VGZ 9600-5266	48YO Nasal field loss.
VGZ 9600-5267	Visual field loss after 7 years of vigabatrin therapy.
VGZ 9600-5268	47YO Nasal visual field loss.
VGZ 9600-5269	38YO Concentric visual field loss.
VGZ 9600-7536	71YO Male Constriction of lateral nasal fields. MRI- Enlarged subarachnoid spaces, some white matter high signal loss.
VGZ 9600-7533	40YO Female Binasal visual field loss.
VGZ 9600-7534	33YO Male Bilateral visual field constriction.
VGZ 9600-7535	26YO Female Bilateral visual field constriction.
VGZ 9700-0904	48YO Constricted peripheral vision.
VGZ 9600-2531	30YO Male Decreased visual acuity, macular degeneration of the retina.
VGZ 9600-6147	54 YO Female Attenuation of the retinal arterioles, optic disc pallor, peripheral cone corpuscle formation, pigmentary retinopathy, retinal cone dysfunction. ERG-borderline abnormality.
VGZ 9700-1683	34YO Male Visual field defect of constriction of the fields. VER/ERG-No evidence of retinal or optic nerve disorder.
VGST-UK07-006(097-335)	43YO Female Macular degeneration.

A history of eye findings associated with Sabril®

Animal studies

During development, concerns about retinal toxicity arise due to the findings of dose dependent toxicity in albino Sprague Dawley rats exposed to vigabatrin (disorganization of the outer nuclear layer, loss of rods and displacement of rod nuclei). No retinal changes were observed in pigmented species.

Vacuolization was observed in the optic tracts in both rats and dogs.

NDA ophthalmologic findings

During review of the NDA, Dr. McCormick identified an increase in eye related adverse events in patients exposed to vigabatrin during controlled trials. These findings included vessel narrowing, vitreous cells, retinal drusen, retinal pigment clumping and RPE dropout. These findings were not explored in detail by the sponsor and therefore, the division suggested an expert review of eye related adverse events be included with the amendment.

NDA amendment presentations

Review of the AE tables from trials included in the NDA amendment demonstrate that nystagmus, vision abnormal, diplopia, and eye abnormality were events that occurred more frequently in those exposed to vigabatrin compared to those exposed to placebo. There were few discontinuations or hospitalizations for eye related events in these studies.

The amendment contained findings from a safety protocol where patients who had eye complaints identified during any of the original North American studies were located and re-examined. Testing included ophthalmologic exams (visual acuity, color testing, confrontational visual field testing, and anterior and posterior segment testing). Unfortunately, few individuals had baseline exams from the original protocols to allow comparison. The sponsor found that 15% of these individuals had evidence of VFDs. Color vision abnormalities were also commonly seen in this group.

As part of the amendment, all eye related complaints were reviewed by a consultant ophthalmologist and 2 consultant neuro-ophthalmologists. The consultants did not identify any ocular AEs that were definitely or probably related to vigabatrin when looking at the controlled trials. Review of non-US studies and spontaneous reports led to the conclusion that there was no definitive evidence of visual system toxicity and only possible toxicity related to the retina or optic nerve. In reviewing the reports of patients with VFD identified in the safety protocol described in the previous paragraph, the consultants did not feel that the abnormalities were due to vigabatrin. Nor did they feel that the VFDs from the spontaneous reports were causally related to vigabatrin.

Spontaneous reports include cases of eye related findings, most notably, reports of VFDs.

Actions Following the Amendment

6/97 The sponsor issues a Dear Doctor letter in Canada alerting providers to reports of visual field constriction, bilateral optic disc pallor, peripheral retinal atrophy, and optic atrophy. They recommend ophthalmologic exams every 3 months for patients taking Sabril®.

7/97 BMJ case series of VFD in 3 patients taking Sabril® is published.

NDA 20-427 Final Safety Update

Sabril® Oral
(Vigabatrin)

Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
CLINICAL PHARMACOLOGY							
Z1754-3-WL-008 Investigators (see listing below) Note: This protocol has been classified as a Secondary study.	Complete (10/90)	Italy UK Tablets 500 mg	Open, interaction study 1° Efficacy: • Plasma/Urine PHT levels Safety: • MRI (screen) • CT Scan (screen) • PE & Neuro Exam (screen) • Treatment-emergent AEs • Clin Lab	PHT 200-500 mg/d; 21 VGB 2-3.5 g/d; 20	20	Population: Epilepsy pts Gender: M:F 15:6 Age: Range: 18-57 Mean±SD: 34.5±11.6	No trtmt: 3 mos PHT (IV): 5 days PHT (Oral) & VGB: 4 wks PHT (IV) & VGB: 5 days
Investigator							
016 030	R Michelucci A Richens	5 4	058 059	F Pisani G Zaccara	6 6		
Z1754-3-WL-014 P Kopelman	Complete (Jun 93)	UK Tablets 500 mg	DBPC, parallel, single center 1° Efficacy: • Blood glucose levels Safety: • ECG (screen) • Treatment-emergent AE • PE • Clin Lab	Single dose VGB 1, 3 g/d; 13 PLAC: 12 Not exposed: 1	13	Population: Insulin Treated Diabetic Volunteers Gender: M:F 26:0 Race: Caucasian: 19 Black: 0 Asian: 6 Other: 1 Age: Range: 20-60 Mean±SD: 39±11	No trtmt: 2 wks VGB or PLAC: 1 g dose No trtmt: 4 wks VGB or PLAC: 3 g dose No trtmt: 4 wks
Investigator							

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Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
VGPR0099 J Doane	Ongoing (05/94)	US Tablets 500 mg	Open, PHT interaction study, single center PK: • Serial plasma, urine sampling Safety: • Treatment-emergent AEs • PE • Clin Lab • Ophthalm Exam • ECG	VGB 3 g/d: 2	2	Population: Well- controlled epilepsy pts receiving PHT Gender: M:F 0:2 Age: Range: 30-39 Mean±SD: NAV	No trtm: 14 days Titration: 11 days Maintenance: 48 days Taper: 10 days
071754PR0259 D Morrison	Ongoing (10/96)	US Treatment A: Chewable Tablets 500 mg Treatment B: Saccharin/paraben Soln 100 mg/ml Treatment C: Xylitol/benzoate Soln 100 mg/ml Treatment D: Film-coated Tablets 500 mg	Open, randomized, 4-way x-over, single center PK: • Serial plasma sampling Safety: • Treatment-emergent AEs • PE • Clin Lab • ECG	Single dose Treatment A: VGB 1 g/d: 16 Treatment B: VGB 1 g/d: 16 Treatment C: VGB 1 g/d: 15 Treatment D: VGB 1 g/d: 15 Early DC: 1	16	Population: Healthy male volunteers Gender: M:F 16:0 Race: Caucasian: 15 Black: 1 Age: Range: 18-39 Mean±SD: 26.8±6.7	Treatment A: Single dose Treatment B: Single dose Treatment C: Single dose Treatment D: Single dose Minimum 7 day washout period between treatments

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigator, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
071754PR0260 D Morrison	Ongoing (07/96)	US Tablets 500 mg	Open, PHT interaction study, single center <u>PK:</u> • Plasma/urine sampling <u>Safety:</u> • Treatment-emergent AEs • PE • Clin Lab • ECG	<u>PHT Loading Dose:</u> 400 mg/d: 15 <u>PHT Steady State:</u> 300 mg/d: 15 VGB 3 g/d: 14	14	<u>Population:</u> Healthy male volunteers <u>Gender:</u> M:F 15:0 <u>Race:</u> Caucasian: 14 Asian: 1 <u>Age:</u> Range: 18-41 Mean±SD: NAV	<u>PHT Loading dose:</u> 1 day <u>PHT Steady state:</u> 10 days <u>VGB Add-on Titration:</u> 11 days <u>Maintenance:</u> 6 wks <u>Taper:</u> 2 days
CONTROLLED STUDIES							
071754PR0223 Investigators (see listing below)	Ongoing (11/95)	US Tablets 500 mg	DB, parallel, dose-response, multicenter <u>1° Efficacy:</u> • Time to meeting escape criteria <u>Safety:</u> • EEG (screen) • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • Ophthalm Exam (visual acuity, visual field, slit lamp, color plate)	VGB 1 g/d: NAV VGB 3 g/d: NAV VGB 4 g/d: NAV VGB 6 g/d: NAV Placebo: NAV	112 enrolled	<u>Population:</u> Epilepsy pts	<u>No trtmt:</u> 8 wks <u>Titration:</u> 6 wks <u>W/D Baseline AED(s):</u> 8 wks <u>Monotherapy:</u> 8 wks

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Protocol No., Investigator, Protocol Amendments		Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered		No. Entered	
1501	L Willmore	5	1487	S Schachter	13			
1502	J King	3	1490	K VanLandingham	3			
1474	V Biton	13	1491	B Vazquez	10			
1475	D Blum	7	1492	D Vossler	8			
1476	P Van Ness	3	1493	F Dreifuss	2			
1478	A Cole	3	1495	W Nowack	3			
1480	R Kuznielky	9	1498	H Corwin	3			
1481	A Lassiter	4	1669	B Fisch	5			
1483	P McCabe	4	1496	J French	1			
1489	R Simkins	5	1497	K Laxer	5			
1477	R Burgerman	1	1484	G Morris	2			
1485	J Pellock	0	1488	S Shinnar	0			
071754PR0222	Ongoing (11/95)	US	DB, active control, parallel, multicenter	VGB 3 g/d; NAV	40 enrolled	Population: Epilepsy pts	No trtmt: 8 wks Titration: 5 wks W/D Baseline AED(s): 8 wks Monotherapy: 8 wks	
Investigators (see listing below)		Tablets 500 mg	1° Efficacy: • Time to meeting escape criteria Safety: • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • Ophthalm Exam (visual acuity, visual field, slit lamp, color plate)	Gabapentin 1800 mg/d; NAV				
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered		No. Entered	
1444	B Abou-Khalil	3	1462	R Ayala	3			
1447	W Bell	3	1667	J Hogan	6			
1449	M Drake	7	1466	L Brown	2			
1454	M Morrell	2	1458	C Watson	4			
1461	K Meador	4	1453	R LeRoy	3			
1464	W Rosenfeld	2	1457	B Wammamaker	1			
1460	S Alemayehu	0	1467	J Slater	0			
1448	A Beydoun	0	1665	S Louis	0			
1451	C Lai	0	1450	J French	0			

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
Z1754-3-W-00Z Investigators (see listing below)	Complete (Feb 93)	Australia Belgium Denmark Finland France Germany Israel Italy Netherlands S. Africa Spain Sweden Switzerland UK Tablets 500 mg	DB, parallel, active control, multicenter, followed by LTFU 1° Efficacy: • Seizure free Safety: • CT scan (screen) • EEG (screen) • Treatment-emergent AEs • Clin Labs • Plasma AED • PE & Neuro Exam • MRI (selected sites) • Cognitive function (selected sites) • EP (selected sites)	VGB 1-4 g/d: 228 CBZ 200-1400 mg/d: 229 Randomized: 459 Exposed to DB Treatment: 457 Safety Eval: 457 Intent-to-Treat: 446 Completed: 262 Early DC: 195	228	Population: Newly diagnosed epilepsy pts Gender* M:F 239:207 Age* Range: 12-75 Mean±SD: 35±16	Titration: 4 wks Maint: 48 wks Open LTFU: Ongoing

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Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment	No. Entered	
								Investigator	Study Site
085	Baldy-Moulinier	1	152	Goldenfienning				1	
103	Bes	3	154	Jankovic				2	
102	Boon	9	123	Neufeld				10	
129	Canger	17	041	Reid				15	
113	Corston	10	110	Seijas				4	
108	Gross/Dowson	41	128	Specchio				16	
114	Howell	5	016	Tassinari				2	
132	Manelis	5	045	Weiser				12	
058	Pisani	4	074	Beran				12	
101	Sanders	36	116	Calandre				8	
148	Somerville	7	100	Chadwick				33	
014	Tartara	8	077	Danta				10	
037	Tettenborn	12	106	Donselaar				10	
104	Weber	2	040	Haan				14	
017	Ben-Menachem	3	131	Kivity				1	
107	Bird	12	064	Pedersen				15	
149	Byrne/Cook	8	068	Reikkinen				32	
111	Cardidge	14	105	Stefan				2	
024	Dam	19	115	Tejerina				4	
125	Dellaportas	27	112	Venables				8	
135	Gale	1	059	Zaccara				4	
Z1754-3-W-012	Complete (May 93)	Austria Belgium Czech Republic France Hungary Italy Netherlands Portugal Slovenia S. Africa Spain UK Tablets 500 mg	DB, parallel, active control, multicenter, followed by LTFU 1° Efficacy: • Mean monthly seizure frequency Safety: • EEG (screen) • CT Scan (screen) • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • Plasma AED	VGB 1-4 g/d: 110 VPA 0.5-2 g/d: 113 Randomized: 227 Exposed to DB Treatment: 223 Safety Eval: 223 Intent-to-Treat: 215 Completed: 139 Early DC: 84	110	Population: Epilepsy pts, resistant to CBZ Gender: M:F 106:109 Age: Range: 12-76 Mean±SD: 37±13	No trmt: 4 wks Titration: 8 wks Maint: 12 wks W/D CBZ: 8 wks Monotherapy: 12 wks Open LTFU: Ongoing		

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered	No. Entered	
007	Loiseau	2	130	W Grosveld		2	
014	Tartara	10	119	Uboda		12	
152	Guidenpfrännig	1	081	Brodie		15	
153	Fritz	1	125	DellaPortas		6	
138	Lima	28	137	Groselj		11	
139	A Bologh	7	141	Halasz		3	
140	B Clemens	17	134	Marnoli		2	
147	I Rektor	7	146	Nespor		6	
150	V László	7	136	Rajna		10	
127	Ayache	3	101	Sanders		7	
117	Boulliat	4	118	Zandjcké		1	
142	Czopf	8	107	Bird		3	
143	Grisar	1	124	Giroud		6	
133	Gupta	1	144	Hovorka		11	
151	Iloria	7	145	Kucerova		4	
121	Moene	7	120	Khaili		5	
122	Rumbach	2	080	Richens		6	
			016	Tassinari		4	
VIFE-0192 (VGPR0257)	Ongoing (10/93)	Canada Soln 40 mg/ml	DBPC, parallel, multicenter 1° Efficacy: • Mean monthly seizure frequency Safety: • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • Plasma AED • Cog Psych • VEP • Ophthal Exam (fundoscopy, visual field, visual acuity) • MRI (selected sites)	VGB 0.5-4 g/d: NAV PLAC: NAV	55 enrolled	Population: Pediatric (3-16) epilepsy pts	No trtmt: 6 wks Titration: 10 wks Maintenance: 7 wks
Investigators (see listing below)							

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered		
001	F Anderman	0	011	S Levin	0		
004	H Darwish	0	003	P Camfield	2		
010	B Lemieux	4	012	N Lowry	6		
013	J Reggin	0	014	G Ronen	4		
002	D Buckley	1	015	B Rosenblatt	1		
008	D Keene	5	016	B Sinclair	6		
005	K Farrell	2	017	J Tribble	3		
006	G Geoffroy	4	018	S Whiting	3		
007	P Hwang	8					
009	P Langevin	6					
Q71754PB0118	Ongoing (4/95)	US	DBPC, parallel, dose response, multicenter	Placebo: NAV VGB 20 mg/kg/d: NAV VGB 60 mg/kg/d: NAV VGB 100 mg/kg/d: NAV	171 enrolled	Population: Pediatric (3-16) epilepsy pts	No trtm: 10 wks Titration: 6 wks Maintenance: 8 wks
Investigators (see listing below)		Soln 20 mg/ml 40 mg/ml 60 mg/ml 80 mg/ml 100 mg/ml	1° Efficacy: • Mean monthly seizure frequency Safety: • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • MRI • VEP • ERG • Cog Psych • Ophthal Exam (fundoscopy with photos, visual acuity, visual field, slit lamp, color plate) • Plasma AED				

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics No. Entered	Duration of Drug Treatment
Study Site	Investigator	No. Entered	Study Site	Investigator			
1270	C Santos	10	1282	D Nordli		5	
1271	R Konkol	4	1283	J Pellock		4	
1272	R Clancy	6	1284	F Rittler		4	
1273	J Conry	7	1285	M Griebel		7	
1274	F Dreifuss	4	1287	J Schimschock		11	
1275	R Elterman	13	1288	S Shinnar		3	
1276	M Sotero	8	1277	C Van Orman		24	
1278	S Helmers	10	1290	E Vining		3	
1279	J Kerrigan	7	1291	J Wheless		8	
1280	E Larson	8	1295	B Vazquez		8	
1292	M Morrell	11				14	
071754PR0221	Ongoing (4/95)	US	DBPC, parallel, multicenter	VGB 0.5-4 g/d: NAV PLAC: NAV	115 enrolled	Population: Pediatric (3-16) epilepsy pts	No trtmt: 6 wks Titration: 10 wks Maintenance: 7 wks
Investigators (see listing below)			<p>1° Efficacy:</p> <ul style="list-style-type: none"> • Mean monthly seizure frequency <p>Safety:</p> <ul style="list-style-type: none"> • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • VEP • ERG • Ophthal Exam (fundoscopy with photos, visual field, visual acuity, slit lamp, color plate) • MRI • Cog Psych • Plasma AED 				

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Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design		Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
			Study Site	Investigator				
1416	M Duchowny	10	1423	C Valentine	15			
1418	D Grisesemer	11	1424	E Wyllie	8			
1419	D Hurst	4	1425	E Babin	15			
1420	A Kanner	13	1427	P Crumrine	7			
1421	J Murphy	11	1428	C Tardo	11			
1422	S Roach	10						
VGPR0101	Ongoing (8/12/94)	US Tablets 500 mg	DBPC, randomized, parallel, multicenter, add-on study 1° Efficacy: • Seizure free • Quality of life Safety: • Treatment-emergent AEs • Clin Lab • Vitals • PE & Neuro Exam	VGB 3 g/d: NAV PLAC: NAV (2:1 randomization active to placebo) Screened: 269 Randomized: 177 Intent-to-Treat: 177 Exposed to DB treatment: 176	177 enrolled	Population: Adult pts with partial epilepsy Gender: M:F 83:94 Race: Caucasian: 154 Black: 20 Asian: 2 Other: 1 Age: Range: 18-66 Mean±SD: 37.9±11.5	No trtmt: 12 wks Titration: 4 wks Maintenance: 24 wks Open-label extension: vigabatrin flexible dose (2-6 gm/day)	
Investigators (see listing below)								

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation		Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
		No. Entered	Study Site					
1320	M Andriola	5	1347		M Salinsky			4
1321	G Walsh	5	1348		J Schechter			10
1322	V Biton	7	1349		M Schiess			14
1323	W Tatum	0	1350		E So			1
1324	J Klapper	7	1351		C Suter			0
1325	J Dengler	7	1352		W Svoboda			2
1326	J Garrison	6	1353		S Chayasirisobhon			5
1327	P Green	2	1354		A Turel			4
1328	J Geenberg	3	1355		B Uthman			13
1329	B Hendin	3	1356		J Valeriano			11
1330	E Tecoma	9	1357		B Wannamaker			2
1331	S Hertz	6	1358		M Spitz			2
1332	R Manon-Espaillet	3	1359		K Edwards			18
1333	D Marks	7	1360		G Chang			16
1334	B Vaughn	2	1361		K Murray			0
1335	G Montouris	7	1363		P Penovich			1
1336	J Moore	2	1364		G Krauss			10
1337	G Morris	3	1443		J Cohen			1
1338	H Morris	10	1564		J Auberle			3
1339	R Nemire	0	1642		K Bergmann			7
1340	R Burgerman	0	1659		P Flutecki			0
1341	S Potolicchio	2	1660		K Henry			5
1342	A Rae-Grant	7	1666		S Ellashiv			4
1343	B Vazquez	15	1685		J Cochran			3
1344	W Rosenfeld	2	1686		W Martinez			0
1345	K Ruggles	3	1687		M Tuchman			0
1346	P Kaplan	10	1726		R Rubinowicz			0

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
UNCONTROLLED STUDIES							
VGBR0098 Investigators (see listing below)	Ongoing (3/16/94)	US Tablets 500 mg	Open-label, flexible dose, long-term, multicenter 1° Efficacy: • Seizure free Safety: • Treatment-emergent AEs • Clin Labs • Vitals • PE & Neuro Exam • Ophthal Exam (slit lamp, visual acuity, funduscopy in selected pts)	VGB 1-6 gm/day; 1093	947 (146)	Population: Adult pts with partial epilepsy Gender: M:F 523:566 NAV: 4 Race: Caucasian: 997 Black: 71 Asian: 9 Other: 12 NAV: 4 Age: Range: 10-80 Mean±SD: 37.5±11.3	Open-label

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Investigator		Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
				No. Entered	Study Site				
1189	W Bell	20	1225	Investigator	W Rosenfield				No. Entered
1190	E Barry	25	1226		E Tescoma				17
1191	A Kanner	17	1227		K Laxer				14
1192	P Van Ness	21	1228		R Homan				24
1193	V Curtis/J Willmore	18	1229		I Leppik				10
1194	E Lee	10	1230		B Abou-Khalil				18
1195	M Drake	15	1231		A Follender				22
1196	R Fisher	9	1232		Snyder/Penovich				13
1198	G Krauss	46	1233		E Faight				2
1199	C Lal	20	1234		G Montouris				15
1200	R LeRoy	25	1235		A Beydoun				20
1201	R Kramer	4	1236		F Dreifuss				8
1202	M Morrell	13	1237		B Uthman				14
1203	G Morris	13	1238		J Dean				24
1204	P Penovich	21	1239		T Browne				25
1205	C Hughes	15	1240		J Pellock				19
1206	B Wannamaker	10	1241		R Ramsay				24
1207	S Stark	11	1242		R Sachdeo				15
1208	F Gengo/R Miletich	15	1243		D Treiman				4
1209	A Ehle	10	1245		V Biton				10
1210	B Vazquez	26	1246		S Hertz				16
1211	N So	20	1247		W Tatum				12
1212	J Miller	15	1248		R Andrews				4
1213	A Cole	10	1250		R Burgerman				10
1214	A Wilensky	15	1251		R Gross				11
1215	J Weissman	15	1252		M Granner				9
1216	R Mattson	19	1253		B Hendin				9
1217	J King	10	1254		K Meador				10
1218	S Shinnar	11	1255		B Vaughn				10
1219	A Wilner	10	1256		R Hogan				12
1220	J Valeriano	13	1257		K Plotkin				11
1221	G Arit	3	1258		R Sachdeo				6
1222	C Harden	20	1259		P McCabe				15
1223	M Jacobsen	15	1260		S Schachter				11
1224	J Aubertie	21	1261		N Schaul				10

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Table 9-1. Table of All Clinical Studies for Final Safety Update									
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment		
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered	No. Entered			
1262	R Simkins	11	1310	H Morris	3				
1263	J Sprie	10	1311	A Rae-Grant	1				
1264	W Sutherland	11	1312	K Ruggles	1				
1265	K Van Landingham	10	1313	P Kaplan	2				
1266	D Vossler	10	1314	M Sainsky	4				
1267	G Walsh	10	1315	J Schecter	4				
1268	C Watson	10	1316	M Schless	8				
1299	J Simsarian	2	1317	E So	1				
1300	C Armon	4	1318	W Svoboda	2				
1302	J French	30	1851	A Turel	1				
1303	A Lassiter	17	1854	K Ashkin	2				
1305	J Dengler	5			3				
Z1754-3-C-022	Complete (1/92)	Canada	Open, LTFU, multicenter	VGB 1-4 g/d; 97	(97)	Population: Epilepsy pts	Total: 52 wks		
Investigators (see listing below)		Tablets 500 mg	1° Efficacy: • Mean monthly seizure frequency Safety: • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • Cog Psych • VEP/SEP • MRI (selected sites) • Plasma AED			Gender: M:F 54:43 Race: Caucasian: 93 Black: 0 Asian: 4 Age: Range: 18-50 Mean±SD: 33.1±8.1			
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered				
076	J Bruni	7	091	A Ogumyemi	8				
079	R McLachlan	9	082	M Sadler	6				
081	M Jones	9	078	M Lee	12				
090	D Weaver	12	080	N Pillay	8				
077	A Guberman	17	083	E Starreveld	9				

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
71754-3-C-028 Investigators (see listing below)	Complete (10/91)	Canada US Tablets 500 mg	Open, LTFU, multicenter 1 ^o Efficacy: • Mean monthly seizure frequency Safety: • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • Cog Psych • VEP/SEP • MRI • Plasma AED	VGB 0.5-6 g/d: 264	(264)	Population: Epilepsy pts Gender: M:F 124:140 Race: Caucasian: 249 Black: 10 Other: 5 Age: Range: 19-70 Mean±SD: 36.6±9.4	2 yrs
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered		
005	T Browne	9	062	C Lai	9		
010	BJ Wilder	15	065	P Penovich	2		
013	F Dreifuss	8	069	B Gallagher	3		
056	D Bergen	7	072	R Sachdeo	10		
060	G Fromm	2	073	A Wilensky	6		
063	I Leppik	2	076	J Bruni	1		
066	RE Ramsey	9	079	R McLachlan	3		
070	M Drake	9	082	RM Sadler	3		
006	R Mattson	11	090	D Weaver	4		
011	J Penry	9	058	G Krauss	13		
054	E Barry	11	074	J Willmore	1		
057	J Ferrendelli	7	077	A Guberman	9		
061	Homan/Lassiter	6	080	N Pillay	6		
064	J Pellock	11	083	E Starreveld	5		
067	S Shinnar	5	091	A Ogunyemi	6		
071	R Fought	4	075	M Yerby	8		
009	DB Smith	5	078	M Lee	6		
012	D Treiman	9	081	M Jones	2		
055	R Brower/Bell	3	089	R Kramer	9		
059	J French	10	093	K Laxer	6		

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigator, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
097-935 R Käiviäinen	Complete (Jan 88)	Finland Tablets 500 mg	Open, active control, parallel, x-over option, followed by LTFU 1° Efficacy: • Time to treatment failure Safety: • Treatment-emergent AEs • PE & Neuro • Clin Labs • Plasma AED	Titrate to response VGB 3 g/d: 50 (max 50/mg/kg/d) CBZ 700 mg/d: 49 (max 35 µmol/L) Not Exposed: 1	66	Population: Newly diagnosed epilepsy pts Gender: M:F 45:55 Age: Range: 15-64 Mean±SD: NAV	Titration: 2-3 mos Maintenance: 24 mos (Optional x-over in case of inefficacy/intolerance) LTFU: Ongoing
Z1754-3-VL-002 EH Reynolds	Complete (4/92)	UK Tablets 500 mg	Open, comparative 1° Efficacy: • Time to first seizure Safety: • Treatment-emergent AEs • Clin Labs • Plasma AED • EEG • CT scan • PE & Neuro Exam	VGB 1-4 g/d: 9 (x-over of 1 pt. to VGB due to AE) CBZ 400 mg/d-12 mg/l serum level: 11	10	Population: Newly diagnosed epilepsy pts Gender: M:F 11:9 Age: Range: 10-67 Mean±SD: 32.5±13.8	1-22 mos
VIGA-4-ST-03 JA Finnegan	Complete (3/93)	UK Tablets 500 mg	Open, comparative 1° Efficacy: • Seizure frequency Safety: • PE & Neuro Exam (screen) • Treatment-emergent AEs • EEG	VGB 1-2 g/d: 12 CBZ 200-1600 mg/d: 12 VPA 0.2-3 g/d: 12	12	Population: Refractory epilepsy pts Gender: M:F 6:6 Age: Range: 28-62 Mean±SD: NAV	8 mos Pts on all 3 AEDs, W/D of CBZ or VPA

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
71754-III-ST-016 Investigators (see listing below)	Complete (3/93)	UK Tablets 500 mg	SB, randomized, parallel, multicenter 1 ^o Efficacy: • Seizure frequency Safety: • EEG (screen) • CT Scan (screen) • MRI (screen) • Clin Lab (screen) • PE & Neuro Exam (screen) • Treatment-emergent AEs	VGB 1-2 g/d: 3 Phenytoin 78-400 mg/d: 3 Screened: 14 Randomized: 7 Exposed to SB Treatment: 6	3	Population: Epilepsy pts receiving CBZ Gender: M:F 3:4 Age: Range: 2-33 Mean±SD: NAV	No trtmt: 4-8 wks Titration: 4 wks Maintenance: 12 wks
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered		
-	R Robinson	6	-	C Panayiotopoulos	8		

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
V1-PE-0294 (VGPR0256) Investigators (see listing below)	Ongoing (3/94)	Canada Tablets 500 mg	Open, multicenter, followup to V1-PE-0192 1° Efficacy: • Mean monthly seizure frequency Safety: • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • Plasma AED • Cog Psych • VEP • Ophthal Exam (funduscopy, visual field, visual acuity) • MRI (selected sites)	VGB 0.5-4 g/d; 44	(44) enrolled	Population: Pediatric (3-16) epilepsy pts	Total: 24 wks
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered		
001	F Anderman	0	017	J Tribble	2		
004	H Darwish	0	011	S Levin	0		
007	P Hwang	7	014	G Ronen	3		
010	B Lemieux	4	003	P Camfield	2		
013	J Reggin	0	009	P Langevin	4		
016	B Sinclair	5	012	N Lowry	6		
002	D Buckley	1	015	B Rosenblatt	0		
005	K Farrell	2	018	S Whiting	2		
006	G Geoffroy	2	008	D Keene	4		

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Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
071754PR0242 Investigators (see listing below)	Ongoing (12/95)	US Tablets 500 mg	Open, LTFU, multicenter 1 ^o Efficacy: • Long term efficacy Safety: • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • Ophthalm Exam (visual acuity, visual field, slit lamp, color plate)	VGB 1-6 g/d: 87	(87) enrolled	Population: Epilepsy pts	52 wks
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered		
1444	B Abou-Khalil	2	1481	A Lassiter	3		
1447	W Bell	2	1483	P McCabe	3		
1449	M Drake	5	1487	S Schachter	10		
1454	M Morrell	1	1490	K VanLandingham	3		
1501	L Willmore	1	1491	B Vazquez	6		
1462	R Ayala	3	1492	D Vossler	4		
1667	J Hogan	4	1493	F Dreifuss	1		
1466	L Brown	1	1495	W Nowack	1		
1502	J King	2	1498	H Corwin	2		
1474	V Biton	8	1669	B Fisch	3		
1475	D Blum	6	1497	K Laxer	2		
1476	P Van Ness	4	1461	K Meador	0		
1478	A Cole	2	1457	B Wannamaker	0		
1480	R Kuzniecky	6	1458	C Watson	0		
1453	R LeRoy	2	1489	R Simkins	0		
1460	S Alemyehou	0	1467	J Slater	0		
1448	A Beydoun	0	1665	S Louis	0		
1450	J French	0	1451	C Lai	0		
1488	S Shinnar	0	1485	J Pellock	0		

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
071754PR0201 Investigators (see listing below)	Ongoing (9/95)	US Soln 10, 20, 40, 60, 80, 100 mg/ml	Open, LTFU, multicenter 1° Efficacy: • Mean monthly seizure frequency Safety: • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • VEP • ERG • MRI • Ophthalm Exam (visual acuity, funduscopy with photos, visual field, slit lamp, color plate) • Cog Psych • Plasma AED	VGB 10-100 mg/kg/d: 175	(175) enrolled	Population: Pediatric epilepsy pts	DB dose adjustment: 4 wks Open label: 48 wks
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered		
1270	C Santos	4	1282	D Nordli	3		
1271	R Konkol	4	1283	J Pellock	3		
1272	R Clancy	1	1284	F Ritter	2		
1273	J Conry	5	1422	S Roach	7		
1274	F Dreifuss	3	1285	M Griebel	5		
1275	R Efferman	10	1287	J Schimschock	4		
1416	M Duchowny	5	1288	S Shinnar	0		
1276	M Sotero	6	1423	C Valentine	7		
1418	D Griesemer	9	1277	C Van Orman	16		
1278	S Helmers	5	1290	E Vining	3		
1419	D Hurst	2	1291	J Wheless	3		
1420	A Kanner	9	1424	E Wyllie	5		
1279	J Kerrigan	5	1295	B Vazquez	5		
1280	E Larson	5	1425	E Babin	11		
1292	M Morrell	10	1427	P Crumrine	2		
1421	J Murphy	8	1428	C Tardo	8		

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
OTHER STUDIES							
097-W-UK-11 P Kopelman	Complete (3/91)	UK Tablets 500 mg	DBPC, x-over 1° Efficacy: • Decrease in weight Safety: • Treatment-emergent AEs • PE • Clin Lab (incl. GTT, ITT, TFT)	VGB 2 g/d: 9 PLAC: 9	16	Population: Extremely obese women Gender: M:F 0:18	VGB or PLAC: 4-6 wks No trtmt: 2 wks X-over Alt Trtmt: 4-6 wks Taper: 2 wks
Z1754-3-W-019 Investigators (see listing below)	Complete (4/94)	Canada Finland France Hungary Netherlands Serbia UK Sachets (Powder)	DBPC, parallel, multicenter 1° Efficacy: • No. of spasms/day Safety: • MRI (screen) • CT Scan (screen) • Treatment-emergent AEs • EEG • PE & Neuro Exam • Clin Lab	VGB 50-150 mg/kg/d: 20 PLAC: 20	40	Population: Infantile Spasms Gender: M:F 19:21 Race: Caucasian: 35 Black: 1 Asian: 3 Other: 1 Age: Range: 4-20 mos Mean±SD: 8±3 mos	No trtmt: 3 days VGB or PLAC: 5 days Open VGB: 6 mos

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation		Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
		Investigator	No. Entered					
		Appleton	5		Harryard			
		Brouwer	1		Katona			1
		Djuric	6		Newton			5
		Kamphuis/Peters	1		Begeer			3
		Neuwirth	3		Dulac			1
		Stroink	3		I Gyögy			2
		Arts	2		Langevin			3
		Camfield	1					3
097WFER03		Complete (4/90)			VGB 150 mg/kg/d: 11 Hydrocortisone 15 mg/kg/d: 12	17	Population: Infantile Spasms 2° to Tuberous Sclerosis Gender: M:F 11:12 Age: Range: 1 mo - 2 yrs Mean±SD: 7.5±3.6 mos	Total: 2 mos (Optional x-over after one month in case of inefficacy/ intolerance)
C Chiron O Dulac		France Tablets 500 mg		Open, randomized, comparative, x-over option 1° Efficacy: • Cessation of spasms Safety: • CT scan (screen) • MRI (screen) • Treatment-emergent AEs • PE & Neuro Exam • Clin Lab • EEG				

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
JAPANESE STUDIES							
JGVG-CL-201 Investigators (see listing below)	Complete (1/91)	Japan Sachet (Powder)	Open, multicenter	Titrate to effect VGB 0.5, 1, 2 g/d: 54	54	Gender: M:F 31:23 Race: Asian: 54 Age: Range: 14-54 Mean±SD: 30.5±9.4	PLAC: 4 wks VGB: ≥20 wks
Study Site		Investigator		No. Entered		No. Entered	
-		T Yamauchi M Saino		8 20		14 12	
JGVG-CL-202 Investigators (see listing below)	Complete (4/92)	Japan Sachet (Powder)	Open, multicenter 3 dose comparison: 0.5 g/d 1.0 g/d 2.0 g/d	Titrate to effect VGB 0.5-4 g/d: 161	161	Gender: M:F 81:80 Race: Asian: 161 Age: Range: 14-56 Mean±SD: 31.4±10.7	Dose comparison: 8 wks Dose titration: 20 wks LT: 1 yr

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation		Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
		No. Entered	Investigator					
•	Y Fukushima	6	•	•	T Onuma	10	•	10
•	T Higuchi	10	•	•	Y Takahashi	1	•	1
•	R Kan	4	•	•	S Totaba	7	•	7
•	M Matsuura	-	•	•	Y Tsukahara	-	•	-
•	S Nakano	3	•	•	H Hazama	3	•	3
•	T Ono	10	•	•	R Inoue	2	•	2
•	H Suwaki	5	•	•	M Seino	10	•	10
•	M Toru	13	•	•	M Nakane	2	•	2
•	T Yamashita	9	•	•	A Ogata	5	•	5
•	S Hasegawa	3	•	•	H Shikame	2	•	2
•	T Hirano	27	•	•	A Takoda	6	•	6
•	I Kawai	5	•	•	S Ueda	5	•	5
•	M Murasaki	9	•	•	Y Yonemasu	4	•	4
•	Y Nakazawa							

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
JGVG-CL-301 Investigators (see listing below)	Complete (4/93)	Japan Sachet (Powder)	Open, multicenter Monotherapy	Titrate to effect VGB 1, 2, 3, 4 g/di: 131	131	Gender: M:F 63:68 Race: Asian: 131 Age: Range: 11-60 Mean±SD: 27.1±12.1	Initial: ≥ 16 wks Long Term: ≥ 3 mos
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered		
-	T Asakura	2	-	N Yamaguchi	1		
-	S Hasegawa	3	-	Y Yonemasu	4		
-	M Iida	2	-	M Mino	4		
-	R Inoue	3	-	T Miura	6		
-	M Seino	1	-	T Nagai	4		
-	Y Fukushima	3	-	T Okada	5		
-	T Higuchi	2	-	M Saito	3		
-	H Ikawa	2	-	M Sato	2		
-	M Ito	2	-	K Shimada	2		
-	T Kojima	1	-	M Tabuchi	4		
-	Y Fukuyama	3	-	M Toru	1		
-	G Hirose	4	-	K Watanabe	2		
-	T Ikeno	2	-	S Yamanoue	2		
-	A Kimura	2	-	T Mita	1		
-	M Kosaka	2	-	M Mivao	4		
-	M Matsushita	2	-	T Nishimura	3		
-	A Mitsutome	3	-	T Onuma	1		
-	M Murasaki	2	-	T Sakaki	4		
-	S Odawara	4	-	Y Sato	4		
-	K Otani	4	-	M Shimizu	7		
-	M Sato	4	-	S Tanaka	2		
-	T Seki	2	-	N Tsuru	2		
-	J Suzuki	1	-	K Yagi	1		
-	N Tashiro	3	-	T Yamauchi	2		
-	S Ushijima	4	-				

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
JGVG-CL-302A JGVG-CL-302B Investigators (see listing below)	Ongoing (10/93)	Japan Sachet (Powder)	DBPC, multicenter with open LTFU (302B)	Titrate to effect VGB 1, 2, 3 g/d; NAV PLAC: NAV	247 enrolled	Gender: M:F 120:127 Race: Asian: 247 Age: Range: 11-77 Mean±SD: 28.3±12.5	Total: 16 wks

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation		Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
		No. Entered	Investigator					
-	T Asakura	3	-	-	A Ogata	-	-	4
-	S Hasegawa	2	-	-	S Otawara	-	-	4
-	T Hirano	2	-	-	M Sato	-	-	2
-	M Lida	0	-	-	T Seki	-	-	1
-	R Inoue	2	-	-	H Suwaki	-	-	3
-	A Kimura	7	-	-	S Tanba	-	-	1
-	M Kosaka	3	-	-	S Totaba	-	-	3
-	M Matsushita	0	-	-	S Ushijima	-	-	2
-	T Miura	4	-	-	N Yamaguchi	-	-	2
-	M Nakano	-	-	-	K Yasuda	-	-	1
-	T Onuma	12	-	-	Y Fukuyama	-	-	4
-	K Otani	8	-	-	T Higuchi	-	-	0
-	T Sakaki	4	-	-	Y Igarashi	-	-	4
-	T Sato	3	-	-	H Inoue	-	-	1
-	M Shimizu	2	-	-	I Kawai	-	-	8
-	S Tanaka	4	-	-	T Kojima	-	-	0
-	M Toru	3	-	-	M Mino	-	-	0
-	S Ueda	2	-	-	A Mitsutome	-	-	11
-	K Yagi	1	-	-	R Nagai	-	-	8
-	T Yamauchi	2	-	-	T Nishimura	-	-	2
-	Y Fukushima	4	-	-	T Okada	-	-	4
-	H Hazama	3	-	-	M Saito	-	-	1
-	G Hirose	2	-	-	M Sato	-	-	4
-	T Ikeno	4	-	-	K Shimada	-	-	1
-	M Ito	4	-	-	M Tabuchi	-	-	4
-	M Seino	4	-	-	N Tashiro	-	-	2
-	T Kurokawa	3	-	-	N Tsuru	-	-	2
-	T Mita	2	-	-	K Watanabe	-	-	3
-	M Murasaki	0	-	-	S Yamanoue	-	-	6
-	Y Nakazawa	4	-	-	Y Yonemasu	-	-	5
-	S Wakai	7	-	-	Y Takeuchi	-	-	4
-	R Kan	4	-	-	M Hanada	-	-	4
-	T Soga	12	-	-	G Ikawa	-	-	4
-	M Momoi	4	-	-	T Hanai	-	-	4
-	J Suzuki	4	-	-	Y Nakane	-	-	4
-	J Asano	2	-	-	H Baba	-	-	12

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
JGVG-CL-401 Investigators (see listing below)	Ongoing (NAV)	Japan Sachet (Powder)	Open, multicenter	Titrate to effect VGB 1, 2, 3, 4 g/d; 167	167 enrolled	Race: Asian: 167 Age: Range: 12-65	Compassionate use

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Table 9-1. Table of All Clinical Studies for Final Safety Update

Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design		Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
			Investigator	Study Site				
			No. Entered	Investigator	No. Entered			
-	Y Yonemasu	3	-	T Yamauchi	1			
-	M Kosaka	8	-	Y Igarashi	2			
-	S Wakai	2	-	R Inoue	5			
-	T Hirano	1	-	M Toru	1			
-	Y Fukushima	3	-	T Seki	2			
-	M Ito	2	-	G Yagi	1			
-	T Mita	2	-	M Shimizu	6			
-	S Totsuka	2	-	Y Fukuyama	2			
-	T Ikeno	3	-	M Matsushita	2			
-	T Soga	4	-	J Suzuki	1			
-	M Sato	2	-	T Onuma	3			
-	M Sato	1	-	M Murasaki	1			
-	N Matsui	1	-	T Miura	5			
-	M Momoi	2	-	M Seino	5			
-	Y Machiyama	7	-	Y Koshino	1			
-	G Hirose	5	-	G Ikawa	1			
-	T Okada	1	-	M Tabuchi	2			
-	A Takeda	1	-	S Otake	4			
-	K Shimada	3	-	R Kawahara	3			
-	J Kimura	3	-	H Suwaki	3			
-	Y Takeuchi	1	-	A Mitsudome	4			
-	I Kawai	17	-	T Hanai	2			
-	T Nishimura	3	-	Y Nakazawa	5			
-	T Nagai	2	-	S Ueda	4			
-	S Yamagami	1	-	Y Nakane	1			
-	M Minou	2	-	H Baba	4			
-	K Otani	3	-	A Ogata	2			
-	M Saito	1	-	S Tanaka	3			
-	M Hanada	1	-	K Koseki	1			
-	T Sakaki	3	-					

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Table 9-1. Table of All Clinical Studies for Final Safety Update							
Protocol No., Investigators, Protocol Amendments	Completion Status (Start Date)	Study Location, Formulation	Study Design	Doses, No. Entered Each Treatment	Total Exposed to Vigabatrin	Demographics	Duration of Drug Treatment
INVESTIGATOR IND FOR INFANTILE SPASMS							
R Eilerman W Shields Investigators (see listing below)	Ongoing (1/23/96)	US Tablets 500 mg	Open, randomized, dose-ranging, multicenter * Efficacy: • Cessation of Spasms (w/in 14 days of treatment) Safety: • MRI or CT (screen) • EEG (screen) • AEs • PE & Neuro Exam • Ophthalm Exam (routine)	Low dose: 3.5-7.0 kg: 125 mg/d 7.1-14.0 kg: 250 mg/d High dose: 3.5-5.0 kg: 500 mg/d 5.1-7.5 kg: 750 mg/d 7.6-10.0 kg: 1000 mg/d 10.1-12.5 kg: 1500 mg/d 12.6-14.0 kg: 1750 mg/d	73 exposed 62 efficacy evaluable	Gender: M/F: 41:32 Age: 1-46 mos Mean±SD: 8.2±6.3 Race: Caucasian: 50 Black: 8 Asian: 1 Other: 14 Population: Untreated Infantile Spasms <3 mo duration	No trtm: 3-7 days VGB: -14 days (spasm free) -7 days LTFU: >3 years
Study Site	Investigator	No. Entered	Study Site	Investigator	No. Entered		
01	R Eilerman	7	05	J Freeman	0		
02	W Shields	14	06	W Mitchell	16		
03	P Crumrine	10	07	E Trevathan	2		
04	M Bebin	14	09	E Wylie	10		
* Demographics based on ITT population instead of Safety Evaluables. () In the Total Exposed to Vigabatrin column, the number outside the parentheses indicates the number of patients exposed to VGB for the first time. The number inside the parentheses indicates the number of patients who were in a previous study. The total of these two numbers equals the number of patients exposed to VGB in the study.							
Note: Bolded information includes new or updated patient data reported from January 1, 1996 through March 15, 1997.							

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Study Type	Analysis Category	Total Number of Exposures in Completed US and Primary and Secondary Non-US Studies (Amendment and Final Safety Update)									
		Placebo		VGB		Active Comparator		Total*			
		Amend	FSU	Total*	Amend	FSU	Total*				
Clinical Pharmacology	US	0	NA	0	66	NA	0	66	NA	66	
	Non-US	52	12	64	215	33	248	18	21	39	261
Total*	US and Non-US	52	12	64	281	33	314	18	21	39	327
Epilepsy Controlled	US	135	NA	135	222	NA	222	0	NA	0	356
	Non-US	356	0	356	409	338	747	0	342	342	1146
Total Epilepsy Controlled*	US and Non-US	491	0	491	631	338	969	0	342	342	1502
Epilepsy Uncontrolled	US	0	0	0	414	1186	1380	0	0	0	1380
	Non-US	504	0	504	1166	188	1354	40	90	130	1432
Total Epilepsy Uncontrolled*	US and Non-US	504	0	504	1580	1329	2699	40	90	130	2767
Total Epilepsy*	US	135	0	135	443	1186	1499	0	0	0	1412
	Non-US	841	0	841	1499	526	1975	40	432	472	2403
Total Epilepsy*	US and Non-US	976	0	976	1942	1667	3399	40	432	472	3770
Other Indications	US	0	NA	0	28	NA	28	0	NA	0	28
	Non-US	191	33	224	280	73	353	30	12	42	370
Total*	US and Non-US	191	33	224	308	73	381	30	12	42	398
Overall Total*	US	135	0	135	537	1186	1503	0	0	0	1506
	Non-US	1084	45	1129	1978	632	2560	88	465	553	3018
	US and Non-US	1219	45	1264	2515	1773	4018	88	465	553	4479

Note: The 6 patients who participated in Protocol 71754-III-ST-016 received concomitant carbamazepine in addition to their randomized treatment (vigabatrin or phenytoin). The numbers are presented correctly in this table; however in all the serious tables which follow that include carbamazepine as a comparator treatment, these 6 patients are counted inappropriately in the denominator and may be counted in the numerator if an adverse event started prior to vigabatrin or phenytoin exposure.

NA Not Applicable

* The numbers in the total rows/columns represent patient exposures in completed US and Non-US studies. Please note that patients may have been exposed to more than one study treatment or may have participated in more than one study. These patients are only counted once in the total rows/columns.

† The numbers in the Total Amendment column represent patient enrollment in completed US and Non-US studies.

SEP 17 1998

Review and Evaluation of Clinical Data

NDA (Serial Number)	20-427
Sponsor:	Hoechst Marion Roussel
Drug:	vigabatrin
Proposed Indication:	epilepsy
Material Submitted:	Updated Safety Information
Correspondence Date:	7/29/98
Date Received / Agency:	7/30/98
Date Review Completed	8/28/98
Reviewer:	Armando Oliva, MD

1. Introduction – Vigabatrin Associated Visual Loss

The British Medical Journal, on 1/18/1997, published three case reports of vigabatrin associated severe and irreversible visual field defects (Eke, et al., BMJ, 1997; 314:180-1). Since then, there have been numerous other similar reports in the literature. In June 1998, the Division requested additional safety information regarding these reports. This submission contains the sponsor's response to that request. The submission consists of several sections, which I review below.

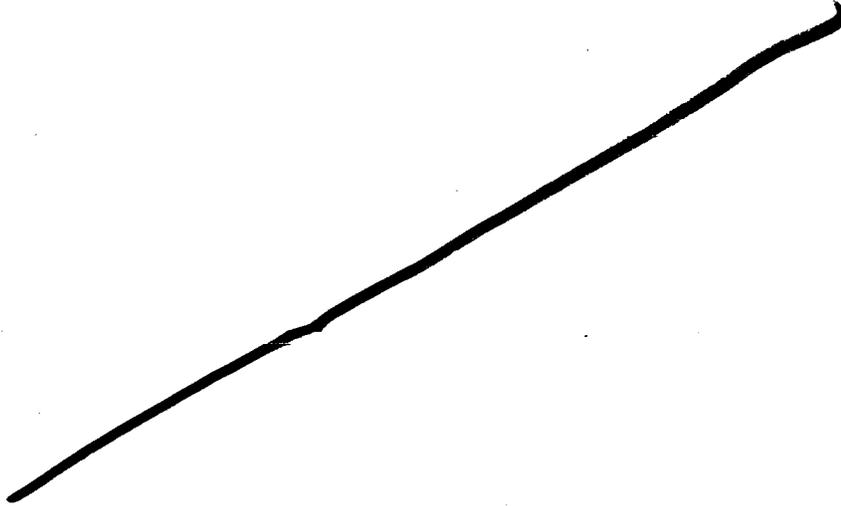
- Proposed ophthalmologic labeling
- Expert Report (John M. Wild) on Perimetry Findings
- Reports from the literature, individual line listings of patients with ophthalmologic findings, and individual MEDWATCH forms
- UK Prescription Event Monitoring (PEM) Study
- Sponsor's Epidemiological Report of Unique VF Defects

I also review an article published in the March 1998 edition of *Neurology*, which describes detailed neuro-ophthalmologic findings in four patients with vigabatrin associated visual loss. This reprint is included in the submission, and the four cases are included in my descriptive analysis.

2. Proposed Ophthalmologic Labeling

The sponsor describes the ophthalmologic findings associated with vigabatrin in the Precautions section of draft labeling.

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3. Expert Report

John M Wild, PhD, at the School of Life and Health Sciences, Aston University, Birmingham, UK, reviewed 73 case reports of patients with vigabatrin associated visual field loss. The 73 cases arose from 10 countries. Those from open label extension trials in Japan and Finland (n=44) had cutoff dates of 7/1/98. Those from spontaneous reports (n=29) had a cutoff date of 2/1/98. The three original cases reported by Eke in the BMJ are included in his report.

Thirty-nine (39) of the cases had been examined using kinetic perimetry using either the Goldmann or Topcon bowl perimetries. In 19 cases, static threshold automated perimetry was performed using either the Humphrey Field Analyzer (n=15) or the Octopus automated perimeter (n=3). Six (6) had been examined with both static and kinetic perimetry. Another 6 were examined using suprathreshold perimetry and the remaining 3 cases by automated kinetic perimetry.

A completely normal VF was graded a "0". One with a VF defect of known cause (*e.g.*, glaucoma), was rated a "4." The type and severity of a VF defect for which no other explanation could be found was termed "unique" and was classified using an empirical, semi-quantitative procedure which permitted the description of the defect on a three point scale, 1=mild, 2=medium (moderate), 3=severe. Also used were a description and the location of the defect. Fields deemed to be unreliable, uninterpretable, or inconclusive were rated a "5."

Of the 73 cases reviewed, six were rated as normal. In another six, the VF defect could be attributed to a known cause, in another 10, the fields were unreliable,

uninterpretable, or inconclusive. In another 2 cases, the fields were rated as either "moderate or due to another cause." (??)

In the remaining 49 cases, the VF defects were distributed among all three severity levels but most were moderate or severe (mild=3, moderate=19, severe=27).

The overall pattern of VF defect seen was a bilateral constriction, which was more marked nasally than temporally.

Localization of the lesion on the basis of perimetry alone is impossible; however, based on the available data (decreased Arden index on the EOG, and increase in the ERG b-wave latency), Dr. Wild suspects it is a retinal lesion. He comments that the fundus appearance ranges from normal, to one involving optic nerve head pallor and/or retinal pigment epithelial disturbance.

4. Individual Case Reports

4.1 Methods

Using data from literature case reports and individual patient line listings, I reviewed 221 cases of visual loss associated with vigabatrin use. I did not review individual Medwatch forms for each patient, but I did randomly compare several Medwatch forms to the line listings to convince myself that there were no major discrepancies. The cases came from several sources:

- 133 came from spontaneous reports from foreign sources
- 58 came from US and non-US studies
- 23 came from published literature reports
- 4 came from the UK Prescription Event Monitoring (PEM) program
- 3 came from non-US compassionate use programs

I created a JMP dataset of all 221 patients. I included the following variables: ID/source, age, sex, daily dose, time to diagnosis of the VF defect in months, concomitant medications, description of the VF defect, presence of symptoms, action (dc'ed, decreased dose, continue rx), outcome, follow-up time in months, diagnosis, ERG (nl or abnl), VEP (nl or abnl). I used JMP version 3.2.2 to perform the following descriptive analyses.

4.2 Results

The mean age was 39 (range 9-73). The gender distribution was 112 men and 84 women (missing=25). The median daily dose of vigabatrin, when reported, was 3 g/d (range 0.5-6 g/d, missing=42). The majority reported taking other anticonvulsants concomitantly (181/221 or 82%).

The mean duration of treatment until the visual defect was diagnosed was 36 months (missing=42), with the range was 10 days – 112 months. This by no means indicates the onset of the abnormality.

The two most common visual abnormalities reported (n=123) were peripheral constriction and/or binasal visual field defects. Many cases were asymptomatic.

Table 1: Distribution of Visual Defects, by Symptoms and Outcome

Symptom	N	Meant time to Diagnosis (months)	Outcome			
			?	Resolved	Improved	Unresolved
?	72	33	28	9	1	34
Asymptomatic	68	44	9	2	0	57
Symptomatic	81	33	22	4	5	50
Total	221	36	59	15	6	141

The following actions and outcomes were reported:

Table 2: Action and Visual Outcome

Action	N	Outcome			
		?	Resolved	Improved	Unresolved
Unknown	59	32	6	2	19
Dose Continued	43	12	1	0	30
Dose Decreased	9	0	0	1	8
Discontinued	110	15	8	3	84
Total	221	59	15	6	141

The majority (141 of 221, or 64%) did not improve, with 59 (27%) having no follow-up data. Only 21 (10%) reported improvement or resolution of their defect. Of the 110 patients that had their medication discontinued, 84 (76%) had persistent visual field abnormalities. The extent and duration of follow-up was generally not reported.

Very few had ERG's reported (n=19). Of those, 17 were reported as abnormal. Very few had VER's reported (n=14). Of those, 6 were abnormal. Patient functional disability was not documented; however, one patient (UK - 199810058) was described "legally blind."

Those who had therapy discontinued and either improved or resolved their VF defect had mean onset of diagnosis of the visual defect of 18-20 months, whereas those who failed to improve upon discontinuation had mean time to diagnosis of 40 months. This suggests that reversibility of the defect upon discontinuation may be related to time to diagnosis; however, further investigation in a future study is necessary since this is retrospective data with small numbers (only 11 in this group improved or resolved).

5. UK Prescription Event Monitoring Program (PEM Study)

The PEM program is not described in the submission. Presumably, it is a systematic monitoring system of patients taking vigabatrin in the UK. It appears

the program also monitors patients taking lamotrigine and/or gabapentin, as well as other drugs (which are not stated). The report was written on 2/6/97, just a few weeks after the initial BMJ report. Based on three reports of VF defects, the authors decided to review all cases of visual field defects coded in the PEM studies. A detailed explanation of the PEM program is lacking, making interpretation of the data difficult. Data were collected from 62 studies. It appears that each study monitors a different drug. It also appears that patients were monitored for only the initial 6 months of therapy. The cohort taking vigabatrin was estimated at 10,178. The cohort taking lamotrigine was estimated at 11,316.

Sixty-three (63) patients with "visual field defect" (VFD) were identified among 62 PEM studies in approximately 11,215 patients. Fifty studies were completed and 12 were ongoing. Of these, 21 had the VFD reported after the monitored drug was stopped. For reasons that are not clear, the number cases classified as VFD was trimmed to 43 based on re-assessment and consideration of additional follow-up information.

Of these 43 cases, 2 occurred in patients taking lamotrigine, and 5 occurred in patients taking vigabatrin. The remaining occurred in patients that had "other probable causes" for their VFD. No cases in patients taking gabapentin were identified.

For the two cases involving lamotrigine, the ophthalmologist concluded the visual impairment was hysterical in one. The other patient had subjective symptoms only and they resolved after discontinuation. Additional follow-up information is pending.

For the 5 cases involving vigabatrin, one had no objective sign of visual impairment and was reversible. The remaining four had signs of peripheral VFD. One had not resolved, and follow-up information was lacking in 3 others.

The author reports knowledge of other patients who developed VFD during treatment with vigabatrin (he cites "personal communication") but were not captured by this report because they occurred after the six-month monitoring period.

Reviewer's note: The UK PEM study is difficult to interpret since a full description of the PEM program is lacking. In particular, the monitoring period appears to have only been six months, which would fail to capture many patients who develop visual field defects late in treatment. In fact, the data from the spontaneous reports indicate that many cases were not diagnosed until several years of therapy.

6. Vigabatrin and the Risk of Unique Visual Field Defects

This report was written by a global pharmacoepidemiology group from Hoechst Marion Roussel (HMR) on 7/23/98. The object of the report was to estimate the

frequency of unique VFD's among vigabatrin treated patients and to explore potential risk groups.

The group used data from six clinical open-label trials from Finland and Japan.

Table 3: Open Label Studies used for Analysis

Country	Study Number	Phase	Regimen
Finland	71754-3-W-007	3	Monotherapy
	097.335	3	Monotherapy
Japan	JGVG-CL-201	2a	Add-on therapy
	JGVG-CL-202	2b	Add-on therapy
	JGVG-CL-301	3	Add-on therapy
	JGVG-CL-302	3	Add-on therapy

All studies were long-term clinical trials. The Finnish studies included patients with newly diagnosed epilepsy. The Japanese studies included patients with poorly controlled epilepsy.

In the fall of 1997, approximately 9 years after the beginning of the first study, patients on vigabatrin who were participating in these studies were asked to undergo visual testing. Those who agreed underwent ophthalmologic examination and perimetry testing. None of the patients had any visual symptoms prior to testing. Those with abnormal perimetries did not have them repeated to demonstrate reproducibility of the defect. All positive perimetries were sent to an independent external visual field expert, Dr. John Wild, of Aston University. His method of review of these (and other) fields is described in section 3 of this review. Those VFD's classified as mild, moderate, severe, or possible were considered unique. All VF's submitted by 7/1/98 were included in this report.

There were 219 patients who took vigabatrin in the six studies in question. Of these, 136 agreed to undergo visual testing. Of these 136, 2 were judged uninterpretable and were dropped from analysis. There were some differences in the demographics. In general, Japanese patients tended to be younger (34 vs 41 years) and have shorter durations of treatment (4.4 vs. 6 years). The duration of epilepsy was much longer for the Japanese patients (23 vs. 9 years).

Of the 134 patients with evaluable perimetry data, 38 (28%) were diagnosed with a unique VFD (35% for Finnish studies, and 26% for Japanese studies). Most cases were moderate (n=14, 37%), or severe (n=17, 45%). The unique VFD's consisted of bilateral constriction with a variable degree of temporal sparing. The 134 patients contributed to 649 years of vigabatrin use. The overall incidence was 5.9 cases per 100 patient-years.

The following variables were examined as potential risk factors for the development of VFD: gender, age, duration of vigabatrin use, cumulative dose of vigabatrin, duration of epilepsy, weight, and BMI. There appeared to be a

potential association between gender and unique VFD. Twenty-two males (37% of all males) and 16 females (21% of all females) were diagnosed with a unique VFD. This pattern was consistent across Japan and Finland. The odds ratio for gender, 2.2, was the only one appreciably different from 1.0. This suggests that males are at greater risk for unique VFD than females. The other variables were negative for a risk association. Since the patients were asymptomatic, the true event onset date is not known and no clear relationship between treatment duration and onset of unique VFD can be established from these data.

The sponsor plans to validate the data, in part, by reviewing the "normal" visual fields for any false negatives. Additional data may also become available. Therefore, the conclusions may be updated and refined. Based on these limitations, the authors conclude:

- The unique VFD's consisted of bilateral constriction with a variable degree of temporal sparing.
- The estimate prevalence of unique VFD's is 28% (95% CI=20-36%) based on the Finnish and Japanese data combined.
- There is a suggestion that men are at greater risk for unique VFD than women (37% vs. 21%, odds ratio: 2.2).

7. Vigabatrin Associated Retinal Cone System Dysfunction

I review below a journal article entitled "Vigabatrin Associated Retinal Cone System Dysfunction" (Neurology 1998;50:614-618). It appears in the March 1998 edition. The article is unique in that it gives detailed neuro-ophthalmologic findings in four patients with vigabatrin associated visual loss. Furthermore, one of the co-authors, Dr. Neil Miller, from Johns Hopkins University, is a very well respected neuro-ophthalmologist and a leader in his field.

The paper reviews four cases of symptomatic visual disturbances associated with vigabatrin treatment. The four patients were taken from a cohort of 38 patients who were undergoing vigabatrin therapy as part of a safety study sponsored by HMR and were undergoing periodic examinations and screening for adverse events at six-month intervals. They underwent ophthalmologic testing as a direct result of their acquired visual complaints. The testing consisted of a complete ophthalmologic exam, color vision testing, perimetry, ERG, and VEP.

Case 1: 58 y/o M took vigabatrin 4.5 g/d and carbamazepine 600 mg/d for complex partial seizures. After starting vigabatrin, seizure frequency went from 56/month to 1.5/month. One year after starting vigabatrin, he began bumping into objects. Visual acuity was 20/30 OU. Visual fields showed non-specific constriction. Four months later, the visual fields were slightly worse. Repeat visual acuity was 20/40 OD; 20/30 OS. There was no relative afferent pupillary defect (RAPD). Color vision (using pseudoisochromatic plates -- PIP) was normal at 10/10 OU. Ophthalmoscopy showed slightly narrowed retinal arteries and an irregular appearance in both maculas, consistent with surface wrinkling retinopathy. Both optic discs had a normal appearance. Both kinetic and static perimetry showed non-specific constriction of the visual fields. Cone system ERG revealed a markedly reduced amplitude of the b wave. Rod function was normal. Cone oscillatory potentials in the mixed rod and cone ERG were sharply attenuated. Pattern VEP were delayed.

The vigabatrin dose was gradually decreased to 3 g/d with no change in ERG or VEP after 2 months.

Case 2: 22 y/o F took vigabatrin 2 g/d monotherapy for complex partial seizures. Her seizure frequency went from 5/month to 0.5/month. She had recently started valproate and was switched to topiramate after the development of gastric symptoms. Two years after starting vigabatrin, she developed blurred vision in both eyes. Visual acuity was 20/30+2 OD and 20/20 OS. Color vision using PIP was 10/10 OU. The pupils were normal without RAPD. Visual fields were full using kinetic perimetry. Ophthalmoscopy revealed a normal right eye, but a slightly irregular macular reflex in the left. ERG showed cone system functional decline in both eyes, a decrease in b wave amplitude. Oscillatory potential amplitudes were also reduced, consistent with both cone system dysfunction and reduced amacrine cell response. Rod function was normal. VEP were normal. The visual symptoms improved as the vigabatrin was tapered from 2 to 0.5 g/d and then discontinued. She is scheduled for a follow-up ERG.

Case 3: 29 y/o F took vigabatrin 4.5 g/d, carbamazepine 1400 mg/d for complex partial seizures. Her seizure frequency went from 38/month to 8/month. Shortly after starting vigabatrin, she noted a gradual constriction in her peripheral vision, left eye greater than the right. Visual acuity was 20/20 OD and 20/20-1 OS. Color vision using PIP was 10/10 OU. Kinetic perimetry revealed slight, non-specifically constricted visual fields in both eyes. Static perimetry was normal. Ophthalmoscopy revealed no evidence of retinal pigmentary disturbances, optic disc pallor, or optic disc swelling. ERG revealed reduced cone system function in both eyes, reduced b wave amplitude, and reduced rod photoreceptor function in the left eye. Oscillatory potential amplitudes were reduced bilaterally, consistent with losses in electrical activity of both the cone system and amacrine cells. The reduction in cone function was greater in the left eye than in the right. VEP were normal.

Case 4: 67 y/o M took vigabatrin 4 g/d as monotherapy for complex partial seizures. Seizures decreased in frequency to one seizure every six months. Three and one half years after starting vigabatrin, he noted difficulty with central vision in the right eye. Visual acuity was 20/50 OD and 20/20 OS. Color vision was 9.5/10 OD and 10/10 OS. The pupils were normal with no RAPD. Ophthalmoscopy revealed a surface wrinkling retinopathy without posterior vitreous detachment in the right eye. The optic discs were normal. Perimetry showed moderate peripheral field constriction, greater temporally. ERG showed cone amplitude and implicit time delay in both eyes and rod photoreceptor loss in the left. Oscillatory potential amplitudes were also reduced, consistent with both cone system dysfunction and reduced amacrine cell response. VEP were normal.

I paraphrase the authors' discussion. The reported cases are similar to those previously reported in the UK, Switzerland, and Germany. Preferential cone system dysfunction is an uncommon finding in the general population and it is unlikely that these patients had abnormal cone function before starting therapy with vigabatrin.

Vigabatrin increases brain GABA, which is an inhibitory neurotransmitter in the vertebrate retina. It occurs in retinal horizontal and interplexiform cells, and in many types of retinal amacrine cells. ERG oscillatory potentials arise mainly from amacrine cells, but also from the ganglion and bipolar cells.

The authors note that phenytoin and carbamazepine have also been shown to decrease ERG b wave and oscillatory potential amplitudes, and two of the patients were taking carbamazepine at the time; however, two others were on vigabatrin monotherapy.

Of the four patients reported, three had peripheral constriction of the visual fields (one severe), two had mild reductions in visual acuity, and all four had reductions in the cone system and oscillatory potential components of the ERG. VEP's were generally normal, consistent with normal or near normal optic nerve function and normal macular function. None had baseline ERG or VEP prior to vigabatrin treatment. The extreme reduction in oscillatory potentials is consistent with impaired function of the highly GABAergic amacrine cells. The reductions may also reflect diminished cone system activity.

The abnormal VEP was seen in the patient with the most severe visual dysfunction and with the longest duration (two years). This suggests that vigabatrin associated retinal changes may progress with length of treatment.

Two of the four patients had extremely severe epilepsy that improved only with vigabatrin. For some patients, the risks from uncontrolled seizures may outweigh the risk to the retina, particularly because visual symptoms are relatively mild and progress slowly.

The remaining 34 patients on vigabatrin will be studied for the presence of asymptomatic visual changes. The visual symptoms may reflect selective vulnerability in some patients to relatively common GABA mediated physiologic changes in the retina.

8. Comments

My review indicates the presence of a significant safety signal involving the visual system. Vigabatrin appears to be associated with visual field defects that are best characterized as peripheral constriction with a propensity to affect the binasal fields preferentially. The lesions appear to be most likely retinal, but co-existing optic nerve dysfunction, particularly in more severe cases, may also be present. The best current estimate of the prevalence is 28%, with an estimated incidence of 5.9 per 100 patient years.

Of greatest concern is the fact that many of these cases were asymptomatic, most of these visual field defects were moderate or severe (82%), and most did not improve after drug discontinuation.

The available data are poor because they lack baseline visual evaluations, other diagnostic tests, or systematic follow-up exams. This safety signal needs further investigation. There are several key questions that remain unanswered.

- What is the true incidence of visual field defects in vigabatrin treated patients?
- How does this compare with the incidence in patients treated with other anticonvulsant medications?
- Are the visual field changes reversible after drug discontinuation if detected early?

I believe these questions should be answered prior to approval. As a result, I recommend that the sponsor collect additional safety data. The data are best collected in the form of a study with the following important design features:

1. Patients enrolled in the trial should undergo detailed monitoring of visual function, both at baseline and periodically throughout the study (*e.g.*, every three months).
2. The visual testing should include:
 - complete ophthalmologic examination including dilated fundoscopy.
 - color vision testing using the Farnsworth-Munsell 100 Hue color test
 - automated static perimetry measurement of both central and peripheral vision, such as the Humphrey Visual Field Analyzer
 - electroretinography (ERG), electro-oculography (EOG)
 - visual evoked potentials (VEP)
3. The study should contain sufficient numbers of patients, and it should be of adequate duration to detect abnormalities that may be late in onset.
4. The sponsor should strongly consider adding a control group, consisting of epileptic patients treated with other anticonvulsant medications; otherwise, they should attempt to determine the incidence of visual field abnormalities in patients using other anticonvulsants, using the best available historical data.
5. The study should specify clear endpoints that will determine when visual function is considered abnormal, and when discontinuation of vigabatrin should occur.
6. Patients taken off drug should be adequately followed in order to determine if the visual abnormality resolves.
7. Reviewers of the data should be blinded to patient ID, dose, duration of therapy, and whether vigabatrin has been discontinued.

AOliva

Armando Oliva, M.D.
Medical Reviewer

R. Katz, M.D. *RK 9/17/98*

ao 8/21/98
cc:
HFD-120
NDA 20-427
Katz, Burkhart, Boehm

SEP 17 1998



**Review and Evaluation of
Clinical Data**

NDA:	20-427
Sponsor:	Hoechst Marion Roussel
Drug:	Sabril (vigabatrin)
Proposed Indication:	Epilepsy
Material Submitted:	Response to Approvable Letter
Serial No.:	001
Correspondence Date:	April 24, 1998
Date Received / Agency:	April 27, 1998
Date Received / Reviewer:	April 27, 1998
Date Review Completed	August 25, 1998
Assignments:	
Project Manager:	Malandrucco, Melina
Medical Officer:	Sherry, James
Chemist:	
Pharmacologist:	
Statistician:	N/A

1. Introduction:

Vigabatrin is a new molecular entity developed by the sponsor for the treatment of epilepsy. Vigabatrin is an irreversible inhibitor of GABA-transaminase. This inhibition results in the decreased catabolism of GABA, and consequently increased brain GABA levels.

1.1 Background:

On May 29, 1997, the sponsor submitted a response to the not approvable letter. That response included an amendment to the NDA. An audit and reanalysis of study C-024 was completed. An In-House organizational meeting was held on June 30, 1997. It was decided that in addition to the analysis performed by the sponsor for this amendment, a traditional intent-to-treat analysis should be performed utilizing the audit data. Analysis of that data as well as review of the safety data with respect to possible Intramylenic Edema (IME) is contained in my review of Nov. 5, 1998. An approvable letter was issued on November 26, 1997.

2. Materials Utilized in Review

In response to the Approvable Letter and Draft Labeling, the sponsor has submitted supporting documentation for MRI findings, evoked potential findings and autopsy findings. Additional information was also provided concerning a possible vigabatrin-associated peripheral neuropathy. Additional information has

been provided by the sponsor concerning ophthalmologic abnormalities associated with vigabatrin. The ophthalmologic abnormalities will be reviewed separately by Drs. Boehm and Oliva. The primary document for this review was the amendment to the NDA (20-427; N(AZ)), Response to the Approvable Letter. This document consists of 22 volumes and was submitted in electronic format (sponsor designed ONDA) and paper format. Specifically, volumes 1 – 14 were reviewed.

3. Supporting Documentation:

3.1 Peripheral Neuropathy:

3.1.1 Background from Clinical Review:

In reviewing the data from the placebo controlled trials, the following could be considered signals for possible peripheral neuropathies. A larger percentage of vigabatrin treated patients in study C-024 had diminished position and touch sense. This pattern was not seen in the studies C-021 and C-025. In studies C-024 and C-025 (not in C-021), a greater percentage of vigabatrin treated patients had diminished vibratory sense. Ankle reflexes were diminished in a larger percentage of vigabatrin treated patients in studies C-021 and C-025 (not C-024). In reviewing follow-up studies (71754-3-C-024, 71754-3-C-025, 71754-3-C-021, 71754-3-C-020, 71754-3-C-026, 71754-3-C-022, and 71754-3-C-028), 39 / 467 patients were identified with "peripheral neuropathy-like" neurological examination results. Nine of these patients had the findings at baseline. The remaining 30 patients had signs consistent with a peripheral neuropathy. Eighteen of 96 patients in examined in protocol 071754PR0253 had abnormal neurological examinations with signs that could be attributed to a peripheral neuropathy. Ten of 18 were not on vigabatrin treatment at the time of evaluation.

In reviewing the adverse events in the US studies (C-024/025), parathesias were reported in 3.0% of the placebo treated patients and 9.9% of the vigabatrin treated patients. Hyporeflexia was reported in 0.7% of placebo treated patients and 5.4% of vigabatrin treated patients.

Four (and possibly 5) cases of peripheral neuropathy have been reported in The Global Adverse Event Reporting System. In two cases, the peripheral neuropathy improved with discontinuation of the vigabatrin. The fifth case involved a case of possible GBS, which was discounted on the basis of electroneuromyography evaluation, the details of which were not provided.

In summary, there are symptoms and signs of peripheral neuropathy

associated with vigabatrin treatment, which exceed those seen in placebo treated patients. The sponsor has focused on associating peripheral neuropathy with IME. Regardless of the mechanism, vigabatrin treatment is associated with a higher incidence of peripheral neuropathy. No evidence has been presented by the sponsor in support of the claim that there is no evidence of a demyelinating peripheral neuropathy.

3.1.2 Agency Request:

The sponsor should:

- provide additional information about the course of the vigabatrin associated peripheral neuropathies, e.g. onset, duration of exposure, resolution.
- provide any additional information concerning characterization of the peripheral neuropathy e.g. electroneuromyography evaluations and nerve biopsies.
- develop a proposed case definition for peripheral neuropathy which should be discussed with us before additional work is done. Once we have agreed on a case definition, please submit comprehensive information about all cases in your database, including nerve conduction studies, if available.
- also provide incidence estimates from your controlled trials

3.1.3 Sponsor's Response:

3.1.3.1 Case Definition of the Vigabatrin associated PN:

In an attempt to create a case definition, the sponsor consulted with [REDACTED] M.D., a specialist in the area of peripheral neuropathy. [REDACTED] reviewed "relevant details of those patients" previously identified as pertinent to peripheral neuropathy by the sponsor's consultant neurologist / epileptologist. The presence of a neuropathy was determined by finding in the case report documents of appropriate symptoms (numbness, tingling, dysethesias, or weakness), signs (loss of sensation, weakness, or loss of reflexes), or both that were usually distally predominant. The signs and/or symptoms should be repeatable. [REDACTED] determined based on his clinical judgement if the case was consistent with a peripheral neuropathy. He identified 36 potential peripheral neuropathy cases. The neuropathies were then characterized as probably (n=6), possibly (n=11), or unlikely (n=19) to be vigabatrin-associated. Of the possible and probable cases, 11 were from protocols 021, 024, 025 with a total of 457 subjects with exposure to vigabatrin. In the controlled portion of those trials there were 0 / 188 subjects in the placebo arm with symptoms / signs of peripheral neuropathy and 4 / 280 (1.4%) in the vigabatrin arms. An additional 7 cases of peripheral neuropathy were identified in the open label portion of these trials.

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3.1.3.2 Incidence Estimates from Controlled Trials:

[REDACTED] identified 11 / 457 (2.4%) of subjects in the placebo-controlled trials in North America with possible / probable peripheral neuropathy.

3.1.3.3 Course of the Vigabatrin associated PN:

The sponsor failed to reach a conclusion with respect to the dose or duration of exposure and the risk of developing a peripheral neuropathy.

3.1.3.4 Characterization of the Vigabatrin associated PN:

The characterization of the peripheral neuropathy has been based on the clinical presentation, symptoms and signs. Of the cases identified as potential PN, only one subject had a nerve conduction study (NCS). The sponsor did not present any additional information concerning this single NCS. No nerve biopsies have been performed during the course of drug development. The sponsor (via Dr. _____) concludes that the presumed vigabatrin associated peripheral neuropathy has the features of a length dependent, large-fiber, sensory polyneuropathy.

b(4)

3.1.3.5 Phase 4 Proposal:

b(4)

3.1.3.6 Proposed Labeling:

b(4)

3.1.4 Agency Review:

3.1.4.1 Case Definition of the Vigabatrin associated PN:

In an attempt to create a case definition, the sponsor consulted with _____ M.D., a specialist in the area of peripheral neuropathy. _____ reviewed "relevant details of those patients" previously identified as pertinent to peripheral neuropathy by the sponsor's consultant neurologist / epileptologist. The presence of a neuropathy was determined by finding in the case report documents of appropriate symptoms (numbness, tingling, dysethesias, or weakness), signs (loss of sensation, weakness, or loss of reflexes), or both that were usually distally predominant. The signs and/or symptoms should be repeatable. _____ determined based on his clinical judgement if the case was consistent with a peripheral neuropathy. He identified 36 potential peripheral neuropathy cases. The neuropathies were then characterized as probably (n=6), possibly (n=11), or unlikely (n=19) to be vigabatrin-associated. Of the possible and probable cases, 11 were from protocols 021, 024, 025 (North American controlled trials in epilepsy and the open-label extensions) with a total of 457 subjects with exposure to vigabatrin. In the controlled portion of those trials there were 0 / 188 subjects in the placebo arm with symptoms / signs of peripheral neuropathy and 4 / 280 (1.4%) in the vigabatrin arms. An additional 7 cases of peripheral neuropathy were identified in the open label portion of these trials. In reviewing the 36 cases presented by _____, I identified 19 subjects with possible (RevClass=1) / probable (RevClass=2) vigabatrin associated peripheral neuropathy, 13 unlikely (RevClass=0) to be vigabatrin associated peripheral neuropathy, and 4 with not enough information (RevClass=4) to make a determination.

b(4)

b(4)

3.1.4.2 Incidence Estimates from Controlled Trials:

I identified 19 / 457 (4.2%) of subjects in the placebo-controlled trials in North America with possible / probable peripheral neuropathy. The source and selection of the cases which were reviewed by _____ is not clear from the provided materials. No information is provided concerning the baseline incidence of similar findings (i.e. peripheral neuropathy) in general population or in a similar population of epilepsy patients not taking vigabatrin.

b(4)

3.1.4.3 Course of the Vigabatrin associated PN:

The sponsor failed to reach a conclusion with respect to the dose or duration of exposure and the risk of developing a peripheral neuropathy. Of the 36 cases identified by _____, 18 subjects were identified with signs / symptoms which developed while on a known dose of vigabatrin (see Figure 1). The minimum dose was 2.0 g/day and the maximum dose was 6.0 g/day with a median dose of 3.0 g/day and a mean of 3.57 g/day (SD 1.08). Analysis of time on vigabatrin until development of symptoms / signs (S/S) is shown in Figure 2. The

b(4)

range was from 20 – 1823 days. The mean time (days) was 488 with a SD of 566. The median time to S/S was 179 days.

3.1.4.4 Characterization of the Vigabatrin associated PN:

Dr. Cornblath, in the absence of NCS and biopsy materials has characterized the vigabatrin associated PN based on symptoms and signs. This is a reasonable approach. He concluded that the PN "has the features of a length-dependent, large-fiber, sensory neuropathy". The potentials recorded in somatosensory evoked potentials (SEPs) represent activity from large-diameter, myelinated fast conducting afferents. Many of the patients in the controlled trials of vigabatrin had SEPs performed. In the upper extremity SEPs, the N9 potential is generated at the level of the brachial plexus usually following stimulation of the median nerve. In the lower extremity SEPs, following stimulation of the tibial nerve, a N8 potential is recorded at the level of the popliteal fossa. A delay, and to a lesser extent reduction of amplitude, of the N8 or N9 potentials could be suggestive of a peripheral neuropathy. Although SEPs are not the ideal test for peripheral neuropathy, the data could be used to identify potential cases of peripheral neuropathy and further clarify the nature of the PN. However, in reviewing the EP data from study C-024, it appears that SEPs were performed only on the upper extremities. This would limit their usefulness in detecting a peripheral neuropathy, since the symptoms would most likely develop in the lower extremities before the upper extremities were affected. In addition, prolonged latencies to Erb's point would be difficult to interpret in light of the potential for median mononeuropathies.

3.1.4.5 Phase 4 Proposal:

b(4)

3.1.4.6 Proposed Labeling:

b(4)

3.2 Human Autopsy Findings:

3.2.1 Background:

The sponsor previously reported that of 42 autopsies performed on subjects that had received vigabatrin, 23 had histologic evaluations. Nineteen of the 23 cases

were reviewed by a consultant and 4 by the medical examiner. Treatment duration for these subjects ranged from 0.6 months to 9.6 years. In 12 of 23 autopsies, the duration of exposure to vigabatrin was less than 12 months. The sponsor concluded "vacuolation in the absence of gliosis was considered to be artifactual". Vacuolization was observed in 4 cases, but utilizing the above criteria was considered artifactual. Three cases of gliosis were reported. Autopsies performed in 11 subjects with epilepsy, but not treated with vigabatrin, revealed 3 reports of vacuolization and 7 reports of gliosis.

3.2.2 Agency Request:

The agency requested that the sponsor submit detailed information about cases of vacuolization or gliosis seen in human autopsy material. Specifically, we are interested in a more detailed description (i.e., extent and location of lesions) about the 4 cases of vacuolization and 3 cases of gliosis seen in vigabatrin treated patients described in your May 29, 1997 amendment, as well as in the 11 untreated patients with epilepsy described. In addition, we are interested in similar information about any additional cases of which you have become aware since submission of your amendment. You argue that vacuolization without gliosis is an artifact; please submit evidence to support this contention.

3.2.3 Sponsor's Response:

In addition to the 23 autopsy cases with histological evaluation previously presented and reviewed, the sponsor reports that an additional vigabatrin-treated autopsy case from a clinical study has been examined since the last submission. Of the 24 cases, 16 were from clinical trials, 5 from compassionate use and 3 from prescribed use. Table 21 from the sponsor submission (see appendix) describes the brain regions examined, number of slides for each tissue block, extent of gliosis and IMV. During pre-clinical development, IMV was observed in specific areas (including anterior and posterior commissure, hippocampus, median forebrain bundle, stria medullaris, cerebellar periventricular area, lateral geniculate body, mamillothalamic tract, corpus callosum, optic tract, optic chiasm, habenular nucleus, pretectal nucleus, reticular formation, columns of fornix, thalamus, and cerebral peduncle) in animals administered vigabatrin. The following areas were examined in the autopsy cases (number of cases examined/total cases):

- cerebellum (20/24)
- thalamus (5/24),
- hypothalamus (7/24)
- brainstem (19/24)
- optic chiasm/nerve/tract (8/24)
- cerebrum (19/24),
- hippocampus (7/24)
- fornix (1/24)

The sponsor again notes that IMV can be observed as post-mortem artifact. In an attempt to distinguish IMV from post-mortem IMV, GFAP staining was used to identify areas of gliosis. The sponsor notes that "In animals from which vigabatrin had been withdrawn, the IMV lesions resolved but left areas of reactive gliosis in some of the areas in which the IMV had been previously observed". The sponsor has defined IMV in the absence of gliosis as postmortem IMV, processing artifact. IMV was reported for 13/24 SABRIL-treated cases and in 7/11 non-SABRIL treated controls. Gliosis was reported in 16/24 SABRIL-treated cases and in 10/11 non-SABRIL-treated cases. The sponsor concluded that the pattern of gliosis was similar for the two groups. The sponsor notes that two of the SABRIL-treated cases had had extensive IMV and gliosis. The sponsor notes that "co-existing clinical conditions" which complicate interpretation of these findings. In one case the patient had liver and respiratory compromise and was on a ventilator prior to his death. In the other case, the patient had West syndrome and hydrocephalus.

3.2.4 Agency Review:

The sponsor has presented no data to support their contention that IMV in the absence of gliosis is post-mortem artifact. In addition, the sponsor has not presented sufficient information about the extent and distribution of the IMV. As noted in my review of November 5, 1997, without validation of the sponsor's definition for artifactual vacuolation and without quantification of the background vacuolation, it is difficult to make any conclusions about the available autopsy data. The ability to draw conclusions is further limited by the small sample size, limited exposure to vigabatrin, and limited evaluation of potentially involved CNS areas.

3.3 MRI Findings:

3.3.1 Agency Request:

MRI Findings:

[Note to Sponsor: Please fill in the blanks contained within this paragraph with the appropriate numbers of patients as described in each sentence.]

Of these patients, ___ had on-treatment MRIs performed at least 12 months after the initiation of treatment, and ___ had on-treatment MRIs done at least 3 years after beginning treatment. An additional ___ patients had an evaluation prior to initiation of treatment and a subsequent evaluation after having been off vigabatrin treatment for periods ranging from ___ to ___ (time period, i.e., days or months). An additional ___ patients had an MRI after initiation of treatment but no pre-treatment evaluation; ___ of these patients had their MRI while still receiving treatment, while ___ patients were evaluated after having discontinued treatment.

In the two controlled clinical trials, 0/181 vigabatrin treated patients and 0/112 placebo treated patients developed any unexplained MRI abnormalities at 4-5 months.

In the uncontrolled experience, there were 3 cases which were consistent with intramyelinic vacuolization.

In 1 case, a 53 year old female treated with vigabatrin (2-4g/day) for approximately 6 weeks developed a well defined 1.2 cm non-enhancing area of T2 prolongation and low T1 signal in the splenium of the corpus callosum, a lesion consistent with intramyelinic vacuolization. The lesion was not present on an MRI obtained ___ months prior to the administration of vigabatrin. An evaluation for demyelinating diseases, including multiple sclerosis, was negative. There was partial resolution of the lesion following discontinuation of vigabatrin. The relationship of these events to SABRIL cannot be determined.

3.3.2 Sponsor's Response:

MRI Findings in Humans: Of patients evaluated pre/post for IMV, 253 had on treatment MRIs performed at least 12 months after the initiation of treatment, and 69 had on-treatment MRIs done at least 3 years after beginning treatment. An additional 40 patients had an MRI evaluation prior to initiation of treatment and a subsequent MRI after having been off SABRIL treatment for periods ranging from 12 to 158 months. An additional 25 patients had an MRI after initiation of treatment but no pre-treatment IMV evaluation; 18 of these patients had an MRI while still receiving treatment, while 9 had an MRI after having discontinued treatment (37,38).

In the three North American controlled clinical trials, 0/280 SABRIL treated patients and 0/188 placebo treated patients developed any unexplained MRI abnormalities at 4 to 5 months (39).

In the uncontrolled experience, there were 3 cases (2 from open-label studies in the US, 1 from a spontaneous UK report) with MRI findings showing white matter changes (40,41,42).

As outlined below, in none of the three cases of MRI white matter changes are the findings strongly suggestive of IMV.

The first case (patient 009-003; (40)) involved a 58-year old woman who had been receiving SABRIL for 11-years in an open-label extension of a study. The patient was discontinued because of emerging neurological symptoms. A follow-up MRI indicated white matter changes and cerebral/cerebellar atrophy, more than expected for the age of the patient. A pretreatment MRI had not been undertaken. There were no significant differences between the follow-up MRI film, MRIs taken 3 months and 3.5 years after SABRIL was discontinued and earlier films taken while the patient was receiving SABRIL. Furthermore, there was no demyelination in the fornix, thalamus, or hypothalamus. Since none of the MRI changes were suggestive of IMV or thought to be related to the evolving clinical picture, it can be concluded that the MRI changes were unrelated to SABRIL.

Another case (patient 96-00101 or number 96002420; (41)) involved a 56-year old female in the UK who reported decline in reading ability following approximately 6-years on SABRIL. Visual field testing demonstrated severe constriction OU and a follow-up MRI revealed multiple foci of increased signal in the posterior periventricular white matter and generalized cerebral atrophy. There was also a small rounded lesion in the medial left temporal lobe probably representing a small cyst. SABRIL treatment was subsequently discontinued with no change in the visual field deficit. An eye exam including fundoscopic exam, VEP, ERG and fluorescein angiography were normal. A pretreatment MRI or visual field test were not undertaken. The MRI findings as reviewed by expert consultants were deemed as being most suggestive of demyelinating lesions of multiple sclerosis (although the patient did not have a clinical history suggestive of multiple sclerosis) or vascular disease. Furthermore, the lack of improvement after discontinuation of SABRIL argues against a causal relationship to SABRIL but, because of the lack of information, a drug effect can not be ruled out.

The last case (patient 1194-0010; (42)) involved a 53 year old female enrolled in an open-label study in the US with medical history significant for left temporal lobectomy for medically-intractable seizures, treated with add-on vigabatrin (2-4 g/day) for approximately 6 weeks and reporting increased seizures. An MRI undertaken to evaluate the increased seizures revealed a well defined and sharply demarcated 1.2 cm non-enhancing lesion within the splenium of the corpus callosum, a region not associated with intramyelinic vacuolization in animals. Additionally, the appearance of the lesion was not similar to the multiple soft-edged IMV lesions observed in the dog. The lesion exhibited increased signal relative to normal white matter on proton density and T2 weighted images and decreased signal on T1-weighted images. No baseline MRI had been taken. Although MRIs obtained 14- and 17-months prior to the administration of SABRIL did not indicate the clear presence of this lesion in the corpus callosum, the region did exhibit vague and questionable hyperintensity. The MRI taken 17-months prior to the initiation of SABRIL therapy also showed equivocal hyperintensity in the midbrain and pons. VEP, median SEP and posterior tibial SEP taken at the time of discontinuation of SABRIL were normal. An evaluation for demyelinating diseases, including multiple sclerosis, was negative. Although the lesion was unchanged or minimally smaller, the lesion did exhibit a considerably lower signal on proton density and T2-weighted images about 3-months following discontinuation of SABRIL. A subsequent MRI taken approximately 8-months following the discontinuation of SABRIL indicated that the signal was almost imperceptible on T2-weighted images and only slightly more visible on proton density images. Although lesions of this type are known to occur as a result of trauma or demyelinating disease, the relationship of these events to SABRIL cannot be ruled out because of the interval appearance.

Each of the cases described above has features, which distinguish it from the characteristics of IMV observed in animals based on the distribution of the lesion,

the number of lesions, their appearance or resolution and therefore is not a clear finding of IMV.

3.3.3 Agency Review:

In the first paragraph, the sponsor has filled in the blanks per the agency request.

In describing the three cases from the uncontrolled experience, the sponsor suggest that these cases are not IMV. Statements such as "in none of the three cases of MRI white matter changes are the findings strongly suggestive of IMV", and "Each of the cases described above has features, which distinguish it from the characteristics of IMV observed in animals based on the distribution of the lesion, the number of lesions, their appearance or resolution and therefore is not a clear finding of IMV" should be amended or deleted.

In the first case the sponsor states "Since none of the MRI changes were suggestive of IMV or thought to be related to the evolving clinical picture, it can be concluded that the MRI changes were unrelated to SABRIL". This conclusion should be amended or deleted.

In the second case the sponsor states "the lack of improvement after discontinuation of SABRIL argues against a causal relationship to SABRIL". This conclusion should be amended or deleted.

In the third case, the sponsor states "Although lesions of this type are known to occur as a result of trauma or demyelinating disease, the relationship of these events to SABRIL cannot be ruled out because of the interval appearance". This statement is misleading, if the sponsor wishes to discuss the differential diagnosis for the case, other etiologies, including IMV, should be included.

Although none of these cases is clearly diagnostic of IMV, each has features consistent with IMV.

3.4 Evoked Potential Findings:

3.4.1 Agency Request:

Evoked Potential Findings:

[Note to Sponsor: Please fill in the blanks contained within this paragraph with the appropriate numbers of patients as described in each sentence.]

Of these patients, ___ had on-treatment EPs performed at least 12 months after the initiation of treatment, and ___ had on-treatment EPs done at least 3 years after beginning treatment. An additional ___ patients had an evaluation prior to initiation of treatment and a subsequent evaluation after having been off vigabatrin

treatment for periods ranging from ___ to ___ (time period, e.g., days or months). An additional ___ patients had an EP after initiation of treatment but no pre-treatment evaluation; ___ of these patients had their EP while still receiving treatment, while ___ patients were evaluated after having discontinued treatment. In the two controlled clinical trials, there were no significant changes in VEPs and SEPs seen in either vigabatrin treated or placebo treated patients

[Note to Sponsor: Please confirm and document that this statement is true for both VEPs and SEPs. Further please submit all EP tracings for patients in Study 024.]

In uncontrolled experience, there were 10 patients who had VEP changes compared to baseline that were unexplained by other pathologies. Of these 10, 6 were being treated with vigabatrin at the time of the abnormality (duration of treatment ranged from ___ to ___), and 4 had been discontinued from treatment (length of time since last exposure ranged from ___ to ___). In these 10 patients, MRIs done at approximately the same time as the post-treatment VEPs did not demonstrate findings consistent with vacuolization. In the uncontrolled experience, there were 11 patients who had SEP changes compared to baseline that were unexplained by other pathologies. Of these 11, 5 were being treated with vigabatrin at the time of the abnormality (duration of treatment ranged from ___ to ___), and 6 had been discontinued from treatment (length of time since last exposure ranged from ___ to ___). In these 11 patients, MRIs done at approximately the same time as the post-treatment SEPs did not demonstrate findings consistent with vacuolization.

3.4.2 Sponsor's Response:

EP Findings in Humans: Of patients evaluated pre/post for IMV, 308 had on treatment EPs performed at least 12 months after the initiation of treatment, and 85 had on-treatment EPs done at least 3 years after beginning treatment. Additionally, 44 patients had an EP prior to initiation of treatment and a subsequent EP after having been off SABRIL treatment for periods ranging from 12 to 158 months. Additionally, 54 patients had an EP after initiation of treatment but no pre-treatment evaluation; all of these patients had an EP while still receiving treatment, while 10 had an EP after having discontinued treatment (44-47).

In the three North American controlled clinical trials, there were 23 of 280 SABRIL patients and 23 of 188 placebo patients with significant changes in VEPs and/or SEPs. In uncontrolled long-term follow-up of 106 clinical trial patients previously identified as having EP or MRI abnormalities, or visual and/or ocular complaints, 9 patients had significant VEP changes compared to baseline which were unexplainable by other pathologies. Of these 9, 6 were being treated with SABRIL at the time of the abnormality (duration of treatment ranged from 57 to 174 months), and 3 had discontinued treatment (length of time since last exposure ranged from 35 to 58 months). In these 9 patients, MRIs done at approximately the same time as the VEPs did not demonstrate findings consistent with IMV. In the

same uncontrolled long-term follow-up of 106 clinical trials patients, 10 patients had significant SEP changes compared to baseline which were unexplainable by other pathologies. Of these 10, 6 were being treated with SABRIL at the time of the abnormality (duration of treatment ranged from 54 to 169 months), and 4 had discontinued treatment (length of time since last exposure ranged from 20 to 54 months). In these 10 patients, MRIs done at approximately the same time as the SEPs did not demonstrate findings consistent with IMV (43,48).

3.4.3 Agency Review:

The sponsor has completed this section per the agency request.

4. Conclusions:

4.1 Peripheral Neuropathy:

The sponsor has concluded that a vigabatrin-associated PN exists. They have not provided adequate information about the background prevalence of PN in this population. If this information is available the sponsor should present the data. If this information is not available, it could be obtained from a phase 4 study of peripheral neuropathy associated with vigabatrin. _____

_____ Until additional data is available, the possibility of a vigabatrin-associated PN should be described in labeling.

b(4)

4.2 Human Autopsy Findings:

Without validation of the sponsor's definition for artifactual vacuolation and without quantification of the background vacuolation, it is difficult to make any conclusions about the available autopsy data. The ability to draw conclusions is further limited by the small sample size, limited exposure to vigabatrin, and limited evaluation of potentially involved CNS areas.

4.3 MRI Findings:

The sponsor has provided the information requested by the agency. Amendments or deletions to this section will have to be made as discussed above.

4.4 Evoked Potential Findings:

The sponsor has provided the information requested by the agency.

5. Recommendation:

The autopsy, MRI, and EP findings should be described in labeling. The possibility of a vigabatrin associated peripheral

neuropathy should be described in labeling. The sponsor should make a commitment to perform a study to characterize this PN, including the background incidence. These recommendations are based on this limited safety review. Additional safety reviews are being prepared by Drs. Oliva and Boehm. Final recommendations, including the timing of the PN study, will depend on the results of their review.

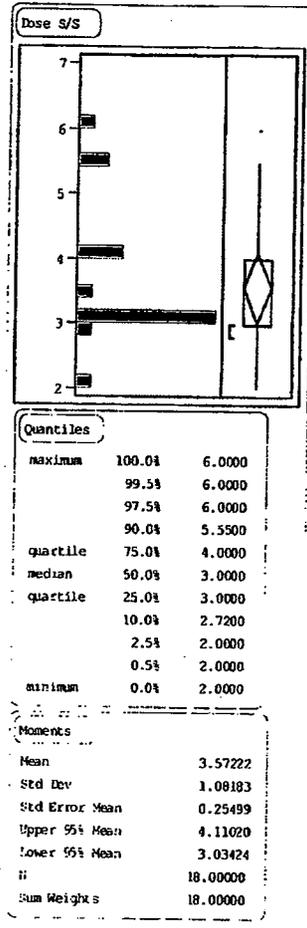
James H. Sherry, M.D., Ph.D.
Medical Reviewer

cc:
HFD-120
HFD-120/Leber/Katz

Deputy Director's note

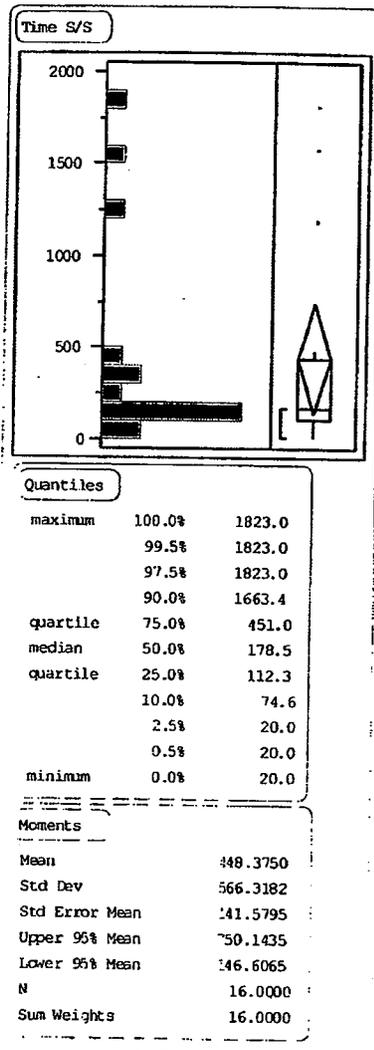
Dr. Sherry has left the Division and is unavailable to sign his review. This review is, however, his final review and, as such, is part of the official file.
R. Katz 9/10/98

Figure 1



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Figure 2



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Table 1

Table 1 Total Neuropathy Score

TNS	0	1	2	3	4
Sensory Symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows or functionally disabling
Motor Symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Autonomic Symptoms	None	1 present	2 present	3 present	4 or 5 present
Pin Sensibility	Normal	Reduced in Fingers/Toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration Sensibility	Normal	Reduced in Fingers/Toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon Reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent/ others reduced	All reflexes absent
Vibration Sensation (QST Vibration)	Normal to 125% ULN	126 to 150% ULN	151 to 200% ULN	201 to 300% ULN	>300% ULN
Sural Amplitude	Normal/ Reduced < 5% LLN	76 to 95% of LL Normal	51 to 75% of LL Normal	26 to 50% of LL Normal	0 to 25% of LL Normal
Peroneal Amplitude	Normal/ Reduced < 5% LLN	76 to 95% of LL Normal	51 to 75% of LL Normal	26 to 50% of LL Normal	0 to 25% of LL Normal

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**Medical Officer's Consultation Review of NDA 20-427
Ophthalmology Consult**

NDA #20-427

Submission: 7/29/98

Consult

Consult received: 8/24/98

Review completed: 8/27/98

Proposed trade name:

Sabril

Generic name:

vigabatrin tablets

Sponsor:

Hoechst Marion Roussel, Inc.

Mail Station H4-M2110

10236 Marion Park Drive

P.O. Box 9627

Kansas City, MO 64134-0627

(816) 966-6790

Pharmacologic Category:

Irreversible inhibitor of gamma-aminobutyric acid
transaminase enzyme

Proposed Indication(s):

Add-on therapy for the treatment of complex partial
seizures with or without secondary generalization in
adults

Background:

During the development and foreign postmarketing use of an anti-epilepsy drug (Sabril/vigabatrin), the sponsor has identified a number of individuals (239) with eye related events including visual field defects, retinal abnormalities, optic atrophy/neuritis/vasculitis that developed during therapy with the drug. Most of the events (n= 192) were visual field defects. Few subjects had baseline exams to allow pre-and on drug comparisons. Most of the cases were from spontaneous reporting and relatively few of these reports contained perimetry data (27) characterizing the findings. The sponsor did perform perimetry studies on volunteers enrolled in extension trials in Finland and Japan. The sponsor forwarded the positive findings and the perimetry data from spontaneous reports to a consultant for review. The consultant determined that a notable percentage of the perimetry reports demonstrated VFDs which were not explained and therefore attributed to drug. The consultant states that most cases exhibit a pattern characterized as bilateral concentric reduction in sensitivity which is more marked nasally than temporally. He commented that this was a rare finding. He felt that the lesion leading to the finding was most likely retinal.

NDA 20-427 Sabril (vigabatrin tablets)

Requested:

We are asking for a review of the individual VFD reports and the sponsor's consultant's report with particular attention to the methodology used and the conclusions. Is there a pattern in the reports and if so is this a unique finding? (Is this finding seen in the background? In epilepsy patients? With other drugs?) Is the lesion likely retinal? (this drug has resulted in vacuolization in the brain in more than 1 animal species) Could the other reported eye events be related?

****Note**** The data within this submission which was recently provided to our Division could potentially effect the type of action for this application and therefore your comments/recommendations are very important to our review. References 1 & 3 contain all ophthalmologic abnormalities and the consultant's report. The sponsor's rationale for this labeling update is included on pages 6-7. A second volume of the submission which includes the individual Medwatch forms is available if needed. Thank you very much in advance for your assistance with this urgent matter. The medical officers on this project are Dr. Oliva (neurophthalmologist) at (4-5518) and Dr. Boehm (safety reviewer) at 4-5565. In addition, if you have any further questions please contact Melina Malandrucchio, at (301) 594-5526.

Reviewed:

1. Published Case Reports
2. Table of Ophthalmologic Abnormalities
3. Table of Visual Field Defects
4. John M. Wild Report (Sponsor's consultant)
5. UK PEM Study Report on Visual Field Defects dated June 1997
6. Risk of Unique Field Defects, Analysis of Data Originating from 6 Long-term Trials dated July 23, 1998
7. Proposed Ophthalmologic Labeling

1. **Published Case Reports**
2. **Table of Ophthalmologic Abnormalities**
3. **Table of Visual Field Defects**
4. **John M. Wild Report (Sponsor's consultant)**

Methodology

The 73 cases comprised 29 spontaneous reports and 44 cases from the 3 open label extension trials. Three of the cases had been previously described by Eke et al 1997 (BMJ 1997; 314: 180-181). In 39 of the 73 cases, the field had been examined with kinetic perimetry using either the Goldmann or Topcon bowl perimeters. In 19 cases, the field had been examined with static threshold automated perimetry (15 with the Humphrey Field Analyzer and 3 with the Octopus automated perimeter). Six of the 73 cases had been examined both with kinetic perimetry (Goldmann or Topcon bowl perimeters) and automated threshold static perimetry (Humphrey Field Analyzer). Six cases had been examined using suprathreshold perimetry and the remaining three cases by automated kinetic perimetry.

The evaluation of the visual field for each case was made in conjunction with the corresponding available medical, ophthalmological and neurological history contained within the Suspect Adverse Reaction Report (CIOMS Form) compiled by the manufacturer's Global Drug Surveillance Department. An entirely normal field or a field defined as 'normal' for the purposes of the study was graded as 0. A visual field defect considered to have a known cause (e.g., glaucoma) was graded as 4. The type and severity of the field loss for which no other explanation could be found was classified using an empirical, semi-quantitative procedure which permitted a description of the severity of the defect on a three-point ordinal grading scale (1, 2, 3 - mild medium and severe) together with a description of the type and location of the defect. Fields deemed to be unreliable, uninterpretable or inconclusive were designated as 5.

The grading scale for severity was based upon a semi-quantitative description of the field rather than in terms of any diagnostic or functional criteria. It attempted to provide some degree of continuum of severity between kinetic and static threshold perimetry. The classification equated the kinetic horizontal approach to the island of vision (i.e., position) with the static vertical approach (i.e., p value depth) based upon the assumption that an 14e stimulus equated to a sensitivity of 20dB with a size III static stimulus. The classification took into account the varying levels of slope of the kinetic field and also the impact of static-kinetic dissociation. Evaluation of the kinetic field was based upon the full extent of the available isopters and referenced to that of the 14e stimulus. The normal limits for the reduction in the extent of the isopters with increase in age were based upon subjective clinical judgement. Evaluation of the static threshold evaluation was based upon the shape probability analysis of the central field out to approximately 30° eccentricity. The description of the type of field loss was undertaken using the terminology appropriate to kinetic and static perimetry. The location of the defect was specified in terms of the principal region(s) accounting for the most profound feature of the field loss.

Reviewer's Comments: *Acceptable, except as noted below.*

Methodology (continued)

In cases where a sequence of fields were present for a given patient, the most recent of the field was evaluated. In cases where static suprathreshold and Goldmann/Topcon kinetic perimetry were available for a given patient, the kinetic field was used for the evaluation. In cases where both kinetic and static threshold perimetry was available for the given patient, the kinetic field was used for the evaluation. However, such cases provided an opportunity to compare the evaluation of severity between the two techniques.

Reviewer's Comments: *In most cases, the static field would have been performed using the more standardized test and less subject to bias from the perimetrist.*

The criteria for the classification of severity were used as a basis for categorization; however, the final decision as to the appropriate Severity Level was also based upon empirical clinical judgement based upon two years experience of evaluating vigabatrin associated visual fields.

It must be stressed that the field plots were interpreted in isolation from the patients and, with the exception of the reliability criteria available from automated static perimetry, in the absence of information concerning compliance during the visual field examination. It must also be stressed that the interpretation of the field for any given patient was undertaken in association with varying levels, and quality, of medical, neurological and ophthalmological histories.

Kinetic perimetry classification

Entirely 'Normal' or 'normal' for the purposes of the study'. (0)

↳ $>70^\circ$ temporally or $>45^\circ$ superiority or $>45^\circ$ nasally or $>50^\circ$ inferiorly

Other, more likely, explanation for visual field abnormality. (4)

Unreliable fields/uninterpretable/inconclusive. (5)

Generalized Depression (GD):

a reduced sensitivity everywhere within the field (although not necessarily to an equal extent in all locations) - i.e. all isopters move inward from all sides

Mild (1) ↳ 50° - 70° temporally or 35° - 45° superiority or 35° - 45° nasally or 45° - 50° inferiorly

Moderate (2) ↳ 30° - 50° temporally or 20° - 35° superiority or 20° - 35° nasally or 25° - 45° inferiorly

Severe (3) ↳ $<30^\circ$ temporally or $<20^\circ$ superiority or $<20^\circ$ nasally or $<25^\circ$ inferiorly

- Localized Depression (LD):** A reduced sensitivity in a localized region i.e., the isopters move inward within the localized region.
- Scotoma (S):** a region of lower sensitivity than the immediately surrounding area.
- Generalized Contraction (GC):** a general extent of the peripheral field absolute to all stimuli i.e., all the isopters crowd together.
- Localized Contraction (LC):** an absolute reduction of sensitivity in a localized region i.e., localized isopters crowd together.

Reviewer's Comments:

Acceptable, although unreliable fields are not defined and it is unclear how the judgement would be made that there is a more likely explanation.

Threshold Static perimetry classification

- Entirely normal or 'normal' for the purposes of the study (0)
- Other, more likely, explanation for visual field abnormality (4)
- Unreliable fields/uninterpretable (5)

Generalized reduction in sensitivity (GRS) a uniform reduction in sensitivity across the field identified by height probability analysis.

Localized reduction in sensitivity (LRS) (LARS indicates a localized absolute reduction in sensitivity): a reduced sensitivity in a localized region. The Severity classification for a Localized reduction in sensitivity was based upon the number and position of the stimulus locations exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis.

Mild (1) One cluster of 3-8 non-edge adjacent stimulus locations within 30° eccentricity exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis.

Normal sensitivity out to 30° eccentricity temporally; normal sensitivity superiorly, nasally and inferiorly out to 21° eccentricity with one cluster of 4-9 adjacent edge stimulus locations between 21°-27° eccentricity superiorly, nasally or inferiorly exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis.

Moderate (2) One cluster of 9-14 non-edge adjacent stimulus locations within 30° eccentricity exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis. or

Two clusters of 4-6 adjacent non-edge stimulus locations within 30° eccentricity exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis. or

Normal sensitivity out to 30° eccentricity temporally, normal sensitivity superiorly, nasally and inferiorly out to 15° eccentricity with a cluster of 10-16 adjacent edge

stimulus locations between 21°-27° eccentricity superiorly, nasally or inferiorly exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis. or

Normal sensitivity out to 30° eccentricity temporally; normal sensitivity superiorly, nasally and inferiorly out to 15° eccentricity with two clusters of 4-7 edge stimulus locations between 21°-27° eccentricity superiorly, nasally or inferiorly exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis.

Severe (3)

One cluster of 15 or more adjacent non-edge stimulus locations within 30° eccentricity exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis. or

Two or more clusters of 7 or more adjacent non-edge stimulus locations within 30° eccentricity exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis. or

One cluster of 17 or more adjacent edge locations exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis and encroaching within 30° eccentricity temporally or within 15° eccentricity superiorly or nasally or inferiorly. or

Normal sensitivity out to 21° eccentricity temporally, normal sensitivity superiorly, nasally and inferiorly out to 15° eccentricity with two or more clusters of 8 or more edge stimulus locations between 15°-27° eccentricity superiorly, nasally or inferiorly exhibiting abnormality at either $p < 0.01$ or $p < 0.005$, or a combination of both, on shape probability analysis.

Reviewer's Comments: *The above criteria are not as strict as the kinetic criteria.*

Suprathreshold Static perimetry classification.

Threshold-related strategy and age-related suprathreshold strategy: The depth of any defect is unknown with these techniques. The results were therefore classified as '5'.

Three-zone suprathreshold strategy: The depth of any defect is quantified in terms of relative or absolute loss with this technique. However, the depth of the relative loss is unknown. The results were therefore classified as '5'.

Reviewer's Comments: *Not acceptable. There has been a considerable amount of work in this area defining normal and abnormal fields. These fields should be reviewable.*

Conclusions:

The measurement of the visual field is dependent upon the subjective response and cooperation of the patient. Visual field data can frequently exhibit large variability within- and between-examinations and can be markedly influenced by patient-related variables such as learning and fatigue, and by extraneous factors under the influence of the perimetrist. It can also be extremely difficult to obtain a reliable field from patients with epilepsy.

Reviewer's Comments: *Agree.*

The results indicate that the visual field defect associated with vigabatrin is a peripheral reduction in sensitivity which is most profound in the nasal field. The presence of a binasal visual field defect is a relatively unique finding. True binasal field loss is a very rare occurrence. The visual field loss is present in both eyes of any given patient and, given the measurement limitations, is relatively symmetrical between the two eyes of the given patient. The pattern is consistent between patients; is present with both kinetic and threshold static perimetry; is present regardless of the type of automated static perimeter; and, in the patient cohort described here, has been reported from 10 different countries.

Reviewer's Comments: *Agree. A binasal visual field abnormality is a relatively unusual finding.*

The specific location of the lesion cannot be identified from the perimetric results alone. However, from the limited amount of available data, it would seem that the visual acuity, intraocular pressure, colour vision, VEPs and orbital and visual tract MRIs are normal. The visual field loss would seem to occur in the presence of a reduced Arden Index of the electrooculogram, and with possible reduction in the oscillatory potentials, and/or possible reduction in the photopic b-wave amplitude, and increase in b-wave latency of the ERG. Vigabatrin has been shown to reduce the Arden index, and increase the ERG b-wave latency within ten days from baseline in a double blind crossover study of placebo, carbamazepine and vigabatrin in normal volunteers; however, none of the changes took the parameters outside the age matched normal limits and the visual field remained unaffected. Patients who manifest a characteristic visual field defect but who have discontinued vigabatrin, appear to show persistent abnormalities of the visual field even though the gross electrophysiological findings return to normal. The visual field defects are now also known to be associated with a reduction in the amplitude of the multi-focal ERG (VERIS). Such findings suggest that the location of the lesion is most likely retinal. The fundal appearance would seem to range from the normal to one involving optic nerve head pallor and/or peripheral pigment epithelial disturbance.

Reviewer Comments: *Conventional teaching would suggest that a matched bilateral nasal constriction is more likely to be due to a lesion at the optic nerve level or above (brain) assuming a single site of injury. Based on the different types of reported ocular findings, it is possible that the drug product is causing injury to multiple sites.*

5. UK PEM Study Report on Visual Field Defects dated June 1997

Methodology

All reports of visual field defect in 62 PEM studies on the DSRU database were identified. The original green forms and/or the computer record were examined for each case. Those identified as possibly representing a visual field defect of unknown cause or for whom insufficient information had been reported were followed up by writing to the doctor who completed the green form questionnaire, for additional information. Patients who had left the original practice were traced via the FHSA and additional information was requested from the patient's current GP.

All the cases of VFD were re-assessed by a physician using the following criteria for classification of these cases originally coded as VFD:

- 1) The doctor has used this term and there is no information which contradicts this.
- 2) There has been an objective demonstration of a VFD defect = blind in that area, not hazy or disturbed or cloudy.

In addition, the green forms were examined for all cases for whom visual disturbance and eye NOS (eye unspecified; that is events for which there was no term in the coding dictionary) were recorded as events in the three anti-epileptic drugs lamotrigine, vigabatrin and gabapentin.

Reviewer's Comments: *The methodology is flawed. VFD can be hazy, cloudy or disturbed vision.*

Discussion

There were five cases of VFD identified with vigabatrin. Excluding case 2 since there were no objective signs of VFD and it was reversible, there are four cases of VFD in the PEM cohort of vigabatrin. No similar cases have yet been found in the 61 other drugs studied by PEM. Other patients who developed VFD during treatment with vigabatrin, have been identified (personal communication). The VFD was not reported at the time the green form questionnaire was returned since it occurred more than six months after the start of treatment with vigabatrin, that is after the end of the PEM study monitoring period. This suggests that there is a possibility that there *could* be other similar cases in the PEM cohort or vigabatrin.

Conclusion

As there is the possibility that other cases of VFD could have occurred after the end of the monitoring period for the PEM study of vigabatrin, it is again recommended that this PEM cohort is investigated further by sending a follow up questionnaire for all patients.

Reviewer's Comments: *This study probably represents an underestimation of the visual field defects.*

Risk of Unique Field Defects, Analysis of Data Originating from 6 Long-term Trials dated July 23, 1998

Since the data in this post-hoc analysis consisted of a single set of perimetry results for each of 136 volunteers that originated from 6 different studies, (as opposed to a sufficient sample of randomized subjects), inferences must be made with caution. When the complete set of perimetries are validated and additional data from other sources become available, both the results and conclusions of this analysis will be updated and refined. Based on these limitations:

The unique visual field defect pattern consisting of a bilateral concentric peripheral constriction with a variable degree of temporal field sparing was confirmed by patients from these 6 long-term clinical trials.

The estimated prevalence of unique VFD is 28% (38/134, 95% CI: 20%-36%) based on the Finnish and Japanese data combined.

Based on the Finnish and Japanese data combined, the prevalence of unique VFD in males and females was 37% and 21% respectively. This meaningful and consistent finding combined with the relatively large odds ratio for gender suggest that males were at greater risk for unique VFD than females.

Reviewer's Comments: *This study also probably represents an underestimation of the visual field defects since potential false negatives have not yet been reviewed. The significance of the higher rate in males is unknown.*

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**Responses to Questions:
Comments on the Consultants Report?**

Reviewer's Comments: *The methodology is basically acceptable, however, a few of the assumptions made are likely to decrease the frequency in which fields are listed as abnormal. The report therefore potentially expresses an under-representation of the events. The conclusion that the finding is most likely retinal is not well supported.*

Is there a pattern in the reports and if so is this a unique finding? (Is this finding seen in the background? In epilepsy patients? With other drugs?)

Reviewer's Comments: *The findings are unusual. It would be unlikely that many of the visual field findings occurred in the background, but good data on visual fields in patients with epilepsy is not available. The findings are not known to occur with other drug products.*

Is the lesion likely retinal? (this drug has resulted in vacuolization in the brain in more than 1 animal species)

Reviewer's Comments: *While the lesions could be retinal, conventional teaching would suggest that a matched bilateral nasal constriction is more likely to be due to a lesion at the optic nerve level or above (brain) assuming a single site of injury. Based on the different types of reported ocular findings, it is possible that the drug product is causing injury to multiple sites including retina.*

Could the other reported eye events be related?

Reviewer's Comments: *It is more likely that multiple events are occurring and at different locations.*

Recommendations:

It is recommended that:

1. Copies of the visual fields be submitted to the agency for review.
2. Additional Phase 3 or Phase 4 studies be conducted with examinations of the visual field at baseline and every 6 months for 4 to 6 years.
3. If the product is approved, Warnings should be added to the product that there is a significant risk of permanent visual field loss and that visual fields should be monitored in all patients.
4. The proposed labeling should be modified as suggested above in this review.


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cc: HFD-120
HFD-105
HFD-550/Consult File
HFD-550/MO/Chambers