

OCT 28 1997

Review and Evaluation of Clinical Data

Safety Review

Application Information

NDA 20-⁴²⁷~~247~~, Amendment

Hoechst Marion Roussel

Drug Name

Generic: Vigabatrin

Proposed Trade Name: Sabril

Drug Characteristics

Pharmacological action: GABA transaminase inhibitor

Proposed Indications: Adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

Dosage forms: 500mg oral tablets

Proposed Use: Sabril starting dose should be 1g given in 2 divided doses with titration occurring in 500mg increments at weekly intervals depending on response. The optimal dose is 3g/day based on response and tolerance. Doses up to 6g/day are associated with an increased incidence of side effects, but may provide additional benefit in some patients. If a decision is made to discontinue Sabril, the dose should be gradually reduced over a 2-4 week period.

Safety Reviewer: Gerard Boehm, M.D., M.P.H.

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1 Introduction

HMR is requesting approval to market vigabatrin as adjunctive therapy in the treatment of partial seizures in adults with epilepsy. Dr. Cynthia McCormick first evaluated the safety experience of VGB with her review of NDA 20-427 in 1995. At that time, the agency found the VGB NDA "not approvable" predominantly for problems identified with the non US safety database. This review focuses on the amendment to the NDA dated 5/31/97. In this amendment, the sponsor addresses the agency's criticisms of the presentation of safety data in NDA 20-247.

Dr. James Sherry is also involved in the current review of VGB. He will be assessing efficacy data related to US clinical study 024, and will be reviewing neurological safety data related to the intramyelinic edema issue.

1.1 Materials Used in the Review

To become familiar with the recent history of vigabatrin (VGB), I read background information that included the NDA review, the supervisory reviews, the not approvable letter, consultations, and minutes from meetings between the sponsor and the agency.

For the safety review of the amendment, I utilized the resources provided by the sponsor. The sponsor submitted an optical NDA (ONDA) amendment which is an electronic document consisting of the scanned images of the sponsor's response to the not approvable letter. This response is contained in 507 volumes. My review of non US safety data focused on Sb-V2-P1 through Si-V507-P314. This material included summaries, patient narratives, CRF tabulations, line listings, and CRF's from patients who died or discontinued due to adverse events from completed non US clinical studies. The sponsor submitted additional CRF's as requested. The sponsor provided an Integrated Review (IR) consisting of a computerized database of the US and Non US studies that were completed at the time of the 120 day safety update. It allows the reviewer to perform analyses and generate reports. The amendment also contains information about serious adverse events occurring in patients from clinical studies that were ongoing at the time of the 120 day safety update (through 3/14/95) and from the 120 day safety update through 12/31/95. The information from these studies has not been integrated with the data in the VGB safety database. In addition, the sponsor submitted a non integrated safety update consisting of 7 paper volumes. It includes summaries and patient narratives for serious adverse events identified between January 1, 1996, and March 15, 1997.

1.2 Development

The administrative history of the development of this drug is summarized in an attachment.

1.3 Pre-clinical studies

The following information is summarized from the NDA review. This material was not resubmitted as part of the amendment.

Vigabatrin irreversibly inhibits GABA-transaminase in vitro. In vivo, single doses of VGB given to animals caused a dose dependent inhibition of GABA-transaminase and a dose dependent increase in brain GABA levels with a peak effect 4-6 hours after dosing. With chronic administration of vigabatrin, brain GABA levels increase gradually to steady state. Vigabatrin causes suppression of seizures in complex partial animal models and generalized tonic clonic animal models. Vigabatrin had both proconvulsant and anticonvulsant effects on generalized absence animal models.

In many of the seizure models evaluated, there was no obvious correlation between maximal increases in brain total GABA levels and seizure protection. The ability of vigabatrin to block seizure activity is thought to be linked to specific brain areas and may require redistribution of GABA. The mechanism of action of vigabatrin in controlling seizures is not actually known.

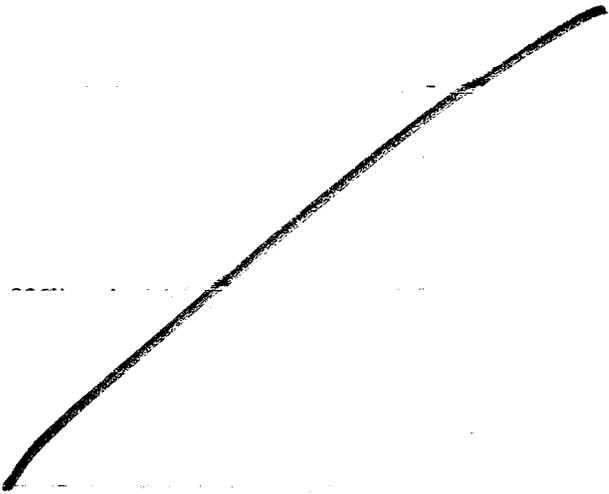
Animal toxicology studies identified two areas of potential concern with this drug. Intramyelinic edema (IME), which manifests as microvacuolization in the brain, has been identified in mice, rats, dogs, and to a lesser extent, monkeys exposed to VGB. It was most notable in the cerebellum, reticular formation, and optic tracts in rats. In dogs, IME was observed in the thalamus, hypothalamus, columns of fornix, and optic tract. In the rat, IME was observed after 6 months of treatment with VGB at a dose of 100mg/kg/day and after 12 months at a dose of 30mg/kg/day. The abnormality regressed 3 months after discontinuation of VGB. In dogs, IME developed in 4 weeks at doses of 300mg/kg/day and in 1 year at 50mg/kg/day. IME also regressed after discontinuation of VGB in the dog. IME was not consistently demonstrated in the monkey and this finding may be related to decreased absorption in this species.

After prolonged administration of VGB, retinal degeneration was observed in albino rats, but not in any pigmented species.

1.4 Human PK

The reader is referred to the NDA review for a more complete description of human pharmacokinetics. Briefly, VGB's T_{max} after a single 1g dose was approximately 1 hour with a mean terminal elimination half life of about 7 hours. VGB is not protein bound and is not appreciably metabolized. Approximately 82% of VGB is excreted unchanged in the urine. C_{max} decreases by 33% and T_{max} increases 2-fold in the fed state. AUC remains unchanged.

1.5 Review of Proposed Labeling



2 **Clinical Data Sources in the Amendment**

The NDA was filed on 5/2/1994. The 120 day safety update cutoff date was 3/14/94. Selected information on serious adverse events up until 12/31/95 was submitted for review with the NDA amendment. A non integrated safety update with information about serious adverse events from 1/1/96 through 3/15/97 was submitted on July 31, 1997.

2.1 *US Clinical Studies*

The amendment does not present any new information about the patients from US studies. The agency felt that this cohort was adequately described in the NDA. The sponsor does make references to data from the US cohort in the amendment. This was done to present a complete review for specific topics (e.g. deaths) or to compare findings between cohorts. The sponsor also referenced data from US studies to create various event tables. The US clinical study group contains 537 patients who were exposed to VGB. This review will provide tables, as attachments, that were part of the NDA review. These tables summarized data from US studies.

2.2 *Non US Clinical Studies*

One of the reasons the reviewers of NDA 20-427 found the original safety database inadequate was that Case Report Forms (CRF's) were not available for audit or review for

a large part of the submitted, non US data. In response to this criticism, sponsor's representatives returned to Europe to collect and review all available non US CRF's.

In the amendment, the sponsor created 3 cohorts for the non US safety data (Primary, Secondary and Non CRF supported). Decisions about the placement of data into the different cohorts were based on data capture criteria, the availability of CRF's from a study, and subjective assessments of the quality of the study data. The sponsor placed CRF's in the Primary cohort if investigators captured data designated by a prospectively written protocol, contemporaneously onto a CRF. The primary data cohort only contains the data for patients from the studies where all the CRF's were located. In some instances, the sponsor was not able to locate all the CRF's from an individual study. When this occurred, the sponsor placed the located CRF's into the Secondary data group. The sponsor included the available data for patients without CRF's in the non-CRF cohort. The primary and secondary data cohorts are mutually exclusive in that they do not contain patients from the same study. The secondary and non CRF supported cohorts do contain patients from the same study. If the sponsor identified problems such as discrepancies with dates for consecutively entered patients in a study, they included the CRF's from these studies in the Secondary data group. The sponsor did this even when the CRF's met all three data capture criteria for inclusion in the primary group. The sponsor created the non-CRF cohort for those studies or individuals without CRF's.

The primary cohort, which included 1189 individuals exposed to VGB, should have the highest quality non US data since all included studies met the above criteria for data capture and had no identified inconsistencies. The secondary cohort is of lesser quality. It contains CRF's from studies that used protocols that were not prospectively written, where data was captured retrospectively, or the sponsor identified serious inconsistencies. It also contains the located CRF's from the studies where not all CRF's were found. Therefore, this cohort is not reliable for calculating frequencies of events. Review of this cohort could be helpful in identifying previously unrecognized adverse events (AE's) or causes of death. The non CRF group contains data collected inconsistently from a variety of sources and generally lacks information on patient exposure to VGB. It has roughly the same value as spontaneous report data. The numbers of patients exposed to VGB in each of the data cohorts are summarized in sponsor's table B-8 (see attachments).

In the supervisory review of the NDA dated March 15, 1995, the sponsor was specifically criticized for providing incomplete dose and duration of exposure information for the non US patients. In addition, the sponsor did not adequately characterize the serious adverse events or reasons for dropout for this group. In response to these criticisms, the sponsor reviewed the located CRF's and extracted information about reasons for termination from study, adverse events, deaths, and discontinuations. The sponsor also created visit windows and dose summaries to better characterize participants' exposure to VGB.

After collecting and reviewing the recovered CRF's and extracting the data, the sponsor created the databases to hold this information. The sponsor did not reconstruct the databases for 17 of the non US studies because they felt those databases contained all of the data from the CRF's. An independent contractor constructed new databases for the

remaining CRF's from 82 studies. The contractor entered data extracted from CRF's by the sponsor's clinical group. The sponsor used these databases to create the summaries, reports, tabulations and listings presented in the amendment.

In the original NDA submission, the reviewer discovered that a portion of the data presented for consideration in the safety database was from a document called the Individual Case Summary (ICS). This document was used to capture data extracted from CRF's or from other information available from the investigator (NDA review p.13). It was not always completed contemporaneously. Dr. McCormick questioned the accuracy of the data. It was unclear if the individuals completing these summaries were blinded to treatment. In the amendment, the sponsor commented that the ICS (Sb-V2-P51) was not the primary data source for this submission. The sponsor did admit that they used ICS's for information they could not find in the CRF (Sb-V2-P77). The ICS might have been used for creating the dose summary (Sb-V2-P81), or death summary tables (Sc-V3-P27). The sponsor did not state how extensively they relied on the ICS's for data. Using the ONDA, I searched the amendment for "ICS". This search turned up only a few references to the ICS being used as a data source. ICS's were used for the creation of visit windows for protocol 097-238 (Si-V358-P114). Four patients from protocol 097-241 had only ICS data. Information about a patient from protocol 097-306 submitted for ophthalmologic review was on an ICS. While reviewing information from various protocols using the protocol summary, additional references to ICS's were discovered. The sponsor stated that for the primary non US protocols 097-332 and 097-332.5 the "CRF is an ICS; however, documentation exists that the ICS was the original data collection form" (Sg-V217-P85-86). For secondary study 097-307 there were 14 patients with only ICS's (Sg-V217-P72).

2.3 *Ongoing Clinical Studies*

Throughout the amendment, the sponsor refers to data about serious adverse events from studies that were ongoing at the time of safety updates. When the 120 day safety update material was presented, the information from clinical studies completed at that time was integrated into the safety database. The data from these studies is accessible through the IR, and is used to calculate the frequencies of events. There were clinical studies that were ongoing at the time of the 120 day safety update. Information about serious adverse events from these studies was summarized and presented but the data is not integrated into the safety database. The same holds true for the safety update from 3/15/95-12/31/95 presented with the amendment and for the safety update covering 1/1/96-3/15/96 which was submitted separately on 7/31/97.

2.4 *Secondary Source Data*

The sponsor's approach to classifying data as primary or secondary was reviewed above. There were 968 individuals exposed to VGB in studies included in the secondary data cohort. Because there is a lack of exposure data for the non CRF cohort, the sponsor is only able to give the number of individuals enrolled in these studies (925). In addition to the secondary data from clinical trials and the non CRF supported data, the sponsor refers

to data from another source, compassionate use, in the amendment. Data from compassionate use comes from a group of patients who had non US pre-marketing exposure to VGB. Adverse event data for these patients was collected passively. There is no reliable estimate of the total number exposed in this group (NDA review p16).

2.5 *Post-Marketing Experience*

The events identified from post-marketing use come from spontaneous reports received by the sponsor through the Global Adverse Events Reporting System. The sponsor estimates global exposure to VGB at 254,597 patient years in [redacted] patients, each exposed for 2 years through December 31, 1995. This estimate is based upon total annual sales of tablets and sachets using [redacted] as the average dose. Assuming an average treatment duration of 6 months, the total number of patients exposed would be [redacted] (Sa-V1-P45).

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2.6 *Other Studies*

The sponsor also presents data from a Prescription Event Monitoring study from the UK. The PEM study is an observational cohort study concerned with post-marketing surveillance of new drugs. The objective of the study is to identify rare adverse conditions. Prescriptions filled by pharmacies or by the GP's are forwarded to a central location. Over a period of months, the study authors collect the prescriptions written for selected drugs. The authors send the prescribing physicians questionnaires about treatment issues and adverse events experienced by their patients. Incidence densities are reported for observed events. In this study, 10,178 patients who took VGB were followed for approximately 6 months.

3 *Methods of Safety Review*

3.1 *Deaths*

Using the ONDA and the Integrated Review (IR), I reviewed deaths among the different data cohorts. I focused on the US clinical study population (unchanged from the NDA) and the newly developed non US primary data cohort. Using the dates of use of VGB in the IR, I estimated exposure and calculated overall mortality rates for the US data group, the non US primary data group and the combined US and non US primary data group. There were no deaths in the placebo exposed group to allow calculation of a relative risk of mortality between VGB exposed and placebo exposed groups. The CRF's, CRF tabulations, death narratives and sponsor's summaries were cross checked for consistency. Data from the secondary data group, non CRF data group, ongoing clinical trials, and spontaneous reports were reviewed. The intent of this review was to identify the common causes of death in these groups as well as the causes of death not observed in the primary data group. The sponsor included a Prescription Event Monitoring (PEM) report from the United Kingdom with the amendment. I reviewed the deaths in this report and compared them to the deaths in the VGB clinical trials. I reviewed the sponsor's analysis of sudden and unexpected deaths. I provided short summaries of patient deaths for the unusual causes of death and for those causes identified as a concern in the NDA review.

3.2 Discontinuations

I reviewed the sponsor's summary of discontinuations from non US clinical trials in the amendment and referred to the NDA review for information about the US clinical trials. Selected CRF's were reviewed for discontinuations due to AE's, "other" and "unknown" reasons. The all cause dropout risk was plotted for one US controlled epilepsy trial and one non US primary controlled epilepsy trial.

3.3 Serious AE's

The sponsor provided a section in the amendment that summarized serious adverse events in US and non US studies. The presentation of the serious adverse events consisted of separate reviews of discontinuations due to AE's, hospitalizations, overdose, pregnancy, status epilepticus, cancer, disability, life-threatening events, and events requiring medical intervention. These presentations were reviewed and summarized.

3.4 Laboratory

The sponsor summarized laboratory findings from the non US data in the amendment. They extracted outliers and potentially clinically significant changes based upon criteria agreed upon by the sponsor and the NDA medical reviewer. I reviewed the data regarding outliers and compared the results to the findings in the NDA review. Data from controlled study C-021 was compared to the results from the US controlled studies.

3.5 Data Quality

I assessed the quality of the non US data throughout the review process. The deaths reported in the sponsor presentations were cross checked with summary death tables, listings, CRF tabulations, IR searches and pathology reports. I compared the discontinuations due to adverse events in the amendment to the integrated review, CRF tabulations and line listings. Case report forms from the primary non US controlled epilepsy studies were reviewed to determine the method of AE ascertainment. To evaluate the reasonableness of AE coding (MDWHO), investigator verbatim terms from listings, the IR, and in some cases from CRF's, were compared to the coded preferred terms. CRF's were reviewed to assess their ability to capture data on hospitalizations. The numbers of and reasons for hospitalizations presented in the amendment were checked against line listings, selected available CRF's and the integrated review (for the clinical studies). Lab and vital sign data from available CRF's were compared to the values in listings, CRF tabulations and the IR.

4 Review Findings

4.1 Study type and design/patient enumeration

4.1.1 *US clinical studies*

The only change the sponsor made regarding the US database was to group the US clinical pharmacology studies and US studies in patients with diagnoses other than epilepsy with the US epilepsy studies data in the IR. In the NDA, the US non epilepsy studies were included with the non US data (for undetermined reasons). The data from these non epilepsy studies were available and were reviewed in the original NDA review. Briefly, there were 537 individuals exposed to VGB in US clinical studies. The US clinical development program included 6 clinical pharmacology studies, 2 placebo controlled studies in epilepsy patients, 4 uncontrolled studies in epilepsy patients and 3 studies in patients with conditions other than epilepsy.

4.1.2 *Primary Non US Clinical Studies*

The sponsor indicates that of the 1290 subjects enrolled in primary non US studies, 1189 were exposed to VGB. The non US primary data cohort exposures occurred in 14 clinical pharmacology studies, 9 controlled trials in epilepsy patients, 17 uncontrolled trials in epilepsy patients and 25 studies in patients with conditions other than epilepsy. Descriptions of the primary non US studies are included in sponsor's table B-1 (see attachments).

The primary non US studies were conducted in the United Kingdom, West Germany, France, Australia, Finland, Italy, Canada, Netherlands, Switzerland, and Ireland. These studies were begun between 1979 and 1993.

Three of the controlled primary non US epilepsy trials were "parallel" design. Study 309 was initially open labeled and then randomized responders to VGB or placebo. Study WUK04 randomized subjects to VGB or placebo for 2 weeks and then all patients received VGB for 4 months. This was followed by long term treatment with VGB in responders. Study C-021 was a double blinded randomized placebo controlled trial which titrated doses upward from 1g per day to 4g per day over the course of the study (36 week exposure). The rest of the primary epilepsy controlled trials were crossover designs, only one of which (097-WAUS01) used a washout period.

Table B-8 summarizes exposures in clinical studies completed by the 120 day safety update (see attachments).

4.2 *Demographics*

4.2.1 *US studies*

A demographic profile for US studies was not presented in the amendment. In the original NDA submission, the demographics of the entire study population were presented together. The sponsor did not provide a separate analysis of the US study population. The sponsor did not provide an analysis of demographics for US studies in the amendment. Children were not included in US studies.

4.2.2 *Non US studies*

Because investigators did not consistently collect information on race, the sponsor only presents demographic information on gender, age and weight. For primary non US

studies, there was roughly an equivalent percentage of males and females enrolled (with the exception of non epilepsy clinical pharmacology studies:128 males, 18 females). The average age of the primary non US population was 30.85 years (range 0-97). There were 13 studies that enrolled children. Three of these studies were specifically designed for a pediatric population, 2 were pediatric designs that also enrolled adults and 7 were designed for adults and also included children. There was a conflict between data sources as to the number of children participating. According to table B-27, there were 199 children (16 years old or less) enrolled in primary non US studies. A search of the IR identified 217 subjects from primary non US studies who were 16 or younger at the start of a protocol.

The sponsor summarizes the demographic information for patients enrolled in primary studies in table B-27(see attachments).

4.3 Extent of exposure for Primary Studies

4.3.1 Duration

4.3.1.1 *US Clinical Studies*

In the NDA, the sponsor presented the duration of exposure data for the different clinical study groups. The sponsor included a separate analysis of US studies (controlled and uncontrolled). Since the clinical pharmacology patients were not included with the US data, the duration of exposure cannot be extracted for this group from the sponsor's original presentation. Of the 221 patients with known exposure data from the controlled US studies, investigators exposed none for more than 6 months (197 exposed ≥ 3 months). In open label US studies, investigators exposed 307 (75%;307/414) patients to VGB for ≥ 6 months. In these same studies, investigators exposed 157 (38%;157/414) subjects for ≥ 1 year.

(see attachment from NDA review, p.20)

4.3.1.2 *Non US Primary Clinical Studies*

Of the 1189 patients exposed to VGB in primary non US studies, investigators treated 28.8% (372/1290) with VGB for at least 6 months, and 10%(129/1290) for at least 1 year. In controlled epilepsy studies, 22.5% (89/396) patients were exposed to VGB for at least 6 months and 5.1% (20/396) for at least 1 year. In uncontrolled epilepsy studies 49.7%(229/461) were exposed for at least 6 months and 16.5% (76/461) for at least 1 year. The sponsor summarized the duration of exposure for primary studies in table B-19(see attachments).

The sponsor has provided adequate data on 286 subjects (from US and primary non US studies) exposed to VGB for at least one year.

4.3.2 Dose

The sponsor lists 3g per day as the effective dose of VGB in proposed labeling, but suggests that doses up to 6g per day may provide additional benefit.

4.3.2.1 *US Clinical Studies*

In the controlled US studies, 60.4% (134/222) of patients were exposed to a maximum dose of VGB between 2.5 and 3.5 g/day. Almost 20% of patients (44/222) were exposed to a dose greater than or equal to 4.5g/day. In the open label US studies, 62.1% (257/414) of patients were exposed to a dose of VGB between 2.5 and 3.5 g/d. Sixty one patients were treated with a dose greater than or equal to 4.5 g/day in open label US studies (see attachment from NDA review, p.21).

4.3.2.2 *Non US Primary Clinical Studies*

In primary non US studies, 49.8% (643/1290) of patients were exposed to a maximum dose of VGB between 2.5 and 4.5 g/day. No patients in controlled epilepsy trials and 5.4% (25/461) in uncontrolled epilepsy trials received a maximum dose of VGB >4.5g/day. Two and a half percent (32/1290) of all primary non US patients received a maximum dose greater than or equal to 5.5g/day. The sponsor summarizes exposure to maximum dose of VGB in table B-23(see attachments).

The sponsor's combined dose and duration analysis did not list separately the US studies in the NDA review. The sponsor did not provide a dose and duration analysis for primary non US studies in the amendment.

4.4 *Review of the AE surveillance, coding of AE's, approach to safety*

There is no discussion of the method used by the investigators to identify AE's. Examination of the available CRF's (deaths, discontinuations, and selected CRF's from primary studies) showed that these documents contained sheets to record AE's at each patient visit. Several different formats were used for the AE data sheets. For most of the primary studies, the CRF's used open ended questions to elicit reports of AE's from subjects. AE's were considered treatment emergent events that occurred for the first time, or worsened during the study period regardless of investigator assessment of causality. Most CRF's were also designed to capture information from the investigator about their assessment of causality, severity, and any action taken for an AE. The sponsor attempted to improve the sensitivity in identifying AE's for the non US subjects. In the amendment, when the non US CRF's were reviewed, the sponsor looked for and extracted AE's that were identified but not captured on the AE sheet. These AE's were extracted from comment fields, concomitant medication pages, physical and neurological exams, laboratory pages, and letters (Sb-V2-P84). The sponsor did not state if the associates carrying out this process were blinded to treatment. These extracted events do not have investigator comments about causality, severity, or outcomes. The sponsor used the MDWHO dictionary to code adverse events presented in the NDA and the amendment. The most recent safety update (1/1/96-3/15/97) uses the MMDWHO dictionary. The sponsor did not present analyses of dose dependency relationships for AE's.

The agency criticized the sponsor's presentation of hospitalizations in the non US population in the NDA. Specifically, the reviewers were concerned that hospitalizations in this group were not consistently identified. To evaluate the ability of the CRF to capture hospitalization data, I examined the CRF's from 25 of the 28 primary epilepsy studies. All included a place to record the severity of an AE (which presumably would include information on hospitalizations). Seventeen of the CRF's asked specifically for information on hospitalizations. The CRF's from the primary epilepsy studies appear to be constructed to capture hospitalization information

The sponsor identified lab outliers using criteria that were agreed upon during the review process.

As part of the quality review, selected CRF's were requested from the sponsor to assess availability and to review patients who withdrew for unknown or other reasons.

4.5 Audit Findings

Investigator verbatim terms were identified in the CRF's from patients who died and from a sample that discontinued due to AE's. These terms were compared to the verbatim terms in line listings and IR searches and were congruent. The narrative summaries from patients who died or discontinued due to AE's accurately described the AE's that were identified in the CRF's.

Generally, the MDWHO coding of the investigator verbatim terms was reasonable. One specific exception was the preferred term thinking abnormal which was listed under the psychiatric SOC. The thinking abnormal preferred term summarized events such as decreased calculation skills, decreased cognitive function, intellectual slowing, and slow mentation. These verbatim terms seem to reflect alterations in cognition and not necessarily psychiatric events. These events would be more appropriately listed under the CNS SOC.

A review of the death data generally demonstrated congruency between sources (narratives, listings, tabulations, IR, summaries, pathology reports and autopsies). A discrepancy was found between the NDA and the amendment regarding hepatic AE deaths. Comparison of hepatic AE deaths from spontaneous reports in the amendment to the NDA review (p.97) turned up two patients who are not found in the amendment. Patient 09223130 was listed as a death in the NDA review and is not found under that number in the amendment. A 10 year old without an ID# is listed as a death in the NDA review and I could not locate a corresponding patient in the amendment.

The lab values in the CRF tabulations and included in the IR were congruent with the lab values recorded in the reviewed CRF's. Through review of recovered CRF's, the sponsor increased the number of adverse events and hospitalizations identified in the amendment compared to the NDA.

The process of extracting information related to discontinuation, dose summary, and visits was generally reasonable. Bias could have been introduced if the associates extracting event data were not blinded to treatment.

Overall review of the data quality demonstrated that CRF's were available for review for the non US primary cohort. The IR reports, sponsor's line listings, narratives and tabulations accurately summarized the data from the CRF's.

4.6 Deaths

Although the amendment focuses on non US data, the sponsor provides a comprehensive presentation of deaths from all data sources. Through December 31, 1995, there were 60 deaths observed in patients treated with vigabatrin in the clinical development program. An additional sixty-three deaths occurred in Non-US compassionate users (n=17) or in post-marketing use (spontaneous reporting, n=46). In the clinical studies group, 49 deaths occurred in patients included in the Non-US secondary studies, Non-US non-CRF studies, or ongoing studies. There have been 11 deaths in patients included in the primary data set. These deaths occurred within 30 days of the last exposure to vigabatrin. I calculated crude mortality rates for those studies included in the primary data set. I estimated patient years exposure using the difference between "First dose of VGB and Last dose of VGB" variables under the patient demographics panel of the Integrated Review. The crude mortality rate for the US NDA population was 1.11 per 100 patient years exposure to vigabatrin (7 deaths per 630 pt years). The crude mortality rate for the NON US primary data group was 0.89 per 100 patient year exposure to vigabatrin (4 deaths per 449 pt years.). The combined crude mortality rate for US and Non US primary data sources was 1.01 per 100 patient years exposure to vigabatrin (11 deaths per 1079 pt years). I could not calculate a relative risk since there were no deaths in patients exposed only to placebo. The crude mortality rate observed in these VGB trials is comparable to the crude mortality rates observed for other recently reviewed anti epilepsy drugs.

Sponsor table C-8 (Sc-V3-Pp25,26) summarizes the reported causes for all deaths in individuals treated with vigabatrin. For some patients, the investigator reported more than one contributing cause of death.

Table C-3. All Causes of Death in Vigabatrin Treated Patients through 12/31/95

| Causes | Clinical Studies | | | | | | Non-US Compassionate (n=17) N(99) | Spontaneous (n=46) N(99) | All (n=23) N(99) |
|-------------------------|----------------------|-------------------------------------|--|---------------------------------------|-------------------------------------|-----------------------------|--|--------------------------------|------------------------|
| | US (n=7) N(99) | Non-US Primary (n=9) N(99) | US + Non-US Primary (n=17) N(99) | Non-US Secondary (n=9) N(99) | Non-US Non-CRF (n=9) N(99) | Ongoing* (n=22) N(99) | | | |
| Seizure (all) | 3(42.9) | 0(0.0) | 3(27.3) | 0(0.0) | 2(23.1) | 14(43.8) | 7(41.2) | 23(50.0) | 34(49.3) |
| Trauma | 1(14.3) | 2(50.0) | 3(27.3) | 0(0.0) | 1(12.5) | 5(15.6) | 0(0.0) | 0(0.0) | 9(7.3) |
| Cardiovascular events | 2(28.6) | 0(0.0) | 2(18.2) | 3(33.3) | 1(12.5) | 6(18.8) | 1(5.9) | 2(4.3) | 16(12.2) |
| Suicide | 1(14.3) | 0(0.0) | 1(9.1) | 0(0.0) | 3(37.5) | 1(3.1) | 3(17.6) | 3(6.5) | 11(8.3) |
| Cancer | 0(0.0) | 0(0.0) | 0(0.0) | 2(22.2) | 0(0.0) | 2(6.3) | 4(23.5) | 2(4.3) | 10(8.1) |
| Respiratory events | 0(0.0) | 1(25.0) | 1(9.1) | 1(11.1) | 0(0.0) | 1(3.1) | 1(5.9) | 6(13.0) | 10(8.1) |
| Cerebrovascular events | 0(0.0) | 1(25.0) | 1(9.1) | 0(0.0) | 0(0.0) | 4(12.5) | 1(5.9) | 5(10.5) | 11(8.3) |
| Drowning | 1(14.3) | 0(0.0) | 1(9.1) | 1(11.1) | 0(0.0) | 6(18.8) | 1(5.9) | 0(0.0) | 9(7.3) |
| Hepatic events | 0(0.0) | 0(0.0) | 0(0.0) | 1(11.1) | 0(0.0) | 1(3.1) | 2(11.8) | 5(10.5) | 9(7.3) |
| Infectious Disease | 0(0.0) | 2(50.0) | 2(18.2) | 1(11.1) | 0(0.0) | 4(12.5) | 4(23.5) | 4(8.7) | 16(12.2) |
| Asphyxiation | 1(14.3) | 0(0.0) | 1(9.1) | 0(0.0) | 0(0.0) | 2(6.3) | 2(11.8) | 1(2.2) | 6(4.5) |
| Aspiration | 0(0.0) | 0(0.0) | 0(0.0) | 1(11.1) | 0(0.0) | 2(6.3) | 0(0.0) | 5(10.5) | 8(6.5) |
| Sudden death† | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 5(10.5) | 5(4.1) |
| Renal events | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 3(6.5) | 3(2.4) |
| Gastrointestinal events | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 1(3.1) | 0(0.0) | 2(4.3) | 3(2.4) |
| Vascular events | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 2(4.3) | 2(1.5) |
| Coma | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 1(5.9) | 1(2.2) | 2(1.5) |

Table C-4. All Causes of Death in Vigabatrin Treated Patients through 12/31/95

| Causes | Clinical Studies | | | | | | Non-US Compassionate (n=17) N(99) | Spontaneous (n=46) N(99) | All (n=23) N(99) |
|---------------------|----------------------|-------------------------------------|--|---------------------------------------|-------------------------------------|-----------------------------|--|--------------------------------|------------------------|
| | US (n=7) N(99) | Non-US Primary (n=9) N(99) | US + Non-US Primary (n=17) N(99) | Non-US Secondary (n=9) N(99) | Non-US Non-CRF (n=9) N(99) | Ongoing* (n=22) N(99) | | | |
| Sudden Infant Death | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 1(3.1) | 0(0.0) | 0(0.0) | 1(0.8) |
| Unknown | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 1(12.5) | 0(0.0) | 0(0.0) | 6(10.5) | 6(4.5) |

* Ongoing includes deaths in clinical studies that were ongoing at the time of the 120-Day Safety Update (3/15/94) (n=8) and deaths reported in ongoing clinical studies from (3/16/94-12/31/95) (n=23).

† Sudden death in this table represents the investigator description of the cause of death rather than SUDEP classification by the Sponsor's consultants.

Supporting Data

| | |
|---|--------------|
| Appendix C2, Listing 4 All Causes of Death in Clinical Studies through 12/31/95 | Page |
| Appendix C2, Listing 5 All Causes of Death in Non-US Compassionate Use through 12/31/95 | Pg-V227-P268 |
| Appendix C2, Listing 6 All Causes of Death from Spontaneous Reports through 12/31/95 | Pg-V227-P271 |
| | Pg-V227-P274 |

Deaths from the primary data cohorts (US, Non US primary group)
 These deaths occurred in patients from clinical studies that were completed at the time of the 120 day safety update. Deaths in patients from studies that were ongoing at the time of the 120 day safety update were presented separately by the sponsor.

4.6.1 US Clinical Studies

Investigators attributed 3 deaths in the US group either completely or partially to seizure (006-003, 012-009, 070-010). Patient (071-009) drowned in the family pond and the investigator thought it likely that the patient had a seizure prior to drowning. Patient 012-007 died without witness at home and an autopsy revealed high grade lesions of several

coronary arteries with possible thrombus in RCA. There was one death due to trauma (012-013) and one suicide (067-010).

4.6.2 *Non US Primary Clinical Studies*

Two patients in this group died of infectious processes (22407, 125701-P3). One patient (125701-P22) died following a fall. The investigator could not determine if this was due to a seizure, or due to the increasing ataxia and drowsiness the patient experienced prior to death. One participant (015-007) enrolled in a PK study died in a motorcycle accident.

4.6.3 *Deaths in patients in clinical trials that were ongoing during the 120 day safety update*

As discussed above, the information from ongoing clinical trials at the time of the 120 day safety update was not integrated into the safety database by the sponsor. There were 9 deaths that occurred in ongoing clinical trials during that period. The CRF's for these patients are included in the amendment. Investigators attributed five of these deaths to seizure activity. Patients 202-15M-02, and 202-180-05 drowned in the bathtub without witness, presumably following seizures. Patient 058-001 died without witness, presumably due to seizure activity. Patient 2401 died from a head injury sustained following a seizure. Patient 3141 died without witness and the presumed cause of death was seizure with fall from bed, facial impact, and suffocation. Patient 4181 died following relapse of an oligodendroglioma that was first diagnosed prior to beginning VGB therapy. Patients 0004 and 0008 died as a result of trauma. Patient 202-06Y-06 a 34 YO female who took VGB, dose titrated to 3.0g per day, for 8.7 months died from hepatic failure/fulminant hepatic necrosis. The adverse event report noted that she had been also taking phenytoin and phenobarbital prior to this event and her physicians could not rule out VGB as the etiology of her hepatic failure.

4.6.4 *Deaths in patients from the secondary data cohorts*

Of the nine deaths in this group, 5 were attributed to seizures. Three patients (30330006, 30330048, 32330925) died without witness after presumably suffering seizures. Patient 41931404 died of aspiration pneumonia following a seizure. Patient 25310 died after developing status epilepticus following knee surgery. Two patients died of cancer (21202-metastatic lung cancer, 30330028-metastatic colon cancer). Patient 30430415 died of coronary artery disease and patient 25816 died of congestive heart failure.

4.6.5 *Deaths in patients from the Non CRF cohorts*

There were 8 deaths reported in this group. Three patients (124701-P5, 20204, and 36631405) committed suicide. One patient 53300024 died as a result of seizure. The other deaths were due to coronary artery disease, trauma, progression of underlying neurological disease, and one unknown.

4.6.6

*Deaths in patients enrolled in clinical trials between 3/16/94 and 12/31/95
(non-integrated update on serious AE's submitted with the amendment)*

This data was submitted separately as part of the data on serious adverse events from ongoing clinical trials after the period of the 120 day safety update. The following table lists the 23 deaths included with these data. The first ten are from US studies. The sponsor provided supporting documentation with the most recent safety update.

| Protocol, patient number, age, sex | Total daily dose of VGB, treatment duration | Event description |
|---|---|--|
| VGCS0005, VGSD-0005-5023, 39YO/female | 4.75G, 241 days | Death (unknown cause) |
| VGPR0098, VGST-1193-0014, 34YO/male | 4G, 273 days | Intracranial hemorrhage |
| VGPR0098, VGST-1204-0003, 34YO/male | 3.5G, 46 days | Epileptiform seizure disorder |
| VGPR0098, VGST-1219-0006, 35YO/male | 1.5G, 64 days | Drowning, seizures |
| VGPR0098, VGST-1225-0013, 23YO/male | 3G, 76 days | Cerebral hypoxia |
| VGPR0098, VGST-1228-0001, 69YO/female | .75G | Lung cancer |
| VGPR0098, VGST-1230-0006, 25YO/male | 6G, 393 days | Status epilepticus |
| VGPR0098, VGST-1241-0012, 27YO/female | 3G, 109 days | Aspiration |
| VGPR0098, VGST-1247-0004, 32YO/male | 3G, 131 days | Possible grand mal seizure |
| VGPR0101, VGST-1349-0007, 43YO/female | Blinded, 34 days | Pulmonary edema, seizure disorder |
| VGPR0032, VGST-1656-0001, 23YO/female | 2G, 163 days | Acute heart failure |
| VGPR0034, VGST-JA09-0002, 21YO/male | Blinded, 319 days | Pneumonia, Status epilepticus |
| VGPR0034, VGST-1680-0004, 18YO/male | Blinded, 121 days | Drowning, epileptic seizure |
| VGPR0034, VGST-1698-0002, 37YO/male | Blinded, 325 days | Suicide |
| VGPR0034, VGST-1740-0002, 39YO/female | Blinded, 19 days | Drowning |
| 097-335, VGST-UK07-0049, 61YO/male | 3G, 1209 days | Drowning |
| 71754-3-E-01, VGZ-9400-6443, 33 months/male | 200mg/kg, 129 days | Death |
| 71754-3-E-01, VGZ-9400-6443, 28 months/male | 1.21G, 28 days | Cardiac arrest, pneumonia, septic shock |
| 71754-3-E-01, VGZ-9400-6444, 17 months/female | .88G, 358 days | Bronchopneumonia |
| 71754-3-E-01, VGZ-9600-0188, 5 months/male | 64mg/kg, 7 days | CMV infection, interstitial pneumonia, kidney infection |
| 71754-3-W-007, VGST-AU24-0634, 64YO/male | Blinded, 2 days | Valvular cardiac failure |
| 71754-3-W-007, VGST-DED1-0103 | Blinded, 60 days | Cardiac arrest, cerebral hemorrhage |
| 71754-3-W-007, VGST-NE03-0849, 69YO/female | Blinded, 222 days | Coronary infarction, epilepsy worsened, bleeding gastric ulcer, elevated transaminases |

Data for this table is from appendix C-9: Serious new adverse events since 120-day update

4.6.7 *Review of deaths from Non Integrated Safety Review (1/1/96-3/15/97)*

The sponsor provided a non integrated summary of serious adverse events from January 1, 1996, through March 15, 1997. During this period of time, the sponsor collected information on an additional 20 deaths. Seventeen deaths occurred in clinical studies and three deaths were spontaneously reported. The causes of deaths from these clinical studies were similar to those reported in the NDA and the amendment. The most frequently reported cause of death in this clinical study group was seizure related. In the spontaneous report group, there was one death due to cerebral edema, one due to a cerebrovascular event and one due to hepatic necrosis. A 3 year old taking phenobarbitone and VGB (for 9 months, maximum dose 100mg/kg) developed hepatic necrosis and died. Liver histology was consistent with a toxic etiology. The literature report states that other causes of hepatic injury (infectious, toxic) had been excluded but did not include any test results.

In this update, the sponsor separates deaths from Japanese clinical studies from the rest of the clinical study population. This was not the approach in the previous updates. There were three newly identified deaths from Japanese studies. Two of these patients drowned and one patient committed suicide.

The sponsor included a death identified in the UKPEM study. A 53 YO male died due to an astrocytoma.

4.6.8 *Deaths in patients in Non US Compassionate use group or from spontaneous reporting sources through 12/31/95*

For the most part, the causes of death seen in these two groups are similar to the causes observed in patients enrolled in clinical studies. The spontaneous reporting group did contain 5 sudden deaths, 3 deaths from renal events, 2 deaths from GI events, and 2 deaths from vascular events, which are unique to this group.

Patient 31730707, a 39 YO M treated with VGB, 3.5g per day, for 6 years died of hepatic failure. He presented as an outpatient with complaint of fever and a physician treated him with clarithromycin, aspirin, and noraminopyridine. A short time later (<30 days) he developed hepatic failure and died. In addition to the above mentioned medications, this patient was taking phenytoin and primidone.

Selected summaries of deaths from spontaneous reports (from death narratives, GADERS reports)

Patient VGZ-9108-594 was a 27 year old male with renal failure and pancreatitis, who developed abdominal pain and vomiting 3 weeks after starting VGB. He also took carbamazepine, and sodium valproate at the time of the event. He died suddenly and physicians suspected a pulmonary embolism (no autopsy performed).

Patient VGZ-9500-1102, an 18YO M treated with VGB, 5g per day, for approximately 4 years died of hepatic failure. A liver biopsy revealed massive acute hepatitis. Serologies were non diagnostic and the patient was taking no other medications.

Patient VGZ-9400-3033, a 10 YO F treated with VGB, 1.5g per day, for 1yr died of hepatic failure. She initially presented with a "febrile enteritis" and subsequently developed

abnormalities of transaminases and liver synthetic function. Autopsy revealed subacute hepatic dystrophy, extensive parenchymal necrosis, intrahepatic cholestasis. Viral serologies were negative. She was also taking carbamazepine and clonazepam at the time of the event.

Patient VGZ-9400-1440, a 34 YO F treated with VGB, 2g per day, for 26 months died of hepatic failure. A physician hospitalized her for elevated AST, ALT, and GGT. She also took phenytoin and carbamazepine at the time of the event. Her physician discontinued the carbamazepine and there appeared to be some improvement. She required hospitalization a short time later for worsening LFT's. At this time the physician discontinued the VGB and reduced the phenytoin dose. Her liver function deteriorated and a liver biopsy revealed subacute hepatitis. The physician attributed the hepatitis to carbamazepine and phenytoin. She developed hepatorenal syndrome and died prior to receiving a liver transplant.

Patient VGZ-9300-3075, a 37 YO M treated with VGB, 1g per day, for 4 days, died of hepatic failure. He developed status epilepticus which resolved with paraldehyde and diazepam. The next morning he was hypotensive, vomited blood, and developed altered mental status and a left sided hemiparesis. He arrested, required resuscitation, and subsequently developed liver failure, renal failure (acute tubular necrosis) and died. In addition to VGB, he took phenytoin and carbamazepine for seizures.

Patient VGZ-9203-130, a 10 YO M treated with VGB, 1g per day, for 17 months died of hepatic failure. On the day of admission he had a generalized TC seizure and prolonged unconsciousness. Admission labs included abnormal LFT's indicating hepatic injury. Liver biopsy immediately following death demonstrated massive hepatic necrosis. A physician proposed viral hepatitis as the diagnosis (no serologies included to confirm this diagnosis). In addition to VGB, he took carbamazepine to control seizures.

Patient VGZ-9301-4792 was a 25 year old male admitted following status epilepticus. He subsequently developed an elevated temperature and then DIC, rhabdomyolysis, and hemothorax. He died within 2 days of hospitalization.

4.6.9 *Deaths reported in the PEM study*

The sponsor provided a copy of a PEM (Prescription Event Monitoring) study report with the amendment. This report describes a cohort of 10,178 patients in the UK that took vigabatrin. The authors observed this group for approximately six months. Estimating the patient time exposure to vigabatrin (using the estimated time of observation of six months) I calculated a crude mortality rate of 2.7 per 100 patient years (139/5089 pt years exposure) for this cohort. This is approximately 3 times greater than the crude mortality calculated for the US and non US primary data. The differences in mortality rates could be explained by different study populations (clinical trial, presumably healthier volunteers vs. an observational cohort study), or potential bias due to selective reporting (response rate 68% for PEM). The causes of mortality in the PEM group were similar to those described above for vigabatrin treated individuals. The vigabatrin PEM study found the following most common causes of death: seizure related (37/139); cardiovascular (15/139); and a group containing pneumonia, bronchopneumonia, and infection chest (15/139). The authors did not ascertain the cause of death for 6 individuals in this group. There were no deaths due to hepatic failure in this cohort.

4.6.10 Sponsor's Analysis of Sudden Death

The sponsor's consultant used criteria proposed by Leestma to identify deaths that could be categorized as "Sudden unexplained deaths in epilepsy." Looking at Primary studies (which have data regarding exposure) the sponsor's consultant classified 3 deaths as SUDEP for 1065 patient years actual drug exposure. This yields a SUDEP rate of 2.8 per 1000 patient years. A cross check performed using the integrated review to determine exposure resulted in a comparable rate (3 deaths in 836 pt years or 3.6 per 1000). This SUDEP rate is similar to the rate observed with other recently approved anti epilepsy drugs (Gabapentin 2.5 per 1000 pt years, Lamotrigine 5.8 per 1000 pt years).

4.7 Overall Profile of Dropouts

The review of the NDA for vigabatrin was critical of the sponsor's presentation of dropouts. The US safety database summary appeared complete, but the sponsor only presented information on dropouts due to adverse events for non US studies. The reviewer could not calculate the overall percentage of dropouts for this group, or be certain that the sponsor identified all dropouts. The sponsor reviewed CRF's to determine reasons for discontinuation and presented the results in the amendment. The following presentation focuses on dropouts from clinical studies completed by the 120 day safety update.

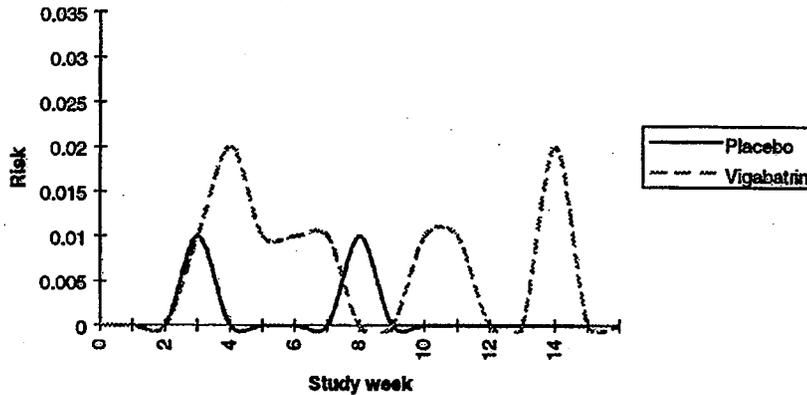
4.7.1 *Overall dropout percentages in US epilepsy studies*

The following data was presented in the original NDA. Almost 45% (198/443) of those exposed to vigabatrin dropped out of US epilepsy studies. The table on p.67 of the NDA review (see attachments) noted that 22.8% (101/443) of those exposed dropped out due to lack of efficacy. Seventeen percent (76/443) of those exposed dropped out due to adverse events.

For US controlled epilepsy studies, 14.4% (32/222) of those in the VGB treatment group dropped out compared to 3.7% (5/135) in the placebo group. There is 3.9 times greater risk for dropout for those exposed to the drug. The majority of withdrawals from controlled US studies were for adverse events (24 VGB, 3 Placebo). For non controlled US epilepsy studies, the percentage of dropouts for those exposed to vigabatrin was 40.8%. The common reasons for discontinuation for these patients were lack of efficacy and adverse events.

For the US controlled epilepsy study 024, the all cause dropout risk in patients taking VGB was 8.7% (8/92) and for those taking placebo was 2.2% (2/90). The following graph depicts the weekly all cause dropout risk. The peaks in risk for discontinuations in VGB patients occurred in weeks 4 and 14. During week 3, patients were taking 2.5g per day of VGB. At week 4, the dose of VGB was increased to 3g per day (the target dose for this study).

Weekly all cause dropout risk in study 024



4.7.2 Overall dropout percentages in primary non US epilepsy studies

In the amendment, the overall percentage of dropouts was 29.2% (223/765) for those exposed to vigabatrin in primary non US epilepsy studies. Lack of efficacy and adverse events were the most common reasons for withdrawal.

Completion status for primary non US studies by protocol type in patients/subjects exposed to vigabatrin

| Protocol type | N | Completed n(%) | Dropout n(%) | Loss of efficacy n(%) | Loss to F/U n(%) | AE n(%) | Death [^] n(%) | Other* n(%) | Unknow n(%) |
|------------------|------|----------------|--------------|-----------------------|------------------|-------------|-------------------------|-------------|-------------|
| Clin Pharm | 178 | 176(98.9%) | 2(1.1%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 0(0.0%) | 1(0.6%) | 1(0.6%) |
| Epilepsy Contr | 335 | 270 (80.6%) | 65 (19.4%) | 21 (6.3%) | 1 (0.3%) | 30 (9.0%) | 0 (0.0%) | 3 (0.9%) | 10 (3.0%) |
| Epilepsy Uncontr | 430 | 272 (63.3%) | 158 (36.7%) | 88 (20.5%) | 2 (0.5%) | 51 (11.5%) | 2 (0.5%) | 10 (2.3%) | 5 (1.2%) |
| Epilepsy Total | 765 | 542 (70.8%) | 223 (29.2%) | 109 (14.2%) | 3 (0.4%) | 81 (10.6%) | 2 (0.3%) | 13 (1.7%) | 15 (2.0%) |
| Other | 246 | 175 (71.1%) | 71 (28.9%) | 14 (5.7%) | 0 (0.0%) | 52 (21.1%) | 1 (0.4%) | 2 (0.8%) | 2 (0.8%) |
| Overall Total | 1189 | 893 (75.1%) | 296 (24.9%) | 123 (10.3%) | 3 (0.3%) | 133 (11.2%) | 3 (0.3%) | 16 (1.3%) | 18 (1.5%) |

Modified from information from sponsor table B-16 (Sb-V2-P110)

[^]Sponsor classified the death of a clinical pharmacology patient (015-007) as other in the completion section. The overall number of deaths presented for this group in the review of deaths is 4.

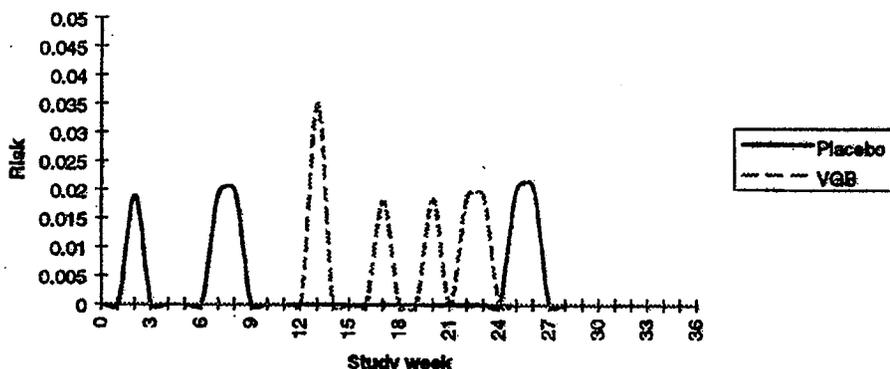
*Including but not limited to non-compliance, death, inability to keep records, insufficient number of seizures, patient/family request, desire for pregnancy (Sb-V2-P106).

It is difficult to interpret the differences listed for placebo exposed versus VGB exposed groups for dropouts. The sponsor lists the placebo exposed and VGB exposed groups separately when reviewing several topics (dropouts, AE's, hospitalizations). Six of the 9 primary controlled studies used a crossover design and only one of these used a washout

period. Without a washout period, there exists the potential to misclassify events with respect to exposure (especially for those AE's occurring near the time of crossover). In addition, in two of the three primary non US parallel design studies, all patients were eventually exposed to VGB. Looking at Canadian study 021, a double blinded placebo controlled parallel design study, the overall dropout rate was 10.3% (6/58) for the group exposed to VGB. For this same study, the dropout rate for the placebo group was 9.4% (5/53).

The weekly all cause dropout risk was determined for study 021. The risk for dropout in patients taking VGB was greatest during weeks 13 through 23. Patients received the 2g per day dose of VGB from week 9 through week 16, and the 3g per day dose from week 17 through week 24.

Weekly all cause dropout risk for study 021



The dropouts due to unknown causes in the non US population are problematic. The sponsor classified 18 patients as dropping out for unknown reasons. Ten of these were from controlled epilepsy studies.

Review of the CRF's from several of these patients indicate that most of these individuals were exposed to drug. Obviously there is concern that these discontinuations could be related to a serious AE. Despite the unknowns, there is a marked improvement in classifying dropouts compared to the NDA submission.

4.8 Adverse Events Associated with Dropout

Discontinuations due to adverse events in Primary epilepsy clinical studies

The sponsor defined dropout due to an adverse event on VGB as a discontinuation that occurs while receiving vigabatrin at the onset of at least one adverse event during the defined protocol (Sc-V3-P164). This definition excludes those discontinuing during extended dosing periods (continued VGB after protocol completion, 4 subjects).

This protocol meets the objective stated in the report. Seventeen percent of all patients enrolled dropped out of US epilepsy studies due to AE's (79/498) while 10.7% (92/857) of patients dropped out of non US primary epilepsy studies for the same reason. The sponsor included data from the US epilepsy studies for comparison in the presentation of

discontinuations due to AE's. The following information is from sponsor's table C-17 of the amendment (see attachments).

4.8.1 *US controlled epilepsy studies*

The sponsor included information about dropouts from AE's in US studies in the amendment (Appendix C-3 listing 1). I referred to the NDA review for additional information. Twenty-seven individuals dropped out of US controlled epilepsy studies due to adverse events. Twenty-four were taking vigabatrin when the AE leading to dropout began (10.8%; 24/222) and 3 were taking placebo (2.2%; 3/135). Participants exposed to drug were 4.9 times more likely to discontinue due to an adverse event than those getting placebo. The most common System Organ Classifications listed for discontinuations in the US epilepsy studies were CNS (10.8%, 48/443) and Psychiatric (6.8%, 30/443). In controlled US studies 6.3% (14/222) of those exposed to VGB and 2.2% (3/135) of those exposed to placebo dropped out due to a CNS AE. Within the CNS SOC, drowsiness (2.7%, 12/443) was the most commonly reported reason for dropout, followed by seizures (combination of convulsions and convulsions grand mal 2.0%, 9/443). Seven patients each reported fatigue, headache, and amnesia as a reason for dropout. For the psychiatric SOC, depression was the most commonly cited reason for discontinuation (2.0%, 9/443) followed by agitation (1.6%, 9/443), paranoid reaction (1.4%, 6/443), and thinking abnormal (1.1%, 5/443). The sponsor did not include a separate presentation of serious AE's in the NDA and did not provide a summary of all serious AE's in patients from US clinical studies in the amendment. No patients withdrew from US epilepsy studies for hepatic AE's.

4.8.2 *Non US controlled epilepsy studies*

Sponsor's table C-18 (see attachments) indicates 8.4% (28/335) of patients in primary non US controlled epilepsy studies exposed to VGB dropped out due to AE's while on drug. The sponsor calculates a dropout due to AE's percentage for placebo exposed patients, 2.5% (7/284) for comparison. Again, any comparison must take into account the crossover study design used in most of the non US controlled studies group. For Canadian study 021, 10.3% (6/58) of the group exposed to VGB discontinued due to AE's. Seven and a half percent (4/53) of the placebo exposed group discontinued due to AE's. For all non US primary epilepsy studies, the most commonly reported SOC's listed for discontinuation were similar to those reported in US epilepsy trials. The preferred terms used to describe the reasons for discontinuation were also similar for these two groups. In Canadian study 021, 8.6% (5/58) of VGB exposed subjects and 3.8% (2/53) of placebo exposed subjects discontinued due to CNS AE's.

4.8.3 *Uncontrolled US and Non US primary epilepsy studies*

There were 52 dropouts due to AE's from uncontrolled US epilepsy studies (12.6%; 52/414). The sponsor identified 51 dropouts (11.9%; 51/430) due to AE's in uncontrolled primary non US epilepsy studies.

4.8.4 *Other Studies*

The sponsor included data in the amendment from studies investigating the use of VGB in patients with diseases other than epilepsy (i.e., Huntington's chorea, Parkinson's disease, tardive dyskinesia, etc.). In US non epilepsy studies, 25% (7/28) of patients exposed to VGB dropped out due to AE's. In non US primary non epilepsy studies, 19.5% (48/246) of those exposed to VGB withdrew due to adverse events.

4.8.5 *AE's listed for subjects who dropped out of secondary or non CRF supported studies*

CNS and psychiatric were the most commonly reported SOC's associated with dropout for subjects enrolled in secondary or non CRF supported studies. Within the CNS SOC, common reasons for drop out were drowsiness and fatigue. In the Psychiatric SOC, subjects most commonly discontinued for agitation and aggressive reactions. The sponsor included a summary of all dropouts from secondary studies in table C-19 (see attachments). The non CRF supported patients were not presented in table format. I reviewed the line listings for these patients and did not find any previously unidentified AE's.

In non US studies, two patients discontinued for "granulocytopenia", and two for "leukopenia". These cases are summarized in the laboratory section. There were no discontinuations from clinical studies for agranulocytosis or aplastic anemia. Two patients discontinued from non CRF supported studies with "erythematous rash" listed as an AE at the time of discontinuation. No further documentation for these patients was available in the amendment. No patients had hepatic failure or renal failure at the time of discontinuation from clinical trials completed by the 120 day safety update. Patient 22002 (see laboratory section) who discontinued for other concurrent medical problems developed an elevated creatinine on VGB. Two patients exposed to VGB discontinued from a controlled clinical study for eye related complaints (blurred vision, eye pain). There were no cases of rhabdomyolysis listed as an AE at the time of discontinuation from completed clinical trials.

The sponsor did not provide analyses of dose related trends for the common AE's leading to discontinuation. They performed an analysis of the duration of exposure prior to discontinuation for all adverse events. Median exposure prior to discontinuation was similar for US and non US controlled epilepsy studies and for non epilepsy studies. The median duration of exposure prior to discontinuation was almost twice as long for uncontrolled US epilepsy studies compared to uncontrolled non US epilepsy studies (8.0 months versus 4.3 months). This may be due to differences in study designs between US and non US trials. The sponsor summarized this analysis in table C-22 (see attachments).

4.9 Serious Adverse Events

The sponsor addresses serious adverse events associated with VGB with the review of all deaths, discontinuations, and other serious adverse events in the amendment (Sc-V3-P2). The sponsor's approach was to present separate analyses of hospitalizations, cancers, episodes of status epilepticus, events leading to disability, life threatening events, overdoses and congenital anomalies. There is no summary section for all of these serious AE's in the amendment. A line listing of serious adverse events (defined as death, hospitalization, cancer, overdose, discontinuation, and status epilepticus) in VGB exposed, non US, CRF supported patients is provided as Appendix C1 Listing 2. Review of this listing identifies 162 patients from the primary non US data cohort with one or more serious AE's.

4.9.1 Hospitalizations

In the amendment, the sponsor reports that 686 patients exposed to vigabatrin have been hospitalized. One hundred seventy-five of these subjects were participants in US and non US clinical studies that were completed by the 120 day safety update(3/14/94). The sponsor identified 182 subjects hospitalized from ongoing clinical studies in the non integrated safety summary (3/15/94-12/31/95). The remaining 329 patients hospitalized were exposed to VGB in a post marketing context or through non US compassionate use. An additional 267 patients were identified as hospitalized in the most recent safety update(1/1/96 through 3/15/97).

4.9.1.1 *Hospitalizations in US epilepsy studies**

The information for this review of hospitalizations from US epilepsy studies was presented in Appendix C4-Listing 1 in the amendment. Eighty-three of 443 (18.7%) patients with epilepsy, exposed to vigabatrin were hospitalized in US studies. In the controlled studies, 6.8%(15/222) of those exposed to VGB and 0.7%(1/135) exposed to placebo were hospitalized (7 additional patients were hospitalized at baseline 4 were to receive VGB and 3 placebo). CNS (18.7%;83/443) and Psychiatric (2.7%;12/443) SOC's were most commonly associated with hospitalization. The common reasons for hospitalization included convulsions (5.2%;23/443), convulsions grand mal (2.7%;12/443), confusion and depression (1.1%;5/443 each) and psychosis (0.2%;1/443). There were no hospitalizations from this group for skin disorders or rashes, or liver abnormalities. Patient 011-055, a 35 YO male was hospitalized for reactive lymphadenopathy which was not clinically characterized as part of the amendment.

4.9.1.2 *Hospitalizations in primary non US epilepsy studies**

The sponsor reports that 39 of 765 (5.2%) patients exposed to VGB in non US primary epilepsy studies were hospitalized. Sixteen of the 516(3.1%) subjects exposed to placebo or other drug in non US epilepsy studies were hospitalized. Comparison of these groups is difficult to interpret because most of the controlled studies used a crossover design without a washout period. The common SOC's associated with hospitalization were CNS

(3.3%; 25/765) and Psychiatric (1.2%; 9/765). The common reasons for hospitalization were similar to those seen in the US epilepsy studies. Patient 069-404 a 32 YO female was hospitalized for purpura (described as a bruise over the right eye).

*There were no reports of hospitalizations of patients from US Clinical Pharmacology or non epilepsy studies. There were no reports of hospitalizations of patients from primary non US Clinical pharmacology studies. One patient was hospitalized from a non US primary non epilepsy study (for seizures).

4.9.1.3 *Hospitalizations of patients from studies that were ongoing at the time of the 120 day safety update*

The sponsor separated out the deaths in patients from studies that were ongoing at the time of the 120 day safety update in the presentation of deaths. In the presentation of hospitalizations, there is no separate summary for this group. It is not clear if these hospitalizations have been omitted or if they are included in one of the other presentations. The sponsor needs to clarify this issue.

4.9.1.4 *Hospitalizations in secondary epilepsy studies**

Fifty-one VGB exposed individuals in the secondary epilepsy studies group were hospitalized. The SOC's most commonly associated with hospitalization were CNS (23), and Psychiatric (15). A 26 YO female (26406) was hospitalized for renal calculus. The CRF contained few details about this hospitalization.

*No patients from non US secondary Clinical Pharmacology or Controlled Epilepsy studies were hospitalized during these protocols. One patient was hospitalized from a non US secondary non epilepsy study (for aggressive reaction).

4.9.1.5 *Hospitalizations during the extending dosing period*

Extended dosing periods occurred when patients were known to have completed a protocol, but continued on vigabatrin (see discontinuations due to adverse events). Hospitalizations that occurred during that period of time were presented separately. The sponsor reported that 21 patients were hospitalized during extended dosing periods. Patient 25510, a 3 YO with a history of mental retardation was hospitalized for maxillary sinusitis, and found to have iron deficiency anemia which responded to iron replacement. Patient 25816, a 60 YO female, was hospitalized due to loss of strength and developed CHF and ECG changes and died (mentioned in the death review section). Seven patients were admitted for seizures, and the rest of the patients were admitted with diagnoses such as confusion, paranoid reaction, aggressive reaction, asthma, sepsis, colon cancer, astrocytoma, knee surgery, prolonged menstruation, suicide attempt(2), and calcified lesion of the right insula.

Appendix C4 Summary 1 (see attachments) provides reasons for hospitalizations for primary, secondary, and extended duration patients .

4.9.1.6 *Hospitalizations in non US non CRF supported studies*

Non US non CRF supported studies did not routinely capture hospitalization data and the sponsor documented one hospitalization for this group. This was a 64 YO male hospitalized for convulsions grand mal.

4.9.1.7 *Hospitalizations in clinical studies since the 120 day safety update*

One hundred eighty-two subjects have been hospitalized from ongoing clinical studies since the 120 day safety update. The most common reasons for hospitalization were seizure (56), aggressive reaction (10), psychosis (9), confusion (8), depression(7), and suicidal tendency (7). Review of the event descriptions for patient's hospitalized for suicidal tendency revealed one actual attempt, the remaining patients in this group had suicidal ideation. From US studies, patient VGST-1192-0002 was hospitalized for rhabdomyolysis (associated with status epilepticus), patient VGST-1200-0022 was hospitalized for pancreatitis and cholecystitis and patient VGST-1212-0007 was hospitalized with DIC. Patient VGST-1202-0002, a 27 YO male taking VGB 4g/day for 176 days, was hospitalized for ulcerative esophagitis and anemia. From non US studies, patient VGST-CA-14-0089 was hospitalized with a generalized purpuric rash. Patient VGST-NE03-0850 was hospitalized with parieto-occipital cysts (remains blinded). No patients were hospitalized for hepatic injury, leukopenia, or neutropenia.

4.9.1.8 *Hospitalizations from the non integrated safety review (1/1/96-3/15/97)*

The sponsor identified 267 patients taking VGB that were hospitalized from January 1, 1996, through March 15, 1997. The most common SOC's leading to hospitalization are the same as presented in the amendment (CNS, Psychiatric). The most common reasons for hospitalizations were seizure, status epilepticus, and confusion. Patient VGST-1218-0008, a 56 YO female exposed to VGB 1G per day for 18 days and taking valproic acid, was hospitalized with hepatic encephalopathy which resolved after these medications were discontinued. There were no hospitalizations in this group for rashes, or rhabdomyolysis. Patient VGST-IN01-0102, a 33 YO male from a post marketing study, was identified as developing jaundice after 56 days of VGB at 1.5 g/day. This patient was hospitalized and the event listed as unresolved. Patient VGZ 9600 4463, an 11 month old female identified from a spontaneous report, was hospitalized for hemolytic anemia. She had received VGB 1.25g/day for 93 days prior to this event.

4.9.1.9 *Hospitalizations from the non US compassionate use group and spontaneous post marketing reports through 12/31/95*

In Sc-V4-P164, the sponsor provided an overview of hospitalizations in these groups. The specific reasons for hospitalizations in these groups were further reviewed in Appendix C-1 (listings 4 and 5) and appendix C-9 (listings 3 and 4) where the sponsor included them in a table with all serious adverse events. There have been 45 patients hospitalized from the compassionate use group, through 12/31/95. The most commonly reported AE's leading to

hospitalization included psychosis (7), seizure (6), status epilepticus (5), agitation (3), confusion (3), and coma (3). Patient VGST-AU20-0632 was diagnosed with Guillan Barre syndrome. Patient VGST SW01JA was hospitalized for an allergic skin reaction and patient VGST MUMF-330 was hospitalized for a generalized exfoliative erythematous rash. Patient VGST MUMF 343 was hospitalized for hepatic and renal insufficiency and patient VGST CA06 DT was hospitalized with pancreatitis.

Two hundred eighty-four subjects have been reported hospitalized in spontaneous reports through 12/31/95. The CNS and Psychiatric SOC's were most commonly associated with hospitalization in these groups. Psychosis was the most commonly reported reason for hospitalization in the spontaneous report group. Patient VGZ 9206-640 was hospitalized for leukopenia, patient VGZ 9203-799 for acquired hemophilia and patient VGZ 9216-187 for hemolysis. Patients VGZ 9301-4657, VGZ 9400-1440, VGZ 9108-795, VGZ 9210-042, VGZ 9213-654, VGZ 9400-0407, VGZ 9203130, and VGZ 9211-278 were hospitalized for hepatic injury. Patient VGZ 9301-3122 was hospitalized with pancreatitis. Patient VGZ 9216 187 was hospitalized with elevated CPK and muscle pain and patient VGZ 9301-4792 was hospitalized with a diagnosis of rhabdomyolysis (associated with status epilepticus). Patient VGZ 9213-455 was hospitalized with Hemolytic uremic syndrome.

4.9.1.10 *PEM reported hospitalizations*

There were 57 non surgical hospitalizations during the first month on vigabatrin for 9702 patients followed in the UK PEM study. For 18 of these hospitalizations, the reason for admission was not specified. Sixteen patients were admitted for epilepsy or convulsion, 4 for pyrexia, 2 for abnormal behavior, and 2 for asthma. There was one admission for each of the following: dental abscess, confusion, drowsiness, fluid retention, fracture, injury, lassitude, muscular spasm, psychosis syncope, tremor, and vomiting.

4.9.2 **Status epilepticus**

The sponsor included this review of status epilepticus with the presentation of serious adverse events. Status epilepticus was not commonly reported for non US studies. To improve identification of this event, a neurologist reviewed all non US seizure AE's (preferred terms including convulsions, convulsions aggravated, convulsions grand mal, convulsions petit mal, and condition aggravated) looking for cases of status epilepticus. The sponsor presented 167 patients who experienced one or more episodes of status epilepticus. Eleven of the individuals developed status during a placebo or no treatment phase of a study. Ninety-four of the 156 individuals who developed status epilepticus while taking VGB were enrolled in clinical studies (the remainder were in a compassionate use program or were detected through spontaneous reports from post marketing use). Of the 94 from clinical studies, 54 were from completed, CRF supported studies. Twenty-nine of these 54 individuals participated in US and primary non US epilepsy studies.

The sponsor calculated the rate of status epilepticus for the US placebo controlled epilepsy trials and for a Canadian parallel designed placebo control trial. In the US study,

the rate of status epilepticus was 2.3% (5/222) in the VGB exposed group versus 0.7%(1/135) in the placebo exposed group. This difference was not supported by observations in the Canadian study, which had a smaller enrollment. In that study, the rate of status on VGB was 0%(0/58) versus 1.9% (1/53) on placebo.

The sponsor also looked at episodes of status epilepticus that occurred during the discontinuation, interruption or tapering of VGB or concomitant anti epilepsy medications. The sponsor identified 14 patients that developed status epilepticus within 1-4 days (when known) of discontinuation of VGB. Eight individuals experienced status epilepticus during a tapering downward of dose and 2 individuals during an interruption of treatment. Four individuals developed status epilepticus when the dose of a concomitant anti epilepsy drug (AED) was altered or interrupted.

4.9.3 Cancer

The sponsor reports that 21 subjects who have taken VGB through 12/31/95 have been diagnosed with one or more cancers. There were no diagnoses of cancer in patients from US studies. The following table summarizes the cancer diagnoses for patients enrolled in non US CRF supported studies.

Cancer diagnoses in patients from non US CRF supported studies

| Patient ID | Protocol | Type of cancer |
|------------|-----------|-----------------------------------|
| 26626 | 097-266LT | Breast |
| 21202 | 097-306 | Lung, small cell |
| 30330028 | 097-306 | Colon, metastatic to liver, brain |
| 30330012 | 097-306 | Astrocytoma |
| 34031911 | 097-345 | Astrocytoma |
| 34031915 | 097-345 | Astrocytoma |
| 40733203 | 097-332 | temporal lobe, histology unk |

Information for this table is from the amendment Sc-V4-P238

Six patients from ongoing clinical studies were diagnosed with cancer. Patient VGST-1228-0001 died of lung cancer, and patient VGST 1225-0010 had a recurrence of basal cell carcinoma that resolved. Patient VGST-AU24-0629 was diagnosed with a teratoma of the testis and died. Patient VGST-NE02-0735 was diagnosed with a left frontal tumor cerebri, patient VGST-UK06-0494 was diagnosed with a meningioma, and patient VGST-1629-0670 was diagnosed with a low grade glioma. It is not clear if there were

any diagnoses of cancer in patients that were enrolled in studies that were ongoing at the time of the 120 day safety update.

The sponsor identified an additional two patients who were diagnosed with cancer in clinical studies that were ongoing from 3/15/94 through 12/31/95. One patient, VGZ-9500-1491 was diagnosed with prostate cancer, and another patient VGZ-9500-3480 died of small cell lung cancer.

Cancer in the Nonintegrated Safety Update (1/1/96-3/15/97)

In Sae-V1-P85, the sponsor lists the cancers identified during this safety update period. The cancers diagnosed were brain (2), lung (1), CML (1), lymphoma (1), throat (1), skin (3), breast (1), ovarian (1), and cervical (1).

Six patients were diagnosed with cancer from the non US compassionate use group and through spontaneous reporting of post marketing users. Patient VGST-SW03-00PY died of metastatic breast cancer. Four patients (VGST-AU16-0001, VGST-MUMF-132, VGST-AU17-0007, and VGZ-9108-469) were diagnosed with malignant brain tumors. Patient VGZ-9204-419 was found to have a temporal lobe tumor on MRI but withdrew from the study prior to diagnosis and the outcome is unknown.

4.9.4 Disability

In this section the sponsor reviews events that occurred in VGB exposed patients that were permanently disabling (definition used for US studies) or that resulted in persistent or significant disability or incapacity (non US studies).

4.9.4.1 *US and non US CRF supported studies*

There were no events identified to have resulted in disability in this group.

4.9.4.2 *Studies ongoing at the time of the 120 day safety update*

Again, the sponsor has been inconsistent in its presentation of the patients in this group. I am uncertain if those patients developing a disability during this period are omitted or presented in another grouping.

4.9.4.3 *US and non US ongoing studies after the 120 day safety update*

The sponsor presents four patients who met the definition of disability from these studies. One patient sustained a cut and subsequent infection of two fingers. Two patients suffered broken bones (ankle, leg), and one patient had post seizure hemiplegia with tonic seizures.

4.9.4.4 *Disability in the Non integrated Safety Update (1/1/96-3/15/97)*

Of the 14 events leading to disability in patients exposed to VGB, six were related to the eye. From non US protocol 097-335, patient 068064 experienced decreased vision and was diagnosed with macular degeneration. The following events were identified from spontaneous reports. Patient VGZ-9600-2985 experienced constriction of the visual fields in both eyes, retinal cone photoreceptor function abnormality, and retinal pigment epithelial dysfunction. The sponsor commented that these events resolved with sequelae. Patient VGZ-9600-2986 experienced visual field loss that resolved with sequelae. Patient VGZ-9600-7533 experienced binasal visual that has not resolved. Patients VGZ-9600-7534 and VGZ-9600-7535 experienced bilateral visual field constriction that has not

resolved. Patient VGZ-9700-0904 experienced constricted peripheral vision that has not resolved.

4.9.4.5 *Disability reports from Non US compassionate use and spontaneous reporting through 12/31/95*

Eight patients in this group developed disabilities related to ocular changes (retinal or optic disc pathology, optic neuritis, decreased visual acuity). Six patients had psychiatric events (aggression, psychosis, or a combination).

Confusion, rheumatism, axonal polyneuropathy, autoimmune thrombocytopenia, and arthralgia were also listed in this section.

4.9.5 Life threatening events

It is not clear from the sponsor's presentation what definition was used for a life threatening event or how these events were extracted. Apparently the determination was made by the reporter. No life threatening events were identified in patients from completed US or non US studies. No mention was made of patients enrolled in clinical studies that were ongoing at the time of the 120 day safety update. The sponsor identified and summarized the details of the life threatening events that occurred while on vigabatrin for 30 persons.

4.9.5.1 *US and non-US Ongoing Studies from 3/15/94 through 12/31/95*

- VGST-1192-0002 - aspiration pneumonia, confusion, hypoxia, pending kidney failure, respiratory failure, rhabdomyolysis, and status epilepticus resulted in hospitalization; all events resolved.
 - VGST-1200-0008 - right upper lobe lung collapse and status epilepticus resulted in hospitalization; all events resolved.
 - VGST-1208-0014 - adult respiratory distress syndrome, near drowning, pneumothorax and sinusitis resulted in hospitalization; all events resolved.
 - VGST-1212-0007 - disseminated intravascular coagulation; the event resolved.
 - VGST-1214-0014 - increased intracranial pressure resulted in hospitalization; the event resolved.
 - VGST-1224-0016 - near drowning due to possible seizure resulted in hospitalization; the event is unresolved.
 - VGST-1364-0006 - near drowning resulted in hospitalization; the event resolved.
- One additional patient (VGST-CA12-0006) from open label non-US Protocol VI-PE-0294 experienced a delayed recovery of consciousness following anesthesia reported as life-threatening which later resolved.

4.9.5.2 *Life Threatening Events from Spontaneous Reports*

Through 12/31/95 events considered life-threatening (by the reporter) occurred in 18 patients and included the following :

- VGZ-9015-702 - depression and overdose resulting in hospitalization and reported as an overdose; outcome of events is unknown.
- VGZ-9209-250 - suicide attempt; the event is resolved.
- VGZ-9216-802 - aggressiveness, depressive disorder, irritability and suicide attempt resulting in hospitalization; all events resolved.
- VGZ-9301-5309 - intentional overdose and intoxication reported as an overdose; outcome of events is unknown.
- VGZ-9016-553 - psychosis and suicide attempt reported as an overdose; all events resolved.
- VGZ-9109-134 - psychosis resulting in hospitalization; the event resolved.
- VGZ-9300-0644 - depression and psychosis resulting in hospitalization; the events resolved.
- VGZ-9208-271 - status epilepticus resulting in hospitalization; the event resolved.
- VGZ-9016-353 - status epilepticus resulting in hospitalization; the event resolved.
- VGZ-9301-0485 - increase in seizure frequency resulting in hospitalization; outcome of event is unknown.
- VGZ-9300-9591 - status epilepticus and toxic encephalopathy resulting in hospitalization; all events resolved.
- VGZ-9109-110 - hematemesis resulting in hospitalization; the outcome is unknown.
- VGZ-9301-4867 - gastric bleeding and vomiting; all events resolved.
- VGZ-9301-1972 - palpitations, sick sinus syndrome, sinus arrest and sinus bradycardia requiring medical intervention (pacemaker placement) and hospitalization; all events resolved.
- VGZ-9301-3599 - angina requiring hospitalization; outcome of event is unknown.
- VGZ-9301-3122 - pancreatitis resulting in hospitalization; the event resolved.
- VGZ-9213-647 - hypoglycemia, joint swelling and nausea; all events resolved.
- VGZ-9016-655 - increased appetite, diabetes, polydipsia, polyuria, and weight decrease resulting in hospitalization; outcome of events are unknown.
- VGZ-9400-1974 - respiratory depression; the event resolved.
- VGZ-9400-2611 - anemia resulting in hospitalization; the event resolved.
- VGZ-9400-7317 - anemia, autoimmune thrombocytopenia, bruising on upper arms, left hemiplegia and right frontal intracerebral hemorrhage resulting in hospitalization and disability; all events resolved.
- VGZ-9400-7742 - fulminant hepatic failure and hepatic coma resulting in medical intervention and hospitalization; the events are unresolved

4.9.5.3 *Life threatening Events from spontaneous reports presented in the Nonintegrated Safety Update (1/1/96-3/15/97)*

A non US patient with neutropenia was identified through spontaneous reporting. This 6 month old male was placed on VGB for myoclonic seizures. Four days after beginning VGB, the patient was noted to have low WBC, and neutrophil counts. The counts remained low and after one month of VGB, the dose was reduced and then discontinued. Two months later, the neutrophil count reached a nadir (380/ μ l) and subsequently it normalized.

4.9.6 Events requiring medical intervention

The sponsor presents two patients who had events requiring medical intervention (medical intervention was not added as a serious criteria until 1993). Both events were identified through spontaneous reports.

Patient VGZ-9301-1972 developed sick sinus syndrome while being treated with VGB, requiring pacemaker placement.

Patient VGZ-9400-7742 developed liver failure and required a transplant. The episode was described in the discharge summary as "thought to be drug induced, secondary to a recent anti-epileptic drug trial with vigabatrin." The patient was also taking gabapentin prior to developing liver failure.

4.9.7 Medically serious AE's in the Nonintegrated Safety review (1/1/96-3/15/97)

In this section, the sponsor clarifies issues related to the reporting of eye events in the amendment. Five spontaneous reports about visual field defects and one about optic atrophy were reviewed in the ophthalmological consultant section but not summarized in the body of the amendment. This occurred because the sponsor received these reports after the cutoff date for the amendment. Six eye events resulting in disability were summarized above. This yields a total of 14 new eye related events identified in patients during this update period.

There were 3 patients exposed to VGB with abnormal MRI exams. Patient 1194-0010, a 53 YO female treated with VGB 4g/day for 46 days, developed increased seizure frequency. A demyelinated lesion of the corpus callosum was observed on MRI. Her symptoms at that time were varied and included visual changes, parasthesias, nausea, and clumsiness. VGB was discontinued. On follow up MRI 8 months later, the radiologist noted that the lesion was "less conspicuous", but that it had not decreased much in size. Multiple consultants felt this lesion was not consistent with a drug effect. A 56 YO female treated with VGB 3g/day for 6 years, developed visual field defects. An MRI revealed possible demyelination. The differential diagnosis of the lesions included multiple sclerosis and small vessel cerebrovascular disease. In addition, a probable benign cyst was identified. No follow up information was provided. A 24 YO male, treated with VGB between 1992 and December of 1994 had an abnormal MRI exam in January of 1995. The MRI demonstrated bilateral temporoparietal gliosis that the reporting physician attributed to perinatal hypoxemia.

New Types of Serious AE's identified in the amendment

The sponsor included as brief section with "new" types of serious adverse events not described in the NDA. Below is a summary of some of these events.

Patient VGZ-9500-4387 was a 28 YO female with a history of elevated liver enzymes temporally associated with both carbamazepine and valproic acid. She was treated with VGB 1g per day for 1 year before developing increased liver enzymes. Biopsy showed mild acute and chronic inflammatory cell infiltrate and hepatic bridging fibrosis. These

findings were considered consistent with a drug induced hepatitis. Transaminases normalized after VGB was discontinued. The reaction narrative stated that the hepatic bridging fibrosis remained as a sequelae but there was no reference to repeat biopsy. Patient VGZ-9500-3964 a male pediatric patient treated with VGB .625g per day for almost a year developed prolonged PT and PTT along with elevated LFT's and coma. The sponsor stated that this patient did not die but admitted that follow up data was not available.

Patient VGZ-9400-1847, a 39YO male treated with VGB for 31 days, developed erythema multiforme. This patient also had hepatitis, porphyria, and had taken phenytoin and other medications near the time of the event.

Oliguria was reported for an 18YO who overdosed on VGB, carbamazepine, and diazepam (presented in overdose section).

Patient VGZ-9400-2362 a 32 YO male treated with VGB for about 7 months (discontinued about 1 month prior to this event) was diagnosed with nephrotic syndrome, developed a DVT and died from a pulmonary embolism.

Patient VGST-1228-0001 a 69YO female with a history of LVH, treated with VGB .75g for 8 days developed sinus tachycardia and ventricular tachycardia following a seizure.

Patient VGST-1200-0008 a 33YO male developed RUL atelectasis following a seizure.

Patient VGZ-9500-2232 a 6 month old with cortical dysplasia treated with ACTH and VGB developed pneumocystis pneumonia and ARDS.

Patient VGZ-9500-0068 a 22YO female treated with VGB 2g per day for 8 months developed schizophrenic psychosis. She abruptly stopped all antiepilepsy drugs, developed status epilepticus, and brain damage.

New types of Serious AE's identified in the Nonintegrated Safety Review (1/1/96-3/15/97)

The sponsor identified 17 new AE's from clinical trials and 10 from spontaneous reports. Three spontaneous reports of a neonatal feeding disorder were identified. These three infants (7 months, 10 months, and unknown) were started on VGB for infantile spasms and within 24 hours of the first dose stopped feeding. Two of the infants were given tube feedings. For these infants, VGB was discontinued for lack of efficacy and subsequently the investigator noted that sucking improved. In the case of the third infant, VGB was discontinued because of the feeding problem. The baby started to feed again after discontinuation of VGB.

The CML, lymphoma and ovarian cancers listed under the cancer section are new. There was a report of a leukocytoclastic vasculitis in a female taking VGB, phenytoin, carbamazepine and conjugated estrogens. A male treated with VGB for 21 months along with phenobarbital and amphetamine was diagnosed with trismus.

4.10 AE Incidence tables

The sponsor presented the common and drug related AE's for US studies in the NDA and did not summarize them separately in the amendment. The appendix includes the table from the NDA review summarizing the adverse events that occurred commonly in US patients (NDA review p.71, see attachments).

In the amendment, the sponsor summarized all AE's from non US studies in tables from various data cohort combinations. Four tables contain the data from primary studies, secondary studies, primary plus secondary studies, and extended dosing periods (Sb-V2-P147). Comparison between the occurrence of AE's in VGB exposed and not exposed individuals as presented in the sponsor's tables B-31, B-32, and B-33 are difficult to interpret. The sponsor lists the placebo exposed and VGB exposed groups separately in these tables but as discussed above, most of the non US primary controlled studies used a crossover design and only one of these used a washout period. Table B-31 is included with the attachments.

The sponsor included AE table F-2 (see attachments) [REDACTED] For this table, the sponsor combined data from the two US epilepsy controlled trials, the non US epilepsy controlled trial 021, the data from the parallel designed study WUK04 (prior to the open label phase for responders); and the first period crossover from primary crossover designed epilepsy studies (247,259,262,263,444,W/AUS/01). Using the first period crossover approach could make interpretation difficult because of data pooling issues. These exposure periods are shorter than those seen with the parallel controlled trials. This could reduce the number of patient's reporting AE's that require longer exposure to drug. The AE's occurring immediately following the end of the first period that are due to treatment could also be missed.

b(4)

In order to evaluate the appropriateness of grouping the data presented in table F-2, I examined the risk associated with drug for evidence of variability between these groupings for selected AE's. I did this by examining the data in Appendix F1(see attachments). In this table, the sponsor lists separately the percentages of AE's occurring in patients exposed to VGB or Placebo in the primary non US controlled epilepsy studies, primary non US study 021, and the first period crossover studies listed above. The total occurrence rate (patients with 1 or more adverse events) was higher for the parallel controlled trials (94% placebo, 98% VGB) than for the first period crossover (60.2% for placebo and 84.1% for VGB). Despite this difference, the relative risk associated with VGB for selected AE's among the groups was comparable. Fewer individuals reported the more common AE's in the first period crossover group, but the relative risks, in general, were similar to the parallel controlled studies. Table F-2 appears to be useful for rough estimates of risk associated with VGB in studies, but is less useful for estimating the frequency of these events.

4.10.1 Dose response data for adverse events

The sponsor did not present in the amendment an analysis of the data by dose to look for evidence of a dose response relationship for adverse events.

4.10.2 Demographic interactions

The sponsor analyzed the AE data for patients exposed to VGB included in the primary data cohort by the following demographic variables: gender, age at study entry, and

weight. The sponsor did not analyze the AE information by race because investigators for most of these studies did not collect this data.

4.10.2.1 Gender

Seventy-six percent of the females exposed to VGB in the primary data cohort reported at least one AE compared to 68% of men. In general, for specific AE's, the percentages of males and females reporting the events were similar. There was a slightly greater percentage of females reporting events such as confusion, hypokinesia, tremor, depression, anxiety, emotional lability, and thinking abnormal. There was a slightly greater percentage of males reporting events such as paresthesias and aggressive reaction.

4.10.2.2 Age

The sponsor stratified the AE's from primary non US studies according to the NDA reviewer's suggestions. In general, the percentage of individuals within a stratum reporting AE's increased with age. The 2-<12 year old stratum had the lowest percentage of individuals with recorded AE's (48%, 60/125) while the >=65 year old stratum had the highest (94.6%, 53/56). The percentages of individuals reporting AE's such as drowsiness, dizziness, and confusion all consistently increased with increasing age. For thinking abnormal, the occurrence did not consistently increase with age. The percentage of individuals reporting thinking abnormal was highest in the >=65 stratum (10.7%, 6/56). The next closest stratum was 16-<40 (0.9%, 6/676). The percentage of individuals reporting amnesia showed a large increase for adjacent strata. In the >=65 stratum, 16.1%(9/56) reported amnesia. In the 40-<65 group 3.3%(8/242) reported that AE.

4.10.2.3 Weight

Analysis of AE's stratified by weight categories did not reveal any apparent drug/weight interactions.

4.11 Laboratory

The analysis of data from laboratory testing for US patients was presented in the NDA and the sponsor did not repeat it in the amendment. The amendment contains information about laboratory results for the non US epilepsy studies (controlled and uncontrolled) and the non US studies in neurological conditions other than epilepsy. The sponsor includes tables that summarize the number of patients with outliers and with potentially clinically important changes for values within a panel of tests. A majority of patients had laboratory testing especially for liver function, renal function, and hematologic parameters. The following table presents the numbers of patients from non US studies with lab values for the stated tests.

Numbers of patients with results for a panel of tests from non US, CRF supported studies

| LAB TEST | # OF SUBJECTS WITH RESULTS |
|----------------|----------------------------|
| Liver function | 1947 |

| | |
|------------------------------|------|
| Renal function | 1844 |
| Hematology with differential | 1944 |
| Electrolytes | 876 |
| Miscellaneous | 1664 |

Data used to construct table from page Sb-V2-P261

Additional tests were collected in some protocols (urinalysis, coagulation studies, AED blood levels, etc.) but were not summarized. The sponsor's laboratory review contains data from 87 different protocols (1957 patients). The data includes lab results collected during specified dosing periods only. Follow up testing to determine if abnormal values returned to normal was not included in this section. The sponsor defined "baseline" as the lab value immediately prior to and including the first day of VGB dosing. "Last time" was defined as lab values taken up to and including the day after the last dose of VGB. The sponsor did not perform analyses of mean changes from baseline on non US data due to a lack of site normal ranges across protocols.

In her review of the NDA, Dr. McCormick compared lab abnormalities between study drug and control groups from controlled US clinical trials. The sponsor presents lab results in the amendment by data cohorts such as primary (controlled epilepsy, uncontrolled epilepsy, and other) exposed to vigabatrin; secondary, exposed to vigabatrin; and combined (all CRF supported data) exposed to vigabatrin. The sponsor's presentation does not allow for a comparison between VGB and placebo exposed groups.

The outlier criteria were reviewed and seemed appropriate. Using the IR, I reviewed lab data for study 71754-3-C-021 (a double blind, parallel, placebo controlled trial from Canada). I did not examine the other controlled non US trials. In the remaining non US "parallel" designed studies, all patients were exposed to VGB. In the crossover design studies, only one used a washout period prior to crossover (Sb-V2-P89). I selected those VGB exposed subjects from study 021 who were considered outliers for a particular lab test using the agreed upon criteria (see attachment). If the subject had a non outlier value at baseline and developed an outlier during the trial, they were counted. If the subject had an outlier at baseline, normalized during the study and subsequently developed an outlier, they were also counted. Subjects with outliers at baseline that did not normalize were not included. This review was repeated for those exposed to placebo and the number of patients developing outliers was compared between these two groups.

This review will first provide a comparison of outliers in VGB and placebo exposed groups from study C-021. It will be followed by the comparison of outliers in VGB and placebo exposed groups from US studies that was included in the NDA review (except for amylase which was extracted from the IR). The sponsor's analysis of outliers at any time for all non US CRF supported studies will be referenced for abnormalities not identified in the controlled studies analyses. The criteria used to identify outliers (table B-39) is included in the appendix.

4.11.1 Liver Function Tests

4.11.1.1 Study C-021

Review of the LFT lab data from study C-021 demonstrated few patients with outliers for these tests. Two patients developed elevated albumin (≥ 5.0). One patient had a GGT result that met outlier criteria (this value was elevated at baseline and normalized on VGB) and one patient had an SGOT result that met the outlier criteria. No patients in the control group had LFT results meeting the outlier criteria.

| Proportion of Patients Having Outliers for LFT's from Study 71754-3-C-021 | | |
|---|-----------------|---------------|
| Liver Function Tests | Vigabatrin N=58 | Placebo N=53 |
| | Abnormal % (#) | Abnormal %(#) |
| Albumin high | 3.4% (2) | 0% (0) |
| GGT high | 1.7% (1) | 0% (0) |
| SGOT high | 1.7% (1)* | 0% (0) |

*This patient had normal LFT's throughout the study except for a single increased SGOT of 196 approximately 4 months into the study. The patient withdrew the same week that this value was obtained (for schizophrenic reaction) and the SGOT normalized within 1 month.

4.11.1.2 US controlled epilepsy studies

GGT and elevated albumin were not included in the review of the LFT lab panel for US studies. There was 1 patient with elevated SGOT in both the VGB and placebo group. There were no patients with elevated SGPT, bilirubin, or alkaline phosphatase in either group.

4.11.1.3 Non US CRF supported VGB exposed patients

The sponsor identified 13 patients and 9 patients as having elevated SGOT or SGPT respectively at any time during the study. Twelve of the 13, and 7 of 9 with elevated SGOT and SGPT were from one study (protocol 097-240). This was an open label study in a pediatric population included in the secondary data cohort. The sponsor noted that lab units and normal reference ranges were not consistent within each patient's lab data. Most of these individuals had elevated transaminases at baseline. There did not appear to be much difference between those with high outliers for transaminases and those without when comparing number of concomitant medications taken. Those with the outlier results for transaminases had a lower mean age (2.9 YO vs. 10.2 YO) compared to those without outliers for SGOT and SGPT in this study. These abnormalities were not observed in the primary non US pediatric protocols. The LFT results from these protocols (332, 9001/VGB, and 332.5) were reviewed and no patients from this group had outliers for transaminases that developed while on VGB.

Nine percent (121/1341) of patients tested had an outlier result for alkaline phosphatase. No patients from the controlled studies were noted to have an outlier for this test. Ninety-four of the 121 who had a high outlier for alkaline phosphatase at any time were <16 YO. The sponsor attributes these results to the presence of elevated bone alkaline phosphatase

isoenzyme in younger individuals who are growing. This hypothesis was not tested. The sponsor also noted that "most of these patients had abnormal alkaline phosphatase levels at baseline."(Sb-V2-267) Twenty-three percent of patients exposed to VGB developed elevated albumin (>5.0g/dl).

4.11.1.4 Adverse events, non US studies, LFT's

No VGB exposed patients from non US CRF supported studies had adverse events due to elevated AST or ALT. The sponsor presented the AE's for combined primary and secondary non US studies. Since the secondary cohort is unreliable for calculating frequencies (see above), the number of events will be provided but not a denominator. Twenty-eight VGB exposed patients from non US CRF supported studies experienced an elevated GGT that was recorded as an adverse event. Seven patients had elevated alkaline phosphatase results that investigators recorded as adverse events.

4.11.1.5 Dose dependent changes in LFT's

The sponsor has provided evidence demonstrating that exposure to VGB is associated with decreases in ALT and to a lesser extent, AST. The result of an analysis of mean laboratory values for these transaminases demonstrates dose dependent decreases in mean ALT and AST in patients exposed to VGB in controlled US studies (Table B-42, see attachments).

4.11.2 Renal Function

4.11.2.1 *Study C-021*

No patients in the VGB or Placebo exposed groups in study C-021 had outliers or potentially clinically significant changes in BUN or Creatinine.

4.11.2.2 *US Controlled epilepsy studies*

No patients in the VGB or placebo exposed groups in the US controlled epilepsy studies had outliers or potentially clinically significant changes in BUN or Creatinine.

4.11.3.3 *All non US, CRF supported studies*

Four patients had elevated creatinine tests and 4 patients had elevated BUN tests that met the criteria for outliers. Sponsor's table B-43 summarizes this data.

Table B-43. Summary of High and Low Outliers at Any Time While Receiving Vigabatrin - All CHF Supported Studies (Renal Function)

| Analyte | Outlier Criteria | Epilepsy Studies | | Non Epilepsy Studies | | Total | |
|-----------------------------|------------------|---------------------|----------------------|----------------------|----------------------|---------------------|----------------------|
| | | At Any Time % (n/N) | At Last Time % (n/N) | At Any Time % (n/N) | At Last Time % (n/N) | At Any Time % (n/N) | At Last Time % (n/N) |
| Creatinine (mg/dL) | High ≥ 2 | 0.3 (4/1226) | 0.1 (1/1226) | 0.0 (0/190) | 0.0 (0/190) | 0.3 (4/1416) | 0.1 (1/1416) |
| Blood Urea Nitrogen (mg/dL) | High ≥ 30 | 0.3 (4/1416) | 0.2 (3/1416) | 0.0 (0/190) | 0.0 (0/190) | 0.3 (4/1416) | 0.2 (3/1416) |

Sponsor's table

Patient 26203 creatinine increased while on 1g of VGB (from 0.89 to 2.5) and then returned to normal at the next visit (was switched to placebo in the interim).

Patient 26217 creatinine went from 0.6 at baseline to 2.2 on 2g of VGB and then returned to 0.8 while continuing on the same dose.

Patient 24162 creatinine was 2.9 on drug. This patient enrolled in another protocol and creatinine was 0.8 at that time.

Patient 30330034 creatinine went from 0.6 to 2.1 to 0.7 while on 4.5 g of VGB

4.11.3.4 Adverse events, non US studies, renal function

Patient 015-109 had an AE due to an elevated urea (highest recorded value for this individual was 22.7). Patient 22002 had an AE due to renal insufficiency with a creatinine of 1.6. This patient had baseline renal insufficiency and developed atrial fibrillation and worsening renal function after 3 days of VGB.

4.11.3.3 Hematology and differential profile

4.11.3.1 Study C-021

Review of the lab results from study C-021 revealed several hematologic parameter outliers that occurred more frequently in those exposed to VGB compared to those receiving placebo. Investigators recorded a low hematocrit outlier for 20.7% (12/58) for those receiving VGB compared to 11.3% (6/53) in the placebo group. Interestingly, there was no corresponding difference noted for hemoglobin values. Seventeen percent (10/58) of those in the VGB group had a low outlier for WBC count compared to 5.7% (3/53) in the placebo group. Ten percent (6/58) of those exposed to VGB had a low outlier for neutrophils compared to 5.7% (3/53) for placebo exposed individuals. A similar difference was seen for low lymphocytes. Eosinophil count outliers were more frequent in VGB exposed group than in the placebo exposed group.

Proportion of patients from study C-021 having hematologic outliers

| Hematologic test | Vigabatrin N=58 | Placebo N=53 |
|------------------|-----------------|----------------|
| | Abnormal % (#) | Abnormal % (#) |
| Hematocrit low | 20.7% (12) | 11.3% (6) |
| Hemoglobin low | 0% (0) | 1.9% (1) |
| RBC low | 6.9% (4) | 7.5% (4) |
| WBC low | 17.2% (10) | 5.7% (3) |
| Platelet low | 1.7% (1) | 1.9% (1) |
| Neutrophil low | 10.3% (6) | 5.7% (3) |

| | | |
|-----------------|------------|----------|
| Lymphocyte low | 22.4% (13) | 9.4% (5) |
| Eosinophil high | 6.9% (4) | 1.9% (1) |

Data from IR

4.11.3.2 *US controlled epilepsy studies*

Thirteen percent (28/221) of the VGB exposed subjects had outliers for low hematocrit compared to 6% (8/135) in the placebo group. Two patients in the vigabatrin exposed group were noted to have outliers for low hemoglobin compared to none for placebo. Ten percent (23/221) of VGB exposed patients had outliers for low WBC count compared to 5% (7/135) in the placebo exposed group. Seven percent (16/221) of patients exposed to VGB were noted to have a low outlier for neutrophils while 4% (6/135) of those exposed to placebo had a low outlier for neutrophils. A analysis of mean change from baseline for RBC, HGB, HCT, demonstrated slight decreases in all three parameters that appeared dose related and that were not observed in the placebo group (Sb-V2-P286).

The sponsor did not identify dose related trends when reviewing data on WBC counts, neutrophils, or lymphocytes.

4.11.3.3 *All non US, CRF supported studies*

Review of the data from table B-45 (see attachments) did not identify any additional information for outliers for hematology lab tests.

4.11.3.4 *Adverse events, hematology*

Four patients from controlled US studies had anemia listed as an adverse event. Two of these patients, both exposed to VGB, had hemoglobin or hematocrit values that met the criteria for low outliers. Neither were hospitalized or dropped out of the study. Patient 064-002 was a 31 YO female exposed to VGB who had an AE with anemia/dietary supplement listed as the verbatim term. Her hemoglobin declined from 12.6 at baseline to a low of 10.8. Her last hemoglobin on drug was 11.9. She did not develop outliers for platelet or WBC counts. Patient 072-016, a 63 YO female exposed to VGB had anemia iron deficient listed as the verbatim term for her AE. Baseline hemoglobin was 12.8, and it declined throughout treatment to a low value of 8.8. There were no follow up labs listed to document normalization. This patient did not develop outliers for platelet or WBC counts.

Search of the IR identified 12 patients in US studies who had anemia listed as an adverse event that occurred while on VGB(2.7%;12/443). Four of these individuals were mentioned above. Ten patients exposed to VGB in primary non US studies had anemia reported as an AE (0.8%;10/1189).

No patients discontinued from US studies for anemia. One patient dropped out of a primary non US study and had anemia listed as an adverse event. Patient 25510, a 3 year old mentally retarded patient, was hospitalized for sinusitis and had was diagnosed with a hypochromic anemia(HGB 10.4) associated with thrombocytosis (480,000). The anemia corrected with iron replacement. The investigator discontinued VGB for behavioral changes.

In an attempt to further characterize the anemia seen, an analysis of patients identified with anemia as an AE was conducted for patients from US studies and all primary non US studies. A search of the IR identified 23 patients from US or primary non US studies with an AE of anemia that occurred while on VGB. One of these patients also had melena which accounted for the anemia. Of the remaining 22 patients, 10 were male and 12 were female. The average age of the males was 45.2 years and of the females 31.8 years. The duration of exposure to VGB prior to development of anemia ranged between 14 and 1547 days. A review of the lab data for these patients demonstrated a range of lowest values for recorded hematocrit between 27 and 39 (Hgb 8.8-12.9). The sponsor did not include red cell indices in the lab summary. Review of bilirubin and LDH (when available) values for these patients did not reveal increases which would be expected with a hemolytic process.

Patient 39431409 discontinued from a secondary study due to anemia. He was a 42 YO male treated with VGB 2g/day and had received the drug for 19.1 months prior to discontinuation due to tongue pain and anemia (HGB 8.7). His HGB prior to taking VGB was 15.7g/dl. The investigator felt the anemia was due to an unspecified concurrent illness. There was no follow up to determine if the anemia resolved with discontinuation of VGB.

There were 4 patients in US studies identified through an IR search who had leukopenia listed as an AE that developed while on VGB(0.9%;4/443). Two patients were identified who had granulocytopenia listed as an AE that developed while on VGB(0.5%;2/443). Eight patients from primary non US studies(0.7%;8/1189) had leukopenia listed as an AE that developed while on VGB and 7 had granulocytopenia (0.6%;7/1189). No patients withdrew from US studies for leukopenia or granulocytopenia. Two patients withdrew from primary non US studies and had leukopenia or granulocytopenia listed as an AE at the time of discontinuation. Patient 23001 was a 55YO female who had a WBC count of 3.0 (45% neutrophils) on placebo. The investigator decided to proceed with the study.

VGB treatment was begun per protocol and the WBC increased to 5.3. The investigator discontinued the subject from the study for neutropenia apparently because of the WBC count obtained on placebo. Patient 25916, a 10 YO female, had a WBC count of 2.2 on VGB and trimethadione. The investigator hypothesized that the leukopenia was due to trimethadione. After discontinuation of trimethidione, the patient had increased seizure activity and withdrew from the study. Follow up labs were not provided. The sponsor identified two patients from secondary studies who withdrew due to leukopenia. Patient 30430474, a 21 YO female dropped out of a protocol for a WBC count of 4.9 (19% neutrophils, 4 bands) which was minimally changed from the pre-study value. Patient 36531402 was a 61 YO male who discontinued VGB due to ataxia and impaired memory and was noted to have WBC counts in the 3.9-4.7 range.

Patient 30236903, a 24 YO female, developed anemia 2 weeks after starting VGB, then 6 months later, while still on the drug she developed moderate thrombocytopenia and leukopenia. These dyscrasias resolved while continuing VGB.

There sponsor identified one spontaneous report of aplastic anemia. An 11YO female from the UK was diagnosed with aplastic anemia after 19 months exposure to VGB at a

dose of 1.5g/day. Concomitant medications were pizotifen, budesonide and terbutaline. The consultant hematologist felt the aplastic anemia was due to a recent EBV infection.

4.11.4 Electrolytes

4.11.4.1 *Study C-021*

No patients in the placebo exposed group had electrolyte lab result outliers. One patient exposed to VGB (1.7%;1/58) had a low outlier for sodium and 3 patients (5.2%;3/58) had low outliers for calcium.

4.11.4.2 *US controlled epilepsy studies*

In the NDA review, 4% of both the VGB exposed patients (8/221) and the placebo exposed patients (5/135) had a low outlier for sodium. Twenty percent (45/221) of the VGB exposed individuals had a low outlier result for calcium while 30% (40/135) had a low outlier result for calcium in the placebo exposed group. The sponsor did not identify any dose dependent trends for mean electrolyte lab values in US studies.

4.11.4.3 *All non US, CRF supported studies*

Review of table B-48 (see attachments) revealed that 2.4 % (6/248) of patients in this group, tested for phosphorus, met the low outlier criteria. No new concerns regarding electrolyte result outliers were identified.

4.11.4.4 Adverse events, electrolytes

Two patients had AE's for hypocalcemia, one for hypokalemia, and one for hyponatremia, but the sponsor reports that none of these met the criteria for outliers for these electrolytes.

4.11.5 Miscellaneous chemistry

The sponsor included a review of miscellaneous chemistry results that included tests such as amylase, glucose, uric acid and cholesterol.

4.11.5.1 *Study C-021*

Three VGB exposed patients (5.1%;3/58) and 4 placebo patients (7.5%;4/53) from study C-021 had a low outlier for glucose. No additional outliers were noted for this group of tests.

4.11.5.2 *US controlled epilepsy studies*

In the US controlled epilepsy studies, 4% of both VGB exposed (8/221) and of placebo exposed (5/135) patients had a low outlier for glucose. Three of the subjects exposed to

VGB (5.2%;3/58) and two of the subjects exposed to placebo (3.8%; 2/53) had a high outlier for amylase. The sponsor did not identify any dose dependent trends.

4.11.5.3 *Non-US CRF supported studies*

Table B-50 (see attachments) did not reveal any new concerns about miscellaneous chemistry tests.

4.11.6 Urinalysis

In the NDA review, Dr. McCormick commented that the sponsor only summarized the specific gravity and pH data from urinalysis results. In the amendment, the sponsor did not provide summaries for the urinalysis results data from the non US studies. A brief examination of the IR revealed that urine testing was done on a large number of patients but it seems the examination for cells and protein was either done or recorded inconsistently.

4.11.7 Coagulation Testing

The sponsor has collected information about coagulation studies but has not summarized these data. Results from these tests can be useful in assessing hepatic synthetic function.

Lab summary

VGB is associated with reduction of the transaminases SGPT and SGOT. This association was observed in US trials but not looked for in non US trials. The sponsor identified a dose response relationship between VGB and SGPT/SGOT reduction. The implications of transaminase reduction on monitoring for hepatotoxicity are not fully recognized and should be acknowledged in labeling. Elevated transaminase outliers were clustered in one non US study (097-240). Many of these individuals had elevated transaminases at baseline. The sponsor also identified inconsistencies with lab units and normal reference ranges in this study. There were few patients with outliers or AE's related to renal function. Analysis of US lab data demonstrated a slight dose dependent decrease in HGB, HCT, and RBC's. The sponsor did not perform this analysis on non US data. There was consistency between the US (024,025) and Canadian (021) studies in demonstrating an increased risk for VGB exposed patients to have low outliers in hematocrit, WBC's, and neutrophils. The sponsor did not find a dose response relationship for low WBC's in the US data. Very little data from urine testing has been analyzed. There is no summary of coagulation testing.

4.12 Vital Signs

Dr. McCormick commented, in the NDA review, that the only notable difference between the placebo and vigabatrin treated groups in controlled US epilepsy studies was weight gain in the VGB group. The sponsor did not provide an analysis of vital sign data for the non US studies. Appendix A, table 6(see attachments) in the amendment is a dose

stratified analysis of mean changes in pulse, respirations, systolic blood pressure, and diastolic blood pressure for patients enrolled in the US study 71754-3-C-025. There appeared to be a linear trend for increased respirations with increased dose of VGB that does not appear to be clinically significant.

4.13 Withdrawal Phenomena/Abuse Potential

The sponsor did not present any additional information about these topics in the amendment

4.14 Human Reproduction Data

For the presentation of human reproduction data, the sponsor reviewed the pregnancies with deliveries on or before 12/31/95. One hundred twenty-five women had 139 pregnancies and received VGB at some time during their pregnancy by this cutoff date. Outcome information is not available for two of the identified pregnancies.

The sponsor classified the abnormal outcomes as major malformations, minor malformations and dysmorphic anomalies and perinatal complications. The review will follow that order. According to the sponsor's data, 12.9% (18/139) of the pregnancies in which the mother was exposed to VGB resulted in major or minor malformations in the children from those pregnancies. This percentage is comparable to the range of rates

(2.3%-18.6%) cited by the sponsor for AED's in a review of the literature appearing in Antiepileptic Drugs. For these 21 abnormal outcomes, 16 mothers were taking at least one other AED. Information on concomitant AED's was not available for 3 mothers and two mothers were not receiving other AED's (one was receiving acyclovir).

Major malformations

The sponsor defined major malformations as "structural defects formed during the development of an organ or organ system that could result in significant dysfunction or death" (Sc-V4-P200). The sponsor includes anomalies requiring surgical repair in this group. The following is a listing of these 11 events:

- Female, congenital dislocation of the hip
- Female, congenital dislocation of the hip
- Female, premature, unspecified musculoskeletal problems
- Therapeutic abortion at 17 weeks, conjoined twins
- Female, squint requiring surgery
- Bilateral cleft palate
- Therapeutic abortion 30 weeks, agenesis of the cardiac septum, microcephaly, pulmonary artery atresia, spina bifida
- Female, choanal atresia, congenital nystagmus, possible craniosynostosis
- Female, ventricular septal defect
- Male, congenital diaphragmatic hernia, died within 24 hours of birth
- Female, Left hemisphere atrophy, decreased right arm motor function, seizures within 10 days of birth

Minor malformations and dysmorphic anomalies

The sponsor defines minor malformations as “structural defects found during the development of an organ or limb that impede or impair function but do not result in serious illness or death if not medically treated or surgically modified”(Sc-V4-P202).

Dysmorphic anomalies are “unusual morphologic features of no serious medical consequence”(Sc-V4-P202). The sponsor presents the following 7 events:

- Male, undescended testicle
- Male bilateral club feet
- Shuddering when handled
- Female, facial palsy, tachypnea
- Female, in utero molding, eye roving, low hairline, low set ears, poor muscle tone, torticollis
- Male, hypospadias, bilateral clinodactyly of the fourth toes, capitated deep palmar flexion creases, diastasis recti abdominis, multiple facial anomalies, wide inter nipple distance.
- Male, minor dysmorphism, plagiocephaly, orbital asymmetry, hyperextensible interphalangeal joints, fifth finger clinodactyly

Perinatal complications

The sponsor lists two perinatal complications in children whose mother was exposed to VGB in pregnancy. One child died from an intracerebral bleed two weeks following birth by C-section and one child had a seizure on the day after birth.

Abortions

The sponsor reports that 11.5% (16/139) of the identified pregnancies ended in spontaneous abortion. Approximately 7% (10/139) of the identified pregnancies were terminated by therapeutic abortion. Two of these were reported in the major malformation section.

UK PEM Study

The PEM study identified 88 pregnancies in 81 women who had received VGB within 3 months prior to or during their pregnancy. There was one still birth following a placental abruption and one intrauterine fetal demise. Seven pregnancies had abnormal outcomes (3 major malformations, 2 minor malformations or dysmorphic anomalies, and 2 perinatal complications). The authors reported 18 (20.5%) spontaneous abortions, 11 (12.6%) therapeutic abortions, and 3 (3.4%) unknown outcomes.

4.15 Overdose Experience

The sponsor identified 33 events in which 31 individuals overdosed on VGB. In 18 of the overdoses (16 individuals, 2 subjects overdosed twice) vigabatrin was the only drug reported as used in the OD. The chart below contains information about the dose,

symptoms, and outcome for these individuals. The most commonly reported symptoms were: coma/semi-comatose 5/18, drowsy/sleepy 2/18, vertigo 2/18, seizure related 2/18, and psychosis 2/18. The dose of VGB taken in the overdose was available for 3 of the 5 who became comatose. The average dose taken for these individuals was 46g (range 22g-65g). One individual was reported to have taken 45g of VGB but the patient's symptoms and outcome are not available for review.

Patients included in the amendment as taking an overdose and the drug used in the overdose was vigabatrin alone

| Pt ID | Gender/Age | Dose of VGB | Symptoms | Outcome |
|-------------------|------------|----------------|--|--|
| 199001 | M/unk | 14gx3days | vertigo, tremor | recovered |
| VGST-MUMF-282 | F/18 | 30g | N/A | resolved, no sequelae |
| 1208-0001 | M/50 | 9g | sleepiness, partial complex status | resolved, no sequelae |
| " " | " " | 9g | seizure flurry 4 days later | resolved, no sequelae |
| 1216-0009 | M/54 | 5g/dayx5months | slowed thinking | resolved, no sequelae |
| CA06-00LC | M/32 | unk | coma | resolved, no sequelae |
| VGZ-96016-327 | F/44 | 11g | psychosis | apparently resolved with VGB taper |
| VGZ-9016-610 | unk/unk | 10g | unk | unk |
| VGZ-9108-641 | F/27 | 65g | agitation, headache vertigo, coma (intubated) | resolved, no sequelae |
| VGZ-9109-062 | F/6 | 7.5g | unk | abnormal behavior and speech disorder following the OD |
| VGZ-9300-3444 | unk/16-20 | unk | coma, apnea | recovered, no sequelae |
| VGZ-9301-5283 | F/18 | 50g | coma, bradycardia (intubated) | resolved, no sequelae |
| Literature report | M/40 | 8-12g | psychosis | resolved |
| VGZ-9400-2339 | F/16 | 22g | irritable drowsy, confused, semi-comatose | resolved, no sequelae |
| " " | " " | 15g | unk | unk |
| VGZ-9400-1341 | F/unk | 3g | none | resolved, no sequelae |
| VGZ-9400-7732 | M/7 | unk | auditory hallucinations | resolved, no sequelae |
| VGZ-9500-1544 | unk/unk | 45g | unk | unk |

Information is from sponsor table C-32

Seventeen individuals overdosed with vigabatrin and at least one other drug. The following is a listing for a few of these patients.

Patient 32731404 took 180 VGB tabs with 30-50 primidone tabs and 30-50 valproic acid tabs. The sponsor does not provided the patient's symptoms but states that he recovered.

Patient JA01-74001 took 20-30g of VGB along with carbamazepine and phenobarbital. She became comatose and her outcome is unknown.

Patient UK03-0015 took 20-30g of VGB along with acetaminophen and chlorpheniramine. His symptoms are unknown but his condition resolved without sequelae.

Patient VGZ-9400-6952 took 25g of VGB along with 7.5g of primidone and developed vomiting which resolved without sequelae.

Patient VGZ-9500-1936 took 55g of VGB with 32g of carbamazepine and 250mg of diazepam and developed coma, agitation, oliguria, irregular breathing, pupillary hippus, pulmonary infiltrates, and somnolence. These conditions resolved without sequelae.

Overdoses in the non integrated safety update (1/1/96-3/15/97)

The sponsor identified 5 individuals who overdosed on VGB during this time period. There were no reported deaths. The symptoms that these patients experienced were similar to those listed in the amendment.

There are no reported deaths from vigabatrin overdoses but outcome information is incomplete for 3 individuals. A six year old was reported to have developed permanent sequelae (behavioral and speech abnormalities) following an overdose.

4.16 Safety Protocol 071754PR0253 and Ocular Toxicity

Protocol Design

The sponsor included, as part of the amendment, data from a new safety protocol. The objective was to provide follow up information of patients who had ocular or MRI abnormalities or prolonged EP latencies after participating in VGB trials. The inclusion criteria were listed as follows:

- 1) any patient with an EP measure $\geq 15\%$ increased from baseline at that patient's last valid EP evaluation
- 2) any patient with an EP measure $\geq 15\%$ increase over baseline in two or more clinical trial protocols, even if subsequent EP measures returned to baseline
- 3) any patient with MRI abnormality suspected of being IME-related
- 4) any patient from Protocols 097-005 and 097-006 cited by FDA as requiring follow up for ophthalmological adverse events
- 5) any patient from Protocols 71754-3-C-021, 71754-3-C-024, 71754-C-025, with a change from baseline in visual acuity or visual field at last evaluation
- 6) any patient with an ophthalmological adverse event which did not resolve by completion of the last vigabatrin clinical study in which the patient participated.

Patients who met the inclusion criteria, who were located, and who agreed to participate, were given physical exams, neurological exams, ophthalmologic exams, MRIs, and EP testing. The ophthalmologic exams included tests of visual acuity, color discrimination, visual field testing, and anterior and posterior segment testing.

The information collected from this protocol was presented as part of the consultant reports. The consultants used this data in addition to information from the controlled trials, uncontrolled trials, and spontaneous reports to develop an opinion about whether or not VGB causes ocular toxicity.

Results

The abnormal test results were presented in the amendment in the CRF tabulations as well as in listings for specific tests (acuity, color, etc.). CRF's were accurately summarized in the tabulations, and there was agreement between CRF's, CRF tabulations, and the line listings.

One hundred forty six patients met the above inclusion criteria. The sponsor tested 106 of these individuals (73%; 106/146). Of those not followed up, 10 died, 9 did not give consent, 8 were lost to follow up, 9 were not tested because the site refused to comply, and 4 did not need follow up (initially identified with ocular or EP abnormalities that subsequently resolved).

Of the 106 located, 66 were male and 40 were female. The duration of exposure to VGB for patients followed up in this protocol ranged from 1.6 months to 14.6 years. Fifty-two patients were being treated with VGB when these data were collected. The sponsor did not provide a demographic profile summary of those identified but not tested in this protocol.

Of the 106 individuals tested, 76 (72%) had at least one ophthalmologic abnormality. Review of the listings identified 29% (31/106) of those tested with posterior segment abnormalities and 23% (24/104) with anterior segment abnormalities. Color vision testing abnormalities occurred in 22.7% (15/66) of the males tested and 37.5% (15/40) of females tested. The sponsor stated that these rates are higher than what would be expected as a result of congenital chromatopsia in a normal population (8% male, <0.5% female). Approximately 15% (16/106) had visual field abnormalities. Ophthalmologists classified 16% (17/106) of those tested with at least moderate visual deficits.

The sponsor gathered and reviewed follow up information for patients identified with potential eye toxicity but the usefulness of the data in evaluating eye toxicity is limited. The protocol had incomplete follow up of the identified patients. Lack of baseline data from the original protocols makes it difficult to interpret abnormal findings (increased finding of abnormal color testing results, visual field findings, posterior segment findings). Abnormalities are documented but there is no group to allow comparison and calculation of a relative risk for VGB. A potentially confounding factor identified by the sponsor is the concomitant use of anti epilepsy drugs by these patients.

4.17 Consultant Reports

The agency asked the sponsor to provide overviews of specific areas of concern that were identified during the review of the NDA. The sponsor employed several consultants to review available data for these specific areas of concern. The following is a summary of these reports.

4.17.1 Sponsor's Consultant Report of Encephalopathy

The agency requested a review of the adverse events related to encephalopathy. The sponsor hired a consultant neurologist to conduct this review. The consultant's review primarily focused on spontaneous reports. He reviewed the GADERS reports and narrative summaries (when available) for patients identified by the preferred terms coma, stupor, encephalopathy, delirium, confusion, and concentration impaired. Absent from this review were adverse events coded with the preferred term thinking abnormal. Although

this term is included under the psychiatric SOC, thinking abnormal summarized verbatim terms such as decreased calculation skills, decreased cognitive function, poor comprehension, intellectual slowing, and slow mentation. At least some of these events should be considered in a review assessing VGB's effect on level of consciousness. As part of the consultant's review, he referred to the incidences of the above listed events in the various clinical study data cohorts.

The consultant provided the opinion that 142 of the 205 cases identified from spontaneous reports with the above preferred terms were related to VGB. The consultant felt that vigabatrin was safe with respect to cognitive complications. He postulated that the enhancement of GABAergic function would carry some increased risk of cognitive impairment. He felt that the incidences of cognitive events from clinical studies was acceptably low. Lack of follow up data from spontaneous reports made it difficult to describe recovery from these events. Of those with sufficient follow up, 5% had sequelae.

4.17.2 Consultant Report of Psychiatric AE's

In response to an agency request, the sponsor hired a consultant to review psychiatric related events and provide an opinion of drug safety. The consultant began by combining preferred terms for individual psychiatric events. The preferred terms hallucination, paranoid reaction, psychosis, and schizophrenic reaction were grouped under psychosis. The preferred terms depression, depression psychotic and depression worsened were grouped under depression. The preferred terms manic reaction, euphoria, libido increased and cyclothymic reaction were grouped under manic symptoms. The preferred terms anxiety and nervousness were grouped under anxiety. Using the grouped terms, the consultant determined the incidences for these syndromes and other psychiatric adverse events. He compared the incidences between VGB exposed and placebo exposed groups in the controlled US and Primary non US controlled clinical trials. For the primary non US controlled trials, the consultant used data from the parallel design trials and from the first period for the crossover designed trials.

The consultant found a statistically significant increased frequency of depression and psychosis in the VGB patients in the controlled trials. Aggressive reaction, manic symptoms, agitation, emotional lability, anxiety, and suicide attempts occurred more frequently in the VGB treated group but did not achieve statistical significance. Because of the short duration and the continued appearance of new events throughout of the studies, the consultant was not able to identify a specific risk period for depression or psychosis. The consultant examined the seriousness of the identified cases of depression. The consultant defined cases of depression as serious if the subject was dropped from the study, was hospitalized, attempted suicide, or was coded as psychotic depression. Nine of the 49 individuals exposed to VGB and identified with depression met the consultant's criteria for a serious event (6 dropped, 3 hospitalized, 2 psychotic depression). None of the 11 subjects exposed to placebo and identified with depression met the consultant's criteria for a serious event. Through review of the case narratives, the consultant concluded that the cases of psychosis and depression that were identified were typically

mild. The consultant suggested that patients be monitored for evidence of depressed mood and psychotic symptoms during treatment with VGB.

4.17.3 Sponsor's Consultant Review of Ocular Toxicity

The agency identified potential VGB related eye toxicity as a concern during the NDA review process. In the amendment, the sponsor's consultant ophthalmologist and two neuro-ophthalmologists reviewed information from clinical studies, spontaneous reports, and the newly collected data from a safety protocol (described above). The consultants based their opinions about VGB related eye toxicity on their interpretations of these data. The sponsor arranged the eye toxicity presentation to address general ophthalmologic issues, retinal events, and visual field events. The sponsor's consulting ophthalmologist reviewed pre and post ophthalmologic tests (when available) to identify any treatment adverse ocular changes. He evaluated verbatim reports of ocular adverse events and assisted in compiling the retinal and visual field data packets reviewed by the neuro-ophthalmologists.

The sponsor stated that 331 patients with epilepsy from non US studies had "formal" pre and post treatment eye exams. The sponsor did not identify the number of these patients included in the primary data cohort. The sponsor did not identify which, if any, of the exams were performed by ophthalmologists. For US studies, the sponsor stated that 28 patients enrolled in US studies 097-005 and 097-006 had pre VGB treatment eye exams. These were the only US protocols with formal ophthalmologic testing. Other protocols collected eye exam data as part of neurological or VEP testing.

In the review of general ophthalmologic issues, the consultants did not find any ocular AE's that were definitely or probably related to VGB from controlled trials. In the safety protocol, the consultants did not identify any definite cases of VGB-induced ocular toxicity. Follow up VEP results, in the consultant's opinion, did not provide evidence of toxic effects associated with VGB. The frequency of abnormal color vision testing results from the safety protocol was higher than expected in a normal population. The consultants could not attribute these findings to VGB exposure because of lack of baseline data and possible confounding due to exposure to other anti epilepsy drugs. After reviewing non US ocular adverse events, the consultants concluded there was no definitive evidence of visual system toxicity and only possible toxicity related to the retina or optic nerve in non US studies. Consultant's review of spontaneous reports yielded similar results. The consultants postulated that VGB may have a pharmacological effect on the eye rather than a toxic effect.

In reviewing the retinal adverse events, the sponsor acknowledged that the short duration of the controlled clinical trials limited the ability to detect functional abnormalities resulting from potential toxicity. For clinical studies, one of the consultants commented that the insufficient documentation of visual adverse events made valid assessments difficult. A consultant felt that normal variants were reported as abnormalities resulting in an inflated incidence of retinal AE's for study 097-006. The consultants review of the safety protocol revealed few patients who had retinal abnormalities possibly related to

VGB. Both consultants identified 9 patients from non US studies or spontaneous reports with retinal events possibly related to VGB.

The consultants evaluated the reports of visual field constriction in 33 patients from clinical studies. One patient was identified as having an event possibly related to VGB. In reviewing the results of the safety protocol, 16 of the 106 patients tested had evidence of visual field constriction by testing. The consultants did not feel that these abnormalities were due to VGB. Upon review of visual field constriction complaints from spontaneous reports, the consultants did not feel these events were causally related to VGB.

The consultants did not identify any definite or probable cases of ocular toxicity related to VGB. They did classify several events as possibly related to the drug. Their analyses, admittedly, were limited by lack of baseline data, incomplete follow up, poor documentation of events during the clinical trials, and concomitant drug use.

4.17.4 Sponsor's Consultant Report on Hepatic Adverse Events

The agency requested that the sponsor present a consultant report reviewing the hepatic adverse events in patients exposed to VGB. The consultant reviewed the available information for each of the 21 identified hepatic serious adverse events identified in the amendment and offered an opinion about the likelihood of VGB as a cause of the event. The consultant was able to rule out VGB involvement in 2 of the 3 hepatic related deaths identified from clinical studies. The consultant reviewed the deaths and transplant case identified by spontaneous reports. Three deaths and the one transplant were felt to be either probably or probably/possibly related to VGB. The consultant did not feel that VGB was a contributing factor in the remaining 2 deaths. In the remaining serious hepatic adverse events, the consultant felt 8 were probably or probably/possibly related to VGB. The consultant felt the remaining hepatic AE case was not related to VGB.

*The consultant lists patient 31730707 as a participant in a clinical trial. The sponsor lists this patient as a non US compassionate use death. I included the patient with the spontaneous report/compassionate use group.

The consultant stated that lack of information made it difficult to determine causality. He offered the opinion that the duration of treatment prior to development of many of these events argued against VGB as the cause of hepatic toxicity. He also noted that many of these patients were taking other medications that are known to cause hepatic injury. Lack of evidence of metabolic conversion in clinical pharmacology studies was felt to be consistent with a low probability of hepatic injury.

4.17.5 Sponsor's consultant report on Pancreatitis

The sponsor was asked by the agency to include a review of the pancreatic related adverse events in the amendment. The sponsor hired a consultant to review the available material from the 5 identified cases of pancreatitis. The consultant felt that 3 cases were possibly but unlikely related to VGB. The remaining 2 cases were unlikely related to VGB. Most of

these patients had history of cholelithiasis or were taking other drugs known to cause pancreatitis.

4.17.6 Sponsor's consultant report on Cardiovascular Risk

The sponsor had a consultant cardiologist assess VGB's overall cardiovascular risk profile. He reviewed ECG tracings from protocols 097-005 and 097-006 where baseline and follow up tracings were available (n=17). He also reviewed CV AE's from placebo controlled studies, the serious cardiac AE's from the clinical safety database, and the cardiac AE's from spontaneous reports and ongoing clinical trials through 12/31/96. Using clinical data from the US trials, he assessed VGB's effect on pulse and blood pressure. The consultant found no signal of cardiovascular effect associated with VGB use (Sa-V1-P280).

The consultant reports provide useful clinical insight and opinion about risk benefit but, in general, are unable to provide additional clarification of the risk associated with VGB use. This is due, in almost all cases, to the limitations of the data available for review.

5 Summary of Key Adverse Findings

5.1 *Central Nervous System*

5.1.1 CNS

Almost 11% (48/443) of patients exposed to VGB in US epilepsy studies and 5.9% (45/765) from primary non US epilepsy studies withdrew due to CNS AE's. In controlled US studies 6.3% (14/222) of those exposed to VGB and 2.2% (3/135) of those exposed to placebo dropped out due to a CNS AE. In Canadian study 021, 8.6% (5/58) of VGB exposed subjects and 3.8% (2/53) of placebo exposed subjects discontinued due to CNS AE's. Drowsiness, fatigue, convulsions, headache, and confusion were the most common CNS AE's leading to dropout (C-17). Data from US controlled epilepsy studies demonstrate a 1.3 times greater risk of CNS related AE's in the VGB exposed group compared to the placebo exposed group. Convulsions grand mal, hyporeflexia, vertigo, parasthesias, concentration impaired, confusion, amnesia, speech disorder, and coordination abnormal were CNS AE's occurring twice as frequently in the US VGB exposed epilepsy patients compared to placebo exposed patients. In non US controlled epilepsy studies the percentage of patients classified with CNS AE's was 1.4 times greater in the VGB exposed group (appendix F-1). Drowsiness, nystagmus, amnesia, ataxia, confusion, speech disorder, and convulsions occurred approximately twice as frequently in the group exposed to VGB compared to the group exposed to placebo. The percentage of patients hospitalized for CNS AE's was similar for the VGB and placebo exposed groups from controlled US studies and for Canadian study 021.

5.1.2 Psychiatric

One of the deaths from a US study was due to suicide. Almost 7% (30/443) of patients with epilepsy exposed to VGB in US studies withdrew due to psychiatric AE's. Depression, agitation, thinking abnormal, and paranoid reaction were the most commonly

occurring psychiatric events leading to discontinuation (Table C-17). Four patients from controlled epilepsy studies in the VGB exposed group were hospitalized with psychiatric AE's compared to none in the placebo group. Data from controlled US studies demonstrate that VGB use has been associated with an increased risk of psychiatric adverse events. In these studies depression, thinking abnormal, and dreaming abnormal, occurred twice as often in VGB exposed individuals compared to placebo exposed individuals (Appendix F-1).

Almost 5% (36/765) of patients exposed to VGB in non US studies withdrew due to psychiatric AE's (table C-17). Depression, insomnia and psychosis were the most commonly occurring psychiatric events leading to discontinuation. In non US controlled epilepsy these studies, 7 patients were hospitalized for psychiatric AE's while taking VGB. The reasons for these hospitalizations were 2 suicide attempts, depression, personality disorder, psychosis, and schizophrenia. In non US controlled epilepsy studies, the percentage of patients experiencing psychiatric AE's was 1.8 times greater for the VGB exposed group compared to the placebo exposed group (Appendix F-1). Depression, anxiety, thinking abnormal, aggressive reaction, and depersonalization occurred at least twice as often in VGB exposed patients compared to placebo exposed patients.

In summary, CNS AE's were commonly observed in these studies. Patients in the VGB exposed group had a higher frequency of CNS AE's than those in the placebo exposed group. There seems to be some agreement between US and non US studies about the risk for certain CNS AE's (drowsiness, ataxia, nystagmus, speech disorder). The data from US and non US primary data cohorts indicate an increased risk for psychiatric AE's in participants exposed to VGB. The increased risk is most consistent for depression. In general the consultants acknowledged the increased level of risk associated with VGB use but felt that the risk was acceptable. The sponsor has failed to analyze the data for evidence of potential dose response relationships.

5.2 *Special Senses*

Initial concern about potential eye toxicity arose with the findings of retinal dose dependent toxicity in albino Sprague Dawley rats exposed to VGB. GABA is also known to be involved in normal inhibitory pathways present in the visual system. IME was also observed in the optic tracts in rats and dogs.

The sponsor coded ocular adverse events are under two different SOC's (CNS and Vision). The preferred term "vision abnormal" generally summarizes the verbatim terms describing blurred vision. The preferred term "eye abnormality" summarizes a variety of verbatim terms including "eyes jumping", and "glassy eye feeling".

Nystagmus, vision abnormal, diplopia, eye pain, and eye abnormality occurred more frequently in the VGB exposed individuals compared to placebo exposed subjects in both US and primary non US controlled trials.

There were three discontinuations for eye AE's from non US primary controlled trials. Two of these patients were classified with vision abnormal. One was taking VGB at the time(verbatim: blurred vision) and the other was taking placebo (verbatim: visual impairment). One patient taking VGB discontinued for eye pain.

One patient from a US controlled epilepsy trial, while in the baseline period, was hospitalized for an eye abnormality (verbatim: viral eye infection). One patient from a Non US Controlled epilepsy study, taking VGB, was hospitalized for diplopia.

Data from the primary controlled epilepsy studies alone do not provide compelling evidence of an increased risk of ocular AE's in VGB exposed patients. It would be unlikely for ocular AE's to lead to discontinuation or hospitalization unless extremely disabling so it is not surprising that these analyses did not reveal an increased risk. An assessment based on eye changes documented by exam is not possible since thorough eye examinations were not part of the protocol for most of these studies. The sponsor did not summarize the results of eye exams from non US protocols that included formal exams. In the NDA review, Dr. McCormick audited study 097-006 to look for evidence of ocular toxicity. This US uncontrolled epilepsy study included eye examinations every 6 months. Dr. McCormick listed the eye abnormalities that were discovered in patients enrolled in this study. Prominent findings included vessel narrowing, vitreous cells, retinal drusen, retinal pigment clumping, and RPE dropout (NDA review p 92).

The sponsor provided follow up for some patients who had eye abnormalities detected in the US and Canadian epilepsy studies. Follow up testing documented abnormalities in these patients but there is a lack of baseline data and potential confounding (use of concomitant anti epilepsy medications). The sponsor's consultants found alternative explanations for abnormalities in most of the patients identified.

Recently there has been interest in the possible association of VGB and visual field defects. On page 1693 of the July 7, 1997 issue of BMJ, 3 letters were published with case reports of VGB exposed patients with visual field defects. On June 27, 1997, at the request of Health Canada, the sponsor issued a "Dear Doctor" letter discussing eye related AE's (see attachments). In the letter, the sponsor refers to "reports of ophthalmologic abnormalities occurring during treatment with Sabril in situations of combination therapy or monotherapy." The sponsor lists visual field constriction, bilateral optic disc pallor, subtle peripheral retinal atrophy, and optic atrophy as specific examples of these abnormalities. Physicians in Canada were advised to perform ophthalmologic exams approximately every 3 months on patients taking VGB. These exams should include *expert* mydriatic peripheral fundus examination and visual field perimetry. In addition, the sponsor recommended that physicians question patients taking VGB *frequently* about narrowing of the field of vision or loss of visual acuity. The sponsor also made recommendations about discontinuing VGB, and the use of VGB in pediatric patients who are difficult to assess. The sponsor's recommendations in proposed US labeling are less specific.

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In studies of shorter duration, and where eye exams were not routinely performed, there is little evidence of ocular toxicity. Certain eye related complaints did occur more frequently in VGB exposed individuals than in placebo exposed individuals. Diplopia and blurred vision (coded by the preferred term "vision abnormal") are most commonly identified throughout the different data sources. In study 097-006, where ocular exams were included in the study protocol, investigators documented eye abnormalities detected by exam. Unfortunately, eye exams were performed infrequently during clinical development. Reports of visual field defects in post-marketing use have been recognized by the sponsor and have led to specific recommendations for ophthalmologic testing in Canadian patients receiving this drug. Abnormalities were documented in the new safety protocol but the sponsor's consultants could not establish a causal link between VGB and eye toxicity. The data that was available for review by the consultants was limited.

5.3 *Gastrointestinal*

5.31 Hepatic AE's

Twelve cases of hepatic toxicity (7 deaths) were summarized in the NDA review. In the amendment, the sponsor reviewed the database and discovered 21 cases of hepatic toxicity (hepatic coma, hepatocellular failure, acute liver necrosis, jaundice, and hepatic bridging fibrosis). There were 8 deaths and 1 transplant included in this group. One death was in a patient from a clinical trial who had metastatic cancer. One death, summarized in the death section, occurred in a Japanese female in an ongoing clinical study. The remaining deaths come from spontaneous reports. The US and non US databases were searched for hepatic AE's using both preferred terms and verbatim terms and did not uncover any previously unidentified serious events. One additional hepatic necrosis death was included in the non Integrated Safety Review (1/1/96-3/15/97). This death was identified by a spontaneous report.

No patients from the US controlled epilepsy studies had a recorded hepatic AE. Aside from the lab abnormalities reviewed in the laboratory section, no additional hepatic AE's were recorded for the primary non US controlled epilepsy participants. Two patients on VGB had AE's recorded for low SGPT lab results (these did not occur in the first period crossover and therefore are not in appendix F1). One US patient from an uncontrolled epilepsy study had portal triaditis listed as the verbatim for an adverse event. One non US patient from an uncontrolled epilepsy study had hepatitis (verbatim viral hepatitis) recorded as an adverse event. According to the line listings for discontinuations, no patients withdrew from US studies for a hepatic AE. One patient who withdrew from an uncontrolled non US study was found to have hepatomegaly on an ultrasound examination. Review of the hospitalization line listings for US and non US studies failed to turn up any patients hospitalized for a hepatic AE.

The bulk of the information on hepatic toxicity comes from compassionate use or post marketing spontaneous reports. Comparison of the hepatic AE deaths from spontaneous reports in the amendment to the NDA review (p.97) turned up two patients who are not found in the amendment. Patient 09223130 was listed as a death in the NDA review and is not found in the amendment. A 10 year old without an ID# is listed as a death in the NDA

review and I could not locate a corresponding patient in the amendment. The remainder of the hepatic AE's deaths and AE's from spontaneous reports in the NDA review are also presented in the amendment. The amendment also contains several new reports.

In the amendment, the sponsor identified 6 deaths due to hepatic necrosis and one liver transplant from post marketing reports in users of VGB. Using the sponsor's estimate of exposure for this time period, an incidence for hepatic failure resulting in death or transplant is 2.7 per 100,000 patient years exposure (7/254,597 patient years exposure). This rate is higher than the rate seen in normal populations. The incidence in patients taking anti epilepsy drugs, the comparator group of interest, is not known.

One additional death due to hepatic necrosis was identified by a spontaneous report in the most recent safety update. The transplant patient mentioned above was exposed for 137 days. One of the patients identified by a spontaneous report who died had been taking VGB for 4 days, and another for 270 days. The rest of the patients who died, identified by spontaneous reports, had been exposed for at least 1 year. For one of these patients, the circumstances are more compatible with hypoperfusion (patient who arrested, developed cerebral, hepatic and renal injury), but it is difficult to rule out VGB in the remaining deaths. There are 11 reports of serious AE's (patients who did not die) related to VGB in the amendment. Of these 11, except for the patient who did not relapse with re-challenge, the role of VGB cannot be dismissed. Two additional hospitalizations due to hepatic injury were identified in the most recent safety update (one from a clinical trial and the other from a post-marketing trial). Obviously, it is difficult to evaluate these hepatotoxicity cases because many of the patients (18/21 reviewed by the consultant) were taking medications with known hepatotoxic effects. Evaluation of a hepatic failure rate is difficult without appropriate comparator groups.

5.4 *Cardiovascular System*

The sponsor has presented several deaths due to cardiac events throughout the development process. In the sponsor's summary table C-8, there were 15 patients who died and had a cardiovascular event listed as a cause of death. An additional 6 cardiac related deaths were identified in the period of the latest non integrated safety update (1/1/96-3/15/97). Many of the deaths that were attributed to seizure were unwitnessed, and did not have autopsy data. It is possible that some of these deaths were due to cardiovascular events. There were no clustering of causes of cardiac related deaths. The cardiovascular events listed as causes of death include myocardial infarction, cardiac arrest, atherosclerotic heart disease, cardiogenic shock, acute heart failure, valvular cardiac failure, and ventricular fibrillation.

Cardiovascular events were not frequently associated with discontinuation in the US epilepsy (0/443) or Primary non US epilepsy clinical studies (2/765; cyanosis, hypertension). There were few VGB exposed individuals hospitalized for cardiac events. Aside from edema, cardiovascular AE's were reported with similar frequency in the vigabatrin and placebo exposed individuals in clinical studies.

The consultant found no signal of cardiovascular toxicity from a review of AE data and re-reading of ECG's from 17 patients.

5.5 *Hematologic*

There have been no deaths identified due to hematologic abnormalities through the most recent safety update. There has been one case of aplastic anemia identified in a patient exposed to VGB. This case was spontaneously reported and was discussed in the lab section. From the US and Primary Non US epilepsy studies, one patient discontinued from a study with anemia listed as an AE. Review of the lab data from controlled studies revealed a greater risk for anemia in patients exposed to VGB compared to those exposed to placebo. The sponsor presented data which was consistent with a dose dependent relationship between VGB and anemia. The anemia associated with VGB has not been well characterized and the cause has not been determined. Two VGB exposed patients discontinued from primary non US studies for leukopenia. The lab data from controlled studies suggested an increased risk for low WBC count for patients exposed to VGB compared to those exposed to placebo. There was one hospitalization for lymphadenopathy and one for purpura (localized) from the US and non US primary epilepsy studies. Purpura, anemia and lymphadenopathy were the hematologic related AE's occurring in >1% of VGB users and more frequently than in placebo patients in controlled epilepsy trials. There is no evidence that VGB exposure is associated with an increased risk of thrombocytopenia.

5.6 *Dermatologic*

There were no deaths or hospitalizations related to dermatologic abnormalities from completed US clinical studies. One patient was hospitalized for eczema and one for a burn from the primary non US studies cohort. Four patients from US clinical trials that were ongoing through 12/31/95 were hospitalized for a skin infections. One patient from a non US clinical trial ongoing through 12/31/95 was hospitalized for a generalized purpuric rash and another for urticarial rash. There was one spontaneous report of a hospitalization for erythema multiforme (discussed above). Four VGB patients withdrew from US studies and 2 from Non US studies for rash. One VGB exposed individual from a secondary study was diagnosed with erythroderma. Pruritis and sweating increased were the two dermatologic conditions occurring in at least one percent of VGB exposed patients and more frequently than in placebo exposed patients. Overall there have been few dermatologic AE's associated with VGB use and the majority of serious ones that resulted in hospitalization were infections.

5.7 *Genitourinary/Renal*

There were few kidney related AE's discontinuations or hospitalizations in VGB exposed patients. There was one patient identified with a renal calculus (discussed above). One patient from the most recent safety update was hospitalized with glomerulonephritis. Urinary incontinence was the only urinary system AE that occurred in at least 1% of VGB exposed individuals and more frequently than in the placebo exposed group in the US and

primary non US trials. The lab data revealed few patients who developed abnormalities with BUN or Creatinine. The sponsor did not summarize urinalysis results.

There were few hospitalizations for AE's associated with the female reproductive system. The reasons for these hospitalizations included ovarian cyst, cervical polyp, menstrual disorder, and ovarian pain. Dysmenorrhea, menstrual disorder, amenorrhea, and vaginitis occurred in at least one percent of those taking VGB and more frequently than in those taking placebo in the controlled clinical trials.

5.8 *Musculoskeletal*

The cases of rhabdomyolysis in VGB exposed patients that have been reviewed have been associated with status epilepticus. Five patients from US epilepsy studies withdrew for arthralgia. Arthralgia, back pain, arthrosis and myalgia occurred in at least 1% of VGB exposed individuals and more frequently than in placebo exposed individuals in controlled US and primary non US studies. There was no systematic testing for CPK in the development program.

5.9 *Metabolic Endocrine*

There were no hospitalizations attributed to metabolic or endocrine disturbances. Five VGB exposed individuals from US epilepsy studies and 1 from a primary non US epilepsy study discontinued for weight gain. One patient from a primary non US study withdrew for a thyroid disorder. Seven VGB exposed patients dropped out of secondary studies for weight gain. Weight gain occurred in almost 8% of VGB exposed individuals in controlled epilepsy trials. This was twice as often as what was observed in placebo exposed individuals.

6 *Conclusions*

VGB use in the US and primary non US patients was not associated with an increase in the crude mortality rate when compared to other recently approved anti epilepsy drugs. The deaths that occurred in VGB exposed patients were most often attributed to seizures. Patients exposed to VGB developed certain CNS and psychiatric AE's more frequently than placebo exposed individuals. Participants taking VGB were more likely to dropout of clinical studies due to AE's than individuals receiving placebo. The AE's most commonly leading to dropout were related to CNS or psychiatric complaints. CNS and Psychiatric events were the most common events leading to hospitalization of patients exposed to VGB. Reports of ocular adverse events and hepatic injury have been documented in patients that received VGB in a post-marketing setting. Analysis of lab data demonstrates a decrease in transaminases in patients exposed to VGB. Lab data also suggests that exposure to VGB is associated with an increased risk of anemia, and decrease in WBC count. The limited analysis of vital sign data indicates an association between weight gain and VGB exposure. At this time, VGB use does not appear to be associated with an increased risk of serious skin rashes, rhabdomyolysis, renal failure, or cardiac toxicity.

6.1 Suggested follow up issues:

Provide a detailed description of the use of ICS's and any other documentation other than CRF's used to develop the primary non US safety database.

Provide a combined analysis of exposure for dose and duration of therapy for patients from the US studies.

Provide a combined dose and duration of exposure analysis for the patients included in the primary non US safety database.

Resolve the conflict between an IR search and table B-27 regarding the number of individuals age 16 or younger at the time of enrollment in a primary non US study.

Develop dose dependency tables for AE's, and AE's leading to discontinuation for US and primary non US studies.

Provide an explanation of where the hospitalizations, cancers, and AE's leading to disability in patients from clinical studies that were ongoing at the time of the 120 day safety update are presented.

Present a summary of US and primary non US urinalysis and coagulation test result data.

Resolve the discrepancy for the two patients who died from hepatic adverse events that are listed in the NDA but who do not seem to be included in the amendment.

Provide an analysis of anemia with focus on assessing the cause.



Gerard Boehm, M.D., M.P.H.

Completed October 28, 1997

CC: Leber, Burkhart, Katz

my comments are in
separate memo 10/28/97
G Boehm

**Division of Neuropharmacological Drug Products
Amendment to Clinical Review of NDA : supplementary information**

NDA 20-427
Sponsor Marion Merrell Dow
Brand Name (generic) Sabril® (vigabatrin)
Indication: Antiepileptic
NDA Classification: 1S
Original Receipt Date May 2, 1994
Clinical Reviewer Cynthia G. McCormick, MD
Date Material Reviewed: April 18, 1995

The reader is referred to the original Clinical Review of NDA #20-427 dated March 5, 1995. Since the completion of the clinical review (which was both preceded and followed by numerous teleconferences with the sponsor) new information has been submitted. The purpose of these teleconferences was to attempt to fully understand the nature of the safety data, to clarify the lack information about dropouts, and to determine if the perceived deficiencies were real or not. In the new submission, the sponsor refers specifically to teleconferences on March 14, 24 and April 3, 1995 in which very specific and probing questions were raised regarding the status of dropouts from the non-US CRF studies. The sponsor has attempted to respond to these questions after having gone back to the individual study databases (which, from the previous discussions with the sponsor, were in part derived from case reports as well as investigator comments) for information. In so doing, the sponsor has, as suggested in one of the teleconferences, accounted for all patients who entered MMD sponsored CRF studies as either completers and dropouts, and if dropouts, categorized them as to the cause.

The sponsor, then, has provided the FDA with a new table of dropouts "Table 1: Summary of Study Termination Information for Vigabatrin patients Participating in non-US CRF processed studies". The total number of patients participating in this cohort is 1312 patients with 1234 of these having received vigabatrin. The table on the following page shows the original tabulation in column 1 and the "revised" tabulation in column 2.

Some clarification of these numbers is indicated. In the original NDA and Safety

Update, the tabulations were given for the NonUS Epilepsy CRF combined with the US Non Epilepsy Population (N=1327). The new tabulations are given only for the nonUS Epilepsy CRF studies, leaving questions about the US nonEpilepsy studies unanswered, as before. Nevertheless, the numbers of total participants differs from the original table because the 94 patients involved in US nonEpilepsy studies are not included. (Total (1327) - Us nonEpilepsy (94) =1233 (NonUS CRF). There is one more patient in the new listing (N=1234) than was previously reported (N=1233) because, as explained by the sponsor, a patient who was originally thought to have dropped out before receiving vigabatrin was later learned to have received one day of vigabatrin treatment.

**FDA TABLE SUMMARIZING DROPOUTS FROM NONUS CRF DATABASE
(ORIGINAL AND REVISED)**

| REASON FOR DROPOUT | NonUS CRF studies Original data N=1233 | NonUS CRF studies Revised data 4/14/95 N=1234 |
|--------------------|--|---|
| Lack of Efficacy | unk | 201 (16.3%) |
| Lost to Follow-up | unk | 29 (2.4%) |
| Adverse Event | 110 (8.3%) | 127 (10.3%) |
| Death | 10 (.8%) | 10 (.8%) |
| Other | unk | 38% (3.1%) |
| Total Dropouts | unk | 405 (32.8%) |
| Total Completers | unk | 827 (67.2%) |

As the table shows, there are 17 more patients reported with withdrawal due to adverse events than were originally reported. Of these the sponsor enumerates 12 for which the investigator has indicated in his comments that the reason for discontinuation was an adverse event, but the adverse event was not listed in the database as the reason for discontinuation. These include such adverse events as increased aggression, depression, allergy, hyperkinesis, ataxia, and weight gain. The second look into the ICS database by the sponsor also revealed two dropouts associated with severe adverse events, that is, in one case, depression associated with overdose of medication (details unavailable), and a second with *status epilepticus*. A third patient was also noted to have dropped out with a history of increased aggression, however neither the investigator's notes nor the data entry

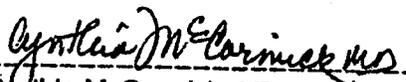
confirmed this as the cause for dropping out.

This information was obtained by a careful look through the individual study databases for very specific information. The sponsor does not indicate whether the original case report forms were reviewed. Equally important information such as hospitalizations, serious adverse events should have been searched as carefully. However absent the original data the completeness of this information is still questionable.

The lack of accurate transcription of data from primary sources and therefore inadequate reporting of adverse event data is not addressed by this new submission and remains a problem in interpreting the sponsors safety reports. If the experience with the US data retrieval (specifically in studies 097-005/6 and C-025) is any indication of what is available from the European studies, there is potentially important information buried in the case report forms which may never be evaluated.

The original concerns of this reviewer regarding the safety evaluation of this drug by the sponsor have not been alleviated. This submission can be viewed as one step toward clarifying the overall categorization of safety data, however the specific elements of the safety analysis of vigabatrin are still lacking. While we appear now to have a more careful accounting of patients in one of the data sets (nonUS CRF), there is still lacking an overall integrated analysis of safety as well as more specifically serious safety events including hospitalizations, collection of certain standard laboratory and EKG parameters. Had the total accounting for dropouts been the only deficiency in this NDA safety database, this new submission would have been one step towards answering that deficiency. However, that was not the case, nor would it likely have been the only reason to recommend that the drug be declined. The deficiencies in this NDA probing this drug's safety as defined by this reviewer included 1) failure to collect normal data on a large cohort of exposed patients, 2) evidence for flaws in the integrity and completeness of the data 3) inaccuracies in reporting the data that is available 4) failure to probe important clinical safety information and follow up abnormal results and 5) failure to adequately analyze important elements of the safety data base. In my opinion, these deficiencies remain.

Recommendation: This NDA should be deemed not Approvable by virtue of the fact that the sponsor has not adequately established this drug's safety.



Cynthia McCormick, MD
Clinical Reviewer

**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
CLINICAL REVIEW OF NDA**

| | |
|---------------------------------|---------------------------------|
| Brand Name (generic) | Sabril® (vigabatrin) |
| Indication: | Antiepileptic |
| NDA Classification: | 1S |
| Original Receipt Date | May 2, 1994 |
| Clinical Reviewer | Cynthia G. McCormick, MD |
| Review Completed | March 5, 1995 |

SECTION 1.0 BACKGROUND

Vigabatrin is a new molecular entity developed by Marion Merrell Dow for the treatment of epilepsy. The history of the drug's development is summarized below.

Administrative History

| | |
|---------------|---|
| February 1980 | The original IND #17,213 was filed with FDA for the study of patients with epilepsy. Development proceeded uneventfully until animal findings of intramyelinic edema were reported. |
| July 1983 | FDA requested halt in patient enrollment in ongoing clinical trials because of animal toxicology findings of IME. CLINICAL HOLD was imposed on the development of this compound after careful deliberation. Following this decision, the first of three advisory committee meetings was initiated to deliberate on the safety profile of gamma vinyl GABA. |
| March 1984 | Permission to begin new trial denied by FDA; Patients already receiving vigabatrin were allowed to continue. |
| May 1984 | FDA Advisory Committee met and concluded that additional clinical testing could eventually proceed if Sponsor agreed to conduct preclinical toxicologic investigations designed to develop a means to detect vacuolar pathology at early stages of development. A |

comprehensive program of animal toxicological testing was to be carried out. It was further stipulated that all clinical testing would halt and the Advisory Committee reconvened if any vacuolar changes were detected in the interim sacrifice in a then ongoing monkey study.

May 1985

FDA requested meeting to discuss preclinical characterization of the toxicity of vigabatrin.

June 1985

Meeting held at FDA to discuss current animal testing and foreign human experience with vigabatrin, in efforts to resume domestic human studies that had been placed on hold by the Agency.

October 1985

FDA Advisory Committee reconvened because of positive results in interim sacrifice in monkey study. The committee recommends that no new human subjects be entered into clinical trials until safety issues (IME) are resolved.

November 1985

FDA letter received outlining FDA's action on the recommendations of the October 1985 Advisory Committee meeting. Specifically, patients currently receiving drug may continue; further clinical testing may not proceed until you are able to develop and validate a method to detect the earliest pathological changes in animal, demonstrate that these changes are reversible and provide for appropriate protocol amendments that will adequately provide for the safety of human subjects; compassionate use will not be allowed at this time.

Development proceeded in Europe. The efficacy studies conducted in Europe were small crossover studies, although it can be said that there was the suggestion even from these studies that the drug had potential efficacy as an antiepileptic.

January 1987

Informal meeting with the FDA to discuss redⁿg clinical trials with vigabatrin in resistant epilepsy in the US.

December 1988

Sections of the European Marketing Approval Application (MAA) and a proposed US study protocol

are submitted to the FDA with the request that clinical trials resume.

| | |
|--------------------------|---|
| November 1989 | FDA Advisory Committee recommends resumption of US clinical trials with neurological monitoring. |
| December 1989 Ireland | Vigabatrin's first approvals for marketing in UK and Ireland |
| April 1990 | CLINICAL HOLD officially lifted |
| September 1990 | Clinical development in the US resumed |
| January 1993 | Pre-NDA meeting was held at FDA to review animal safety relevant to IME, discuss new clinical data, and style and format of NDA. |
| July 1993 | Pre-NDA CMC meeting was held at FDA to present and discuss specific NDA issues (ie, optical isomers, environmental assessment) as well as the content and format of the ADME section. |
| August 1993 | Agreement with FDA to perform optical rotation measurements of drug product from 2-3 long-term stability batches. This would be a one-time event and not a specification for drug product. |
| May 1994 | NDA #20-427 submitted to FDA. |

b(4)

Foreign marketing

Vigabatrin 500 mg tablet was approved for marketing in 31 countries as of January 1994. A sachet dosage form (dry powder in 0.5 g, 1 g, 2 g, or 3 g packets) is also marketed in some of these countries.

| | |
|----------------|-------------------|
| December 1989 | Ireland, UK |
| April 1990 | France |
| September 1990 | Denmark, Portugal |
| October 1990 | Netherlands |
| November 1990 | Italy, Sweden |
| April 1991 | Belgium |
| August 1991 | Argentina |
| September 1991 | Luxembourg |
| October 1991 | Austria, Spain |

| | |
|----------------|------------------|
| November 1991 | Hong Kong |
| December 1991 | Brazil, Germany |
| January 1992 | Kuwait, Finland |
| February 1992 | Cyprus |
| June 1992 | Switzerland |
| August 1992 | Bahrain, Iceland |
| September 1992 | New Zealand |
| November 1992 | Israel, Greece |
| January 1993 | Tunisia |
| February 1993 | Korea, Paraguay |
| November 1993 | Qatar |
| December 1993 | Mexico |
| January 1994 | Canada |

SECTION 2.0 MATERIAL REVIEWED

NDA and Safety Update

The primary document for review was the main body of the NDA volumes 1.1 a,b and 1.90 to 1.507, the Clinical Section and volumes 2.1-2.256 containing the case report forms for the two US pivotal studies. The NDA contained detailed information about the two pivotal US studies, as well as summary information regarding the small European efficacy studies, some controlled, some uncontrolled. Safety data from four sources was presented, in summary form in the integrated summary of Safety as well as the Safety Update volumes 6.1-6.117, volumes 10.1-10.12 and 12.1-3 which contained data on evoked potentials..

CANDA

The CANDA consisted of two parts, the ONDA which was an identical copy of the NDA but on optical disc and the ENDA, which was a relational database on which were entered all adverse events reported to the NDA with correlating information regarding dose, exposure data (if available) time on drug to adverse event, response to adverse event, deaths, hospitalizations, withdrawals. etc. It provided a more focused avenue to obtain specific safety data than the NDA itself, and was a useful adjunct to review, if not a primary tool during much of the review period. Its drawbacks were in the data entry, such that data on specific topics were not readily retrievable through just one query, such as deaths, which yielded 27 patients from the combined NDA and SU, where there were actually 37 deaths in that group.

Dates corresponding to the various parts of the NA are shown below.

| Document | Filed | Cutoff Date for Data |
|---------------|-----------|----------------------|
| NDA | 5/2/1993 | 2/28/1993 |
| Safety Update | 4/29/1994 | 3/15/1994 |

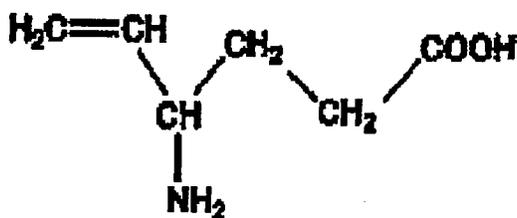
Existing IND (17,213) safety reports and annual reports, and the transcripts of the three advisory committee meetings held to discuss the safety profile of this drug were also reviewed.

SECTION 3.0 CHEMISTRY

Drug Substance:

Vigabatrin is a white to off-white powder, freely soluble in water. The pH of a 1% aqueous solution is about 6.9. Vigabatrin is stable when stored for up to 5 years at ambient room temperature conditions ($23 \pm 2^\circ\text{C}$).

The structure of vigabatrin is chemically based on gamma-aminobutyric acid (GABA).



Vigabatrin exists in the solid state as a zwitterionic racemate. Its crystal contains equal amounts of the two enantiomers.

Chemical names: 4-amino-5-hexanoic acid; (\pm)-4-amino-5-hexanoic acid

Generic name: Vigabatrin

Proprietary name: Sabril®

Synonyms: VG, GVG, VGB, Vinyl GABA

Empirical formula: $\text{C}_6\text{H}_{11}\text{NO}_2$

Molecular weight: 129.16

Drug Product:

Sabril® tablets are white film-coated, debossed with SABRIL on one side and scored in half on the other side. Each tablet contains 500 mg of vigabatrin.

SECTION 4.0 PHARMACOLOGY

4.1 Preclinical Pharmacology

Vigabatrin causes an irreversible inhibition of GABA-transaminase (GABA-t) *in vitro*. *In vivo*, single doses of vigabatrin given orally or parenterally to animals produce a dose-dependent inhibition of GABA-t and a dose-dependent increase in brain GABA levels with a peak effect 4 to 6 hours after dosing. Increases in brain GABA are maintained for several hours after which they decrease slowly. With chronic administration of vigabatrin, brain GABA levels increase gradually to steady-state. CSF levels of total GABA appear to correlate well with brain GABA concentration.

Animal models of epilepsy:

Vigabatrin causes suppression of seizures in complex partial models (kindling, pilocarpine) and generalized tonic-clonic seizure models (audiogenic, photic, seizure-prone gerbil, hyperbaric oxygen, maximal electroshock, and chemically-induced models). Vigabatrin had both proconvulsant and anticonvulsant effects on generalized absence model (seizure prone rats). Seizure symptoms were exacerbated after electrical stimulation of the spinal cord. These results suggest that vigabatrin may be effective in generalized and partial complex seizures. The anticonvulsant effect of vigabatrin was potentiated by glycine.

Vigabatrin does not appear to be selective for seizures evoked by agents known to interfere with the GABAergic system. In fact, in many of the seizure models evaluated there was no obvious correlation between maximal increases in brain total GABA levels and seizure protection. In analogy with these results, other GABA-t inhibitors causing sustained elevations in brain GABA levels do not have the same anti-seizure profile as vigabatrin. The ability of vigabatrin to block seizure activity is thought to be linked to specific brain areas and may require redistribution of GABA. However, this is only speculative. The mechanism of action of vigabatrin in controlling seizures is not actually known.

Animal Toxicology:

The following positive findings will be discussed at length by the pharmacology reviewer. Selective summary is provided below.

IME

Intramyelinic edema (microvacuolation) in the brain has been a consistent histopathologic finding in mice, rats, dogs, and to a lesser extent, monkeys. It is most notable in certain areas of white matter (cerebellum, reticular formation and optic tract in rats, and thalamus, hypothalamus, columns of fornix and optic tract in dogs). In the rat, microvacuolation was observed after 6 months of treatment with

100 mg/kg vigabatrin and at 30 mg/kg/day after 12 months. Withdrawal of rats from treatment for 3 months resulted in regression of the microvacuolation. In dogs it took approximately 4 weeks for microvacuolation to develop at doses of 300 mg/kg/day or at low 50 mg/kg/day after one year of treatment. While no residual effects were observed in dogs, in rodents swollen axons (spheroids) and microscopic mineralized bodies persisted in the cerebellum. It was much more difficult to demonstrate the lesions in monkey and it is thought that this may be related to poor oral absorption in this species.

Evoked potentials and magnetic resonance imaging (MRI) were studied as noninvasive techniques for detecting intramyelinic edema in dog. Increased central latencies (SERs) and cortical onset latency of the flash VEPs have been observed after 4-8 weeks of treatment with 300 mg/kg/day of vigabatrin. Data in dogs indicate that MRI is also capable of detecting the intramyelinic edema and may be nearly as sensitive as evoked potentials.

Retinal Degeneration

Retinal degeneration has been observed in albino rats after prolonged administration of vigabatrin, however, this same effect has not been observed in any pigmented species.

Teratogenicity

Toxicity studies were conducted to evaluate the effect of vigabatrin on fertility, teratology, and peri/postnatal development. Reduced fetal weight and a low incidence of cleft palate was noted in rabbit teratology studies at maternally toxic doses (body weight loss, resorption) of 150 and 200 mg/kg/day. In the offspring of rats exposed to vigabatrin (100-150 mg/kg/day) in utero, histopathological examination at maturity revealed very mild brain microvacuolation at all doses. There was no indication that myelin development was otherwise adversely affected.

Miscellaneous

Vigabatrin was not genotoxic in a battery of mutagenicity tests and was not thought to be carcinogenic in the mouse or rat.

SECTION 5.0 PROPOSED INDICATIONS-DOSAGE FORM-ROUTE OF ADMINISTRATION

Vigabatrin is an antiepileptic drug available in 500 mg tablets for oral administration. It is proposed for the treatment of partial complex seizures with secondary generalization. Doses studied were 1g, 3g and 6g. The maximum proposed labeling dose is 6g.

SECTION 6.0 CLINICAL DATA SOURCES

6.1 Clinical Development Program

Primary Development Program

Most of the premarketing development of vigabatrin took place outside of the US during which time the drug was on clinical HOLD in the US. The formal program has consisted of clinical pharmacology studies in the US and outside the US in which a total of 348 subjects were enrolled, 15 controlled clinical studies (all but 2 were nonUS), and a large number of long term open label clinical studies. The exact number of clinical studies in this NDA is not known. Innumerable small open label studies were performed some without protocols others with very informal record keeping. The firm has attempted to reconstruct a database from much of this material. It will be discussed below. There have also been 37 nonepilepsy studies (nine controlled and 28 uncontrolled). These included studies of tardive dyskinesia, psychiatric disorders, Huntington's disease, spasticity, Parkinson's disease (levodopa-induced dyskinesia), Parkinson's disease (untreated), blepharospasm, ataxia and tremor, dystonia and torticollis, and tinnitus. Only those studies which were performed in the US were "IND" studies (N=537).¹

The total 537, noted above, reflecting those patients who received vigabatrin in "IND" or US studies includes all epilepsy controlled trials (222 patients received drug) and epilepsy uncontrolled studies (443 patients received drug), pharmacokinetics studies (66 subjects or patients)² and patients who were enrolled in US non Epilepsy studies (28 patients)³ under the IND. The firm indicates that there are 193 patients who received vigabatrin in both controlled and uncontrolled epilepsy studies.⁴ The firm also quotes a total of 324⁵ patients from the two US controlled studies who

¹This information was obtained verbally during a telecon with the sponsor on March 2, 1995. The number 537, found in the NDA volume 6.3 page 9-459 is given as the number of patients/subjects in the US studies who received vigabatrin.

²NDA, volume 6.3, p. 9-460

³NDA, volume 6.3, p.9-467

⁴NDA volume 6.3, 9-459

⁵NDA, volume 6.3, p 9-455

continued into the long term US uncontrolled follow-up studies. A total of 353⁶ patients were exposed to vigabatrin in the controlled studies (C024 and C025) and in the uncontrolled one year follow-up studies (C020 and C026) and are broken down as follows:

| N | <u>Study</u> |
|----------|--|
| 29 | Patients were exposed to vigabatrin in C024 and C025 and did not continue into extended treatment C020 or C026 |
| 193 | Patients were exposed to vigabatrin in both C024 and C020 (controlled and uncontrolled epilepsy, respectively) and C025 and C026 (controlled and uncontrolled, respectively) |
| 131 | Patients were exposed to vigabatrin in C020 or C026 (uncontrolled epilepsy studies) alone (placebo exposures from C024 or C025) |
| 353 | Total exposures to vigabatrin from four trials |
| 90 | <u>Patients from open label studies 097-005 and 097-006⁷</u> |
| 443 | Total number of patients in epilepsy studies in the US |

The 28 patients in nonEpilepsy studies and the 66 patients or subjects from PK studies added will total 537. This represents all patients who were studied under the IND.

| | |
|----------------------------------|------------|
| Patients in Epilepsy studies | 443 |
| Patients from PK studies | 66 |
| <u>Patients from nonEpilepsy</u> | <u>+28</u> |
| Total exposed | 537 |

The table on the next page displays the number of patients and subjects who have participated in each group of studies, and of these, how many received vigabatrin, and how many received placebo.

⁶NDA. vol 6.3 p.9-556

⁷NDA volume 6.3, p.9-465 Table 9-6

| SUMMARY OF ALL STUDIES | | |
|---|---------------------------------------|-------------------------|
| Pools by Study Design | Enumeration by Treatment Group | |
| | Vigabatrin | Placebo |
| PHASE I (CLINICAL PHARMACOLOGY)⁸ | | |
| <i>US</i> | 66 | |
| <i>Non US</i> | 282 | |
| SUBTOTAL | 348 | |
| PHASES 2-3 (ALL STUDIES) | | |
| PLACEBO CONTROLLED (Epilepsy)⁹ | | |
| <i>US Studies</i> | 222 | 135 |
| <i>Non US Studies</i> | 415 | 257 ¹⁰ |
| SUBTOTAL | 637 | 492¹¹ |
| UNCONTROLLED (Epilepsy)¹² | | |
| <i>US Studies</i> | 414 | N/A |
| <i>Non US Studies</i> | 1893 | N/A |
| SUBTOTAL | 2307 | N/A |
| CONTROLLED OR UNCONTROLLED (non Epilepsy)¹³ | | |
| <i>US Studies</i> | 28 | N/A |
| <i>Non US Studies</i> | 263 | N/A |
| SUBTOTAL | 291 | N/A |
| GRAND TOTAL | 3320 | 492 |

⁸NDA volume 6.3, p. 9-460

⁹Safety Update vol 6.3, p.9-46, text and p.9-464 Table 9-6

¹⁰This number includes patients in 9 nonUS ARF studies in which there were two period crossover design. Therefore a number of patients in this group received vigabatrin also.

¹¹This number includes patients in 9 nonUS ARF studies in which there were two period crossover design. Therefore a number of patients in this group received vigabatrin also.

¹²Safety Update vol 6.3, p.9-463

¹³NDA, vol. 6.3, p.9-467

The sponsor has provided a completely unique breakdown of the data in this NDA according to the sources of information, and how the data was processed, and this organization has been retained throughout the safety portion of the NDA. This will be explained in detail in the pages that follow. To begin, the Sponsor's table below outlines the various groupings of data and the numbers of patients found in each category.

| Table 9-4. Summary of All Subjects/Patients in All Clinical Studies: Clinical Pharmacology and Pharmacokinetics, Controlled and Uncontrolled Epilepsy, and Neurological Conditions Other Than Epilepsy | | | | | | | |
|--|--------------|-----------------|--------------|-----------------|--------------|-----------------|--------------|
| Location | CRF/ARF | NDA | | NEW | | NDA+NEW | |
| | | Total† Patients | VGB Patients | Total† Patients | VGB Patients | Total† Patients | VGB Patients |
| US | CRF | 540 | 406 | 324 | 324 | 540 | 537 |
| | Total US | 540 | 406 | 324 | 324 | 540 | 537 |
| Non-US | CRF | 959 | 948 | 353 | 285 | 1312 | 1233 |
| | ARF | 1361 | 1332 | 428 | 428 | 1789 | 1760 |
| | Total Non-US | 2105 | 2070 | 781 | 713 | 2886 | 2783 |
| Total | | 2645 | 2476 | 1105 | 1037 | 3426 | 3320 |
| Supporting Data: | | | | | | | |
| | | | | | | Page, Vol | |
| Appendix A1: Summary 1, Extent of Exposure and Demographics in Clinical Pharmacology and Pharmacokinetic Studies | | | | | | 9-995, v3.4 | |
| Appendix A1: Summary 2, Extent of Exposure and Demographics in Epilepsy Studies | | | | | | 9-997, v3.4 | |
| Appendix A1: Summary 3, Extent of Exposure and Demographics in Neurological Conditions Other Than Epilepsy | | | | | | 9-1001, v3.4 | |
| Appendix A2: Listing 1, Exposure and Demographic Information by Study and Patient | | | | | | 9-1006, v3.4 | |
| † Includes patients exposed to vigabatrin and patients receiving placebo or other active medication. | | | | | | | |

The sponsor has divided the clinical data into three groups, : the US epilepsy trials (controlled and Uncontrolled), nonUS CRF and US nonEpilepsy CRF studies, and finally ARF studies. There is actually a fourth group in the premarketing program, that of compassionate use. These will be described below. However, the data in the clinical portion of this NDA is of actually of two types: (*reviewer's distinction*) **primary**, data collected as part of studies via case report forms, and **secondary or tertiary**, data transcribed from various sources to abbreviated reporting forms, individual case study forms, and case report forms (*reviewer's distinction*).

Group 1 US Epilepsy-Controlled and Uncontrolled (N=443)
type of studies

In this grouping there are two placebo controlled efficacy studies : C024 and C025, and four open label extension or primary safety studies (US Studies C020, C026, 097-005 and 097-006). The total number of patients accounted for by this group (and exposed to vigabatrin) is 443. The PK and non

Epilepsy studies are not included in this group by the sponsor.

nature of data

These are studies in which safety and/or efficacy data is prospectively collected in case report forms and the data for collection was designated by protocol. This data remains in its original form and the case report forms are available for review.

Group 2 nonUS CRF studies and US non Epilepsy studies (N=1327)

type of studies:

This group includes four nonUS controlled epilepsy studies (small, crossover design, generally), numerous nonUS safety studies and the 37 non epilepsy studies including those from the 4 US studies (28 US patients) and the US Pharmacokinetics studies (66 US patients) noted previously. The sponsor has not been able to recall¹⁴ why the US non Epilepsy studies and the non US CRF studies have been combined in this way.

nature of data

In all US non epilepsy studies (N=94) and in some nonUS studies data was entered directly onto a protocol-specified CRF (case report form). However, in some nonUS studies, an Individual Case Study (ICS) was prepared from *either* a case report form *or* other information available from the investigator.¹⁵ While the sponsor describes the origin of these ICS forms in two different locations in the NDA¹⁶ and is internally consistent, the MMD staff have indicated that all of the ICS forms originated from CRFs.¹⁷ This disparity cannot be resolved by this reviewer.

The firm asserts that the process of filling out the ICS was in some cases contemporaneous with the conduct of the study, but cannot estimate the percent of the data collection was contemporaneous.¹⁸ Furthermore, this reviewer has no way of knowing when these transcriptions took place, whether the investigator was still blinded¹⁹ when the data were transcribed and whether the information was altered in any way when it was transcribed. Since the ICS

¹⁴Telecon with firm on February 28 and March 2

¹⁵Safety Update, NDA volume 6.3, p9-450

¹⁶NDA vol. 1.201 p.8-36854 and vol. 6.3 p.9-450

¹⁷Telecon with MMD on March 14, 1995

¹⁸Telecon with MMD on March 14, 1995. RKatz, CMcCormick, RPitts, GHeilman, KWhite, and SRook

¹⁹While most of the studies in this group were open label studies, some were double blind.

studies were transcribed onto specially designed new case record forms, it appears that only that information that was required by the form was captured. An unknown to this reviewer is the following: if the CRF contained information that was not required by the form, was it not captured in the transformation? Conversely, if there was information needed for the form that was not in the CRF, the information was obtained from the investigator through medical records or other sources. The investigator then signed the form and returned it to MMD for data entry.²⁰

The ICS studies can sometimes be identified in the NDA by "ICS" and/or "OLD VIGABATRIN DATA RE-PROCESSED FOR THE SAS SAFETY DATABASE" . The proportion of studies in which the data was handled in this manner was (639/1233) 51% of the nonUS "CRF" database.²¹ The remainder of the studies, presumably had only prospectively designated data collected in case report forms. ICS studies gathered information on adverse events, "causality" as interpreted by the individual investigator, dropouts, deaths, but *not* serious adverse events and hospitalizations. The original case report forms for most of the studies are not available for independent review.

The firm has been unable on numerous occasions to explain why in some cases the data were removed from CRFs and transferred to ICS forms and in other cases retained on their original forms.

Group 3 nonUS ARF studies (N=1760 (est))

type of studies

This group includes nine of the nonUS controlled epilepsy studies, including one with no protocol, several in whom protocol was not adhered to, numerous non protocol studies carried out by individual investigators, as well as compassionate use.

nature of data

A number of non-US studies did not have data collected into a prospective database. Retrospectively, then, adverse event data was gathered from either clinical study reports, publications or manuscripts which served as a substitute for study reports, or in some cases from actual case report forms. The sponsor attempted to reconstruct a database from this information. The data was transcribed onto ARF's (Abbreviated Adverse Report Forms) so that the data could be entered into a protocol-specific database. The data in the ARF may include some or all of the following: protocol number, investigator name, patient ID, age, gender, description of adverse event, name of study

²⁰Telecon with MMD on March 14, 1995

²¹Telecon with MMD March 2, 1995

medication, and whether the patient withdrew because of a given adverse event. No information regarding outcome of adverse events, duration of treatment or dose is required or was captured in many cases. The only distinction between an ICS-CRF study and an ARF study is in the information on investigator-assigned causality which was only captured in the ICS studies.²² This reviewer, in an effort to better understand the nature of the data, queried the sponsor during a telecon March 2, 1995 whether most of the ARF data was passively collected or obtained during studies via protocol. The sponsor indicated in a telecon on March 2, 1995 that "most ARF data was passively collected and that some of the reports were from studies which had no protocol."

The firm has indicated more recently that approximately 75%²³ of the ARF data had some origin in CRFs. When asked why the ARFs were created, the firm responded that "many of the ARF studies are old and the data was not in an accessible database. The volume of data dictated that we could not reopen every CRF in these older studies in a reasonable time to collect efficacy and other data which would ultimately not be used. A decision was made to collect adverse event data from the bulk of these studies for the safety database. Since the adverse event data was summarized in the study reports, the ARFs were generated from the reports."²⁴

The data for this cohort is therefore tertiary (extracted then extracted and transcribed) and in many cases retrospectively collected. There is no certainty that the denominator of 1766 is an accurate one, but it represents the sponsor's best effort to obtain a handle on premarketing exposure in a retrospective manner. In these cases the original CRFs are not provided (even though they might have existed in some cases) but narrative summaries are provided where appropriate.

***Group 4 nonUS Compassionate use N=unknown
type of studies:***

While many of the patients in Group 3 could be considered compassionate use patients, there is a separate category of compassionate use designated by the firm. The difference between this group and group 3 is not clear.

nature of the data:

²²Telecon February 28 and March 2, 1995..

²³Telecon with MMD on March 14, 1995

²⁴Sponsor's notes from telecon with FDA on March 2, 1995 and faxed to FDA on March 14, 1994

This is premarketing exposure, in which only adverse event data is collected, passively. In many ways it resembles a postmarketing surveillance cohort. The data is limited in its information about dose, duration, demographics, and even descriptions about adverse events. There is absolutely no good estimate on the number of patients in this group. The firm handles these reports in much the same way it handles postmarketing surveillance (see below). The data presented by this portion of the data base can be said to be transcribed, largely, from various sources, including studies, manuscripts, publications, case reports.

In the sponsor's summaries, the above groups are always reported separately. For both convenience and integrity of data the same dichotomy will be used in this review, particularly for development of safety profiles. The core of the primary development program, however, would appear to be the US Controlled and Uncontrolled epilepsy studies (443 patients), some 51% of the nonUS CRF studies (639 patients) and patients enrolled in US nonEpilepsy studies (28 patients) for whom case report forms were collected. It is in this fraction of the entire exposed population which clinical safety and efficacy data were carefully collected in a prospective manner. It is estimated by this reviewer that prospective contemporaneous data, then, is available for 1110 patients. This is not the same grouping, however used by the firm in displaying its analyses of exposure, demographics and adverse events. Nor is it readily separated out of the huge mass of exposure and adverse event data.

Secondary Sources

NonUS Compassionate Use:

While these are actually grouped by the sponsor along with postmarketing surveillance they are actually premarketing exposures (see above). The data, however, is retrospective, passively collected adverse event data for which there is no accurate denominator. In this way it bears such similarity to postmarketing surveillance data that in the sponsor's summaries, it is usually not included with the other premarketing exposures.

There are actually two sources of compassionate use data. The first is the *nonUS compassionate experience* in which safety data are gathered from the compassionate programs conducted in Europe, Australia, and Canada for intractable patients with epilepsy or other conditions. The second source was the *non-protocol data from pharmacovigilance report*. "Tolerability and Efficacy of Vigabatrin in Europe, 1987, Pharmacovigilance report" was a summary of the European safety data to that time. Most of the report is included in clinical study reports but some patients continued to use vigabatrin compassionately following completion of certain studies. Some of the patients in this report were never in a clinical study and so they were given the drug on a "compassionate" basis. Those patients who continued compassionately or

who were never in a study are included in this "Compassionate Use group". Unlike the premarketing safety studies in which safety data is collected by prospectively designated criteria over time, this merely represents passive reporting of adverse events.

Postmarketing Surveillance:

Estimated postmarketing estimates of exposure are 200,000 patient years on drug. This is a typical postmarketing passive reporting system. Serious adverse events are reported to the sponsor using the MMD Global Adverse Event Reporting System (GADERS) which contains all adverse events from clinical studies and postmarketing spontaneous adverse reporting worldwide.

The table below summarizes the sources and nature of data contained in the vigabatrin development program contained in this NDA.

Summary of Data Sources in Primary Development Program of Vigabatrin

| <i>Data Group</i> | <i>Nature of Data</i> | <i>N</i> |
|--|---|----------------------------------|
| <i>US Epilepsy</i> | <i>Prospective, primary</i> | <i>443</i> |
| <i>NonUS CRF US nonEpilepsy</i> | <i>Prospective, primary</i> | <i>594 +28</i> |
| <i>NonUS ICS->CRF</i> | <i>uncertain, secondary</i> | <i>639</i> |
| <i>NonUS ARF</i> | <i>Retrospective, secondary</i> | <i>1760</i> |
| <i>NonUS Compassionate</i> | <i>Retrospective, primary and secondary</i> | <i>unk</i> |
| <i>Postmarketing Surveillance (GADERS)</i> | <i>Retrospective, primary</i> | <i>>2x 10⁵</i> |

In summary, the core of data which was prospectively collected and submitted in primary form is estimated to be 1110. The Sponsor's groupings will be used for the purposes of review with the knowledge of their limitations.

6.2 Demographics

Gender and age were the only two demographic variables consistently collected in all US and non US studies. Race and weight were not available in a majority of non-US studies.

Overall Population

Not all of the 3320 patients who participated in premarketing vigabatrin studies and other programs only demographic data collected. Of those who did 1811(57 %) were

male and 1404 (35 %) were female; 791 (94 %) were caucasian, 28 (3 %) were black and 28 (3 %) were "other". The demographic distributions by study groupings for which there is data can be found in the following two tables. The first table displays the demographic breakdown in the phase 1 studies.

| Demographic Profile for Phase 1 Studies | | | |
|---|-----------------------------|-------------------------------------|----------------|
| | Epilepsy Patients (N=35) | Non Epilepsy Subjects (N=313) | Total N=348 |
| AGE | | | |
| Mean (yrs) | 32 ±10.2 | 34±19.6 | 34 |
| <18 | 3 (9%) | 0(0%) | 3 (<.1%) |
| 18-65 yrs | 32 (91%) | 260 (90%) | 292 (90%) |
| >65 yrs | 0 (0%) | 29(10%) | 29 (9%) |
| Unknown | 0 | 24 | 24 |
| SEX (%) | | | |
| Male | 20(57%) | 282 (90%) | 302 (87%) |
| Female | 15(43%) | 31 (10%) | 36 (13%) |
| RACE | | | |
| Caucasian | 13 (100%) | 136 (93%) | 149(94%) |
| Black | 0 (0%) | 5 (3%) | 5 (3%) |
| Other | 0 (0%) | 5 (3%) | 5 (3%) |
| Unkown | 22 | 167 | 189 |
| MEAN WEIGHT (kg) | 75 ±13.8 | 78±22.5 | 78 |

The next table shows the demographic breakdown for groupings of clinical studies. The primary source of information was sponsor's table 9-18. Note that the total numbers add up to 3550, which is greater than the total exposed population. The sponsor has indicated that the ARF and CRF groups have considerable overlap. As patients may have gone from a "CRF" or "ICS" study to an "ARF" designated study (for example, compassionate use). There is no means of determining which or how many patients are represented in both groups.

| Demographic Profile for Groupings of Clinical Studies | | | | |
|---|---------------------------------|--------------------------|-------------|------------------|
| | Epilepsy Controlled N=637 | Epilepsy Uncontrolled | NonEpilepsy | Total N=3320† |
| AGE | | | | |
| Mean (yrs) | 32±10.6 | 28±14.1 | 49±16.6 | 31±15.7 |
| <18 | 36 (9%) | 559 (23%) | 6 (2%) | 579 (17%) |

| | | | | |
|--------------------|-----------|------------|-----------|------------|
| <i>18-65</i> | 596 (94%) | 1749 (78%) | 224 (77%) | 2604 (79%) |
| <i>> 65 yrs</i> | 0 (0%) | 8 (4%) | 61 (2%) | 97 (3%) |
| <i>unknown</i> | 5 | 11 | 0 | 40 |
| <i>SEX (%)</i> | | | | |
| <i>Female</i> | 325 (51%) | 1037 (45%) | 132 (45%) | 1891 (57%) |
| <i>Male</i> | 307 (49%) | 1248 (55%) | 150 (55%) | 1404 (57%) |
| <i>unknown</i> | 5 | 22 | 0 | 25 |
| <i>RACE (%)</i> | | | | |
| <i>White</i> | 373 (95%) | 426 (94%) | 23 (82%) | 791 (94%) |
| <i>Black</i> | 10 (3%) | 16 (4%) | 5 (18%) | 28 (3%) |
| <i>Other</i> | 10 (3%) | 12 (3%) | 0 (0%) | 22 (3%) |
| <i>unknown</i> | 244 | 1853 | 263 | 2497 |

†These totals include the phase I dropouts

The demographic breakdown of clinical studies with vigabatrin can be summarized as largely caucasian and covering the adult but not elderly population. Extremes of age and non white races were not represented in these studies.

6.1.4 Extent of Exposure (dose and duration)

The next three pages contain tables which enumerate available data regarding duration of treatment with vigabatrin (regardless of dose), dose (regardless of duration), and exposure by dose and duration. The two US controlled studies (C024 and C025) evaluated vigabatrin doses 1g, 3g and 6g/day. The uncontrolled US studies allowed for titration based on therapeutic response and tolerability within the range of 1-4g/day or 50mg/kg/day.

Dosing data was available of 1735 subjects and patients exposed to vigabatrin. Therefore for 1585 patients there was no such data. The majority of these patients for whom there is no data on dose were in nonUS ARF and some nonUS CRF studies. A total of 1134 patients and subjects received doses of 2.5 to 4.5g/day. This dose brackets the 3g dose determined to be the optimal dose based on US trials C025 and C024. Only 84 patients received doses of 5.5g/day or higher, the dose proposed in US labeling and of these, 44 patients received vigabatrin 6g/day in US controlled Study C025.

| Duration of Exposure of All Subjects to vigabatrin According to Study Design (N = 3320) | | | | | | | | | |
|---|---------------------|------------------------|-------------------|-----------------------|------------------|-----------------------|----------------------------|------------|--|
| Duration (Days) | PK Epilepsy * | PK Non Epilepsy* | Controlled US* | Controlled Non US* | Open Label US | Open Label non US* | Other Indica- tions* | TOTAL * | |
| <2weeks | 13 | 161 | 221 | 212 | 414 | 764 | 28 | 1554 | |
| ≥2 weeks | 0 | 83 | 220 | 208 | 412 | 757 | 26 | 1449 | |
| ≥1 month | 0 | 0 | 217 | 207 | 407 | 750 | 20 | 1345 | |
| ≥3 months | 0 | 0 | 197 | 191 | 391 | 695 | 0 | 1230 | |
| ≥6 months | 0 | 0 | 0 | 84 | 307 | 539 | 0 | 907 | |
| ≥1 year | 0 | 0 | 0 | 15 | 157 | 334 | 0 | 506 | |
| ≥2 years | 0 | 0 | 0 | 0 | 40 | 131 | 0 | 155 | |
| ≥4 years | 0 | 0 | 0 | 0 | 31 | 16 | 0 | 47 | |
| ≥6 years | 0 | 0 | 0 | 0 | 26 | 0 | 0 | 26 | |
| Unknown | 22 | 152 | 1 | 203 | 0 | 1129 | 263 | 1766 | |
| TOTAL | 35 | 313 | 221 | 415 | 414 | 1893 | 291 | 3320 | |

* For these studies the data on duration of treatment are given only where available. The numbers of patients for whom no duration of exposure data are known are shown in the row labeled "Unknown". These data are available for 1554 patients/subjects, roughly 47 % of the entire exposed population. Taken from sponsor's table 9-11, page 9-473 volume 6.3

Note that the rows do not add up to the totals in the last column, because of considerable overlap between the groups, as patients may have participated in more than one study and received different doses in those other studies.

| Exposure by Dose of all Subjects Receiving Vigabatrin According to Study Design (N = 2476) | | | | | | | | |
|---|-----------------|------------------------|-------------------|-----------------------|------------------|-----------------------|----------------------------|-------|
| Dose (g/day) | PK Epilepsy* | PK Non Epilepsy* | Controlled US* | Controlled Non US* | Open Label US | Open Label non US* | Other Indica- tions* | TOTAL |
| <.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| .5-<1.5 | 0 | 98 | 44 | 0 | 2 | 55 | 0 | 159 |
| 1.5-<2.5 | 1 | 14 | 0 | 51 | 13 | 210 | 8 | 297 |
| 2.5-<3.5 | 0 | 2 | 134 | 95 | 257 | 343 | 5 | 717 |
| 3.5-<4.5 | 12 | 47 | 0 | 45 | 80 | 218 | 15 | 417 |
| 4.5-<5.5 | 0 | 0 | 0 | 0 | 12 | 30 | 0 | 40 |
| 5.5-<6.5 | 0 | 0 | 44 | 0 | 48 | 23 | 0 | 84 |
| >6.5 | 0 | 0 | 0 | 0 | 1 | 20 | 0 | 21 |
| Unknown | 22 | 152 | 0 | 224 | 1 | 994 | 263 | 1585 |
| TOTAL | 35 | 313 | 222 | 415 | 414 | 1893 | 291 | 3320 |

* For these studies the data on dose are given only where available. The numbers of patients for whom no data on dose has been collected are shown in the row labeled "Unknown". These data are available for 1735 patients/subjects, roughly 52 % of the entire exposed population.

Note, as in the previous chart, that the rows do not add up to the totals in the last column, because of considerable overlap between the groups, as patients may have participated in more than one study and received different doses in those other studies.

| Summary of Maximum Dose by Duration of Exposure Using all Subjects Receiving Vigabatrin (N = 3220) | | | | | | | | | |
|--|--------|---------|--------------|-----------|----------|---------|------|---------|-------|
| Duration (Days) | 5-1.5g | 1.5-2.5 | 2.5- <3.5 | 3.5-4.5 g | 4.5-5.5g | 5.5-6.5 | >6.5 | Unknown | TOTAL |
| ≤2 weeks | 68 | 18 | 7 | 12 | 0 | 0 | 0 | 0 | 105 |
| 2-<4 weeks | 39 | 11 | 4 | 47 | 0 | 1 | 0 | 2 | 104 |
| 1-<3 months | 16 | 44 | 27 | 21 | 0 | 4 | 0 | 3 | 115 |
| 3-<6 months | 21 | 104 | 135 | 40 | 1 | 4 | 0 | 18 | 323 |
| ≥6 mos-<1yr | 6 | 47 | 206 | 115 | 4 | 19 | 0 | 4 | 401 |
| 1-<2a | 7 | 29 | 183 | 76 | 11 | 42 | 3 | 0 | 351 |
| 2-<4yrs | 0 | 16 | 42 | 29 | 8 | 6 | 5 | 2 | 108 |
| 4-<6 yrs | 0 | 0 | 4 | 8 | 1 | 3 | 5 | 0 | 21 |
| >6 years | 0 | 0 | 4 | 16 | 5 | 1 | 0 | 0 | 26 |
| Unknown | 2 | 28 | 105 | 53 | 10 | 4 | 8 | 1556 | 1766 |
| Total | 159 | 297 | 717 | 417 | 40 | 84 | 21 | 1585 | 3320 |

* For these studies the data on dose and duration are given only where available. The numbers of patients for whom no data on dose has been collected are shown in the row labeled "Unknown", those for whom no data on duration have been collected are shown in the column labeled "Unknown".

Summary:***Treatment for ≥ 6 months:***

Approximately 796 patients or fewer have been exposed to vigabatrin in the dosage range encompassing 3-6 grams, expected to show efficacy based on clinical trials for 6 months or more. One cannot tell from these figures, however how many patients were treated with precisely 3g or greater, since the sponsor has included these exposures in the 2.5-3.5g range. Further breakdown shows that there have been less than 84 patients exposed to the range encompassing and exceeding the 6g dose (5.5- <6.5g to >6.5g) for more than 6 months. Again, one cannot tell from these figures, however how many patients were treated with precisely 6g or greater.

Treatment for ≥ 1 year:

Approximately 454 patients or fewer have been exposed to vigabatrin in the dosage range expected to show efficacy based on clinical trials (2.5->6.5g/day) for more than 1 year, and there have been less than 65 patients exposed to the higher dose range encompassing and exceeding 6g (5.5-<6.5g and >6.5g) for more than than 1 year.

This reviewer is not able to determine which of these exposures have yielded the primary safety data, such as adverse events.

SECTION 7.0 HUMAN PHARMACOKINETICS

Human Pharmacology

The following represents a brief summary of what will be covered in detail in the Biopharmacology review.

- Vigabatrin is completely and rapidly absorbed in humans following oral administration. It is not protein-bound and it is not appreciably metabolized, as up to 82% of vigabatrin is excreted unchanged in the urine. Two metabolites are known, one identified as a vigabatrin-lactam, the other unidentified. They are thought to be inactive.
- Vigabatrin's time to maximum concentration (T_{max}) is approximately 1 hour, and maximum plasma concentration (C_{max}) ranges from 28.8 to 46.3, u/mL for a single 1g dose. With multiple dosing of 2 g BID, steady-state t_{max} and C_{max} were 1 hour and 74.8 u/mL, respectively.
- The apparent volume of distribution of vigabatrin is approximately 1 L/kg.
- Its terminal plasma concentration profile is described by a two-compartment model with an elimination half-life of approximately seven hours. Vigabatrin exhibits linear pharmacokinetics during single (0.5 g to 4 g) and multiple dose (0.5 g BID to 2.0 g BID) administrations.
- Food affects the bioavailability of vigabatrin. C_{max} decreases by 33% and t_{max} increases 2-fold in the fed state, compared to fasting. AUC however remains unchanged.
- There have been no formal drug interaction studies investigating the potential interaction of vigabatrin with carbamazepine, barbiturates, or valproic acid. The interaction of vigabatrin and phenytoin has been studied, and it has been shown that vigabatrin affects the plasma phenytoin levels by 16-33%.
- The effect of standard antiepileptics on vigabatrin pharmacokinetics has not been studied.
- Vigabatrin pharmacokinetics have been formally evaluated in renal insufficiency. In patients with mild to moderate renal insufficiency, mean AUC increased by 1/3 and terminal t_{1/2} increased by 1/2 (from 8 to 12 hours). In patients with moderate to severe renal insufficiency mean AUC increased by 3.5X and t_{1/2} increased by 3X.

SECTION 8.0 CLINICAL STUDIES: EFFICACY

8.1 OVERVIEW OF EFFICACY STUDIES

Two adequate and well controlled studies were offered as evidence for efficacy in epilepsy. In addition there were 13 non-US placebo controlled studies which were conducted to explore the claim for efficacy in complex partial seizures. US Studies #71754-3-C-024 and #71754-3-C-025 were submitted as the pivotal trials in epilepsy. They attempt to evaluate vigabatrin as adjunctive therapy in patients with refractory epilepsy who are maintained on a base of 1-2 antiepileptic drugs. The designs of the studies are similar on the surface on design and outcome. Study C-024 evaluated efficacy of 3g vigabatrin given daily compared to placebo as adjunctive therapy for complex partial seizures. Study #71754-3-C-025 evaluated the dose response across three doses of vigabatrin, 1g, 3g, and 6g, and placebo. They were reviewed in detail and are presented below. The remaining 13 European studies were generally small studies, using either a crossover or open label design. They will be described briefly, however detailed analysis was not performed for these trials as they were not considered critical material.

8.2 SUMMARY OF EFFICACY STUDIES

8.2.1 US STUDY #71754-3-C-024

Materials reviewed: Integrated Summary of Efficacy, Protocol and Amendments for C024 and C025, study reports and appendices, all CRFs for study C025 and random CRFs in study C024, Amendments to NDA

PROTOCOL SYNOPSIS:

TITLE: Double-blind, randomized, placebo-controlled, parallel group study of vigabatrin in patients with uncontrolled complex partial seizures .

OBJECTIVE/RATIONALE: To evaluate the efficacy of vigabatrin 3g/day compared to placebo, when added to currently prescribed antiepilepsy therapy in patients with uncontrolled partial complex seizures.

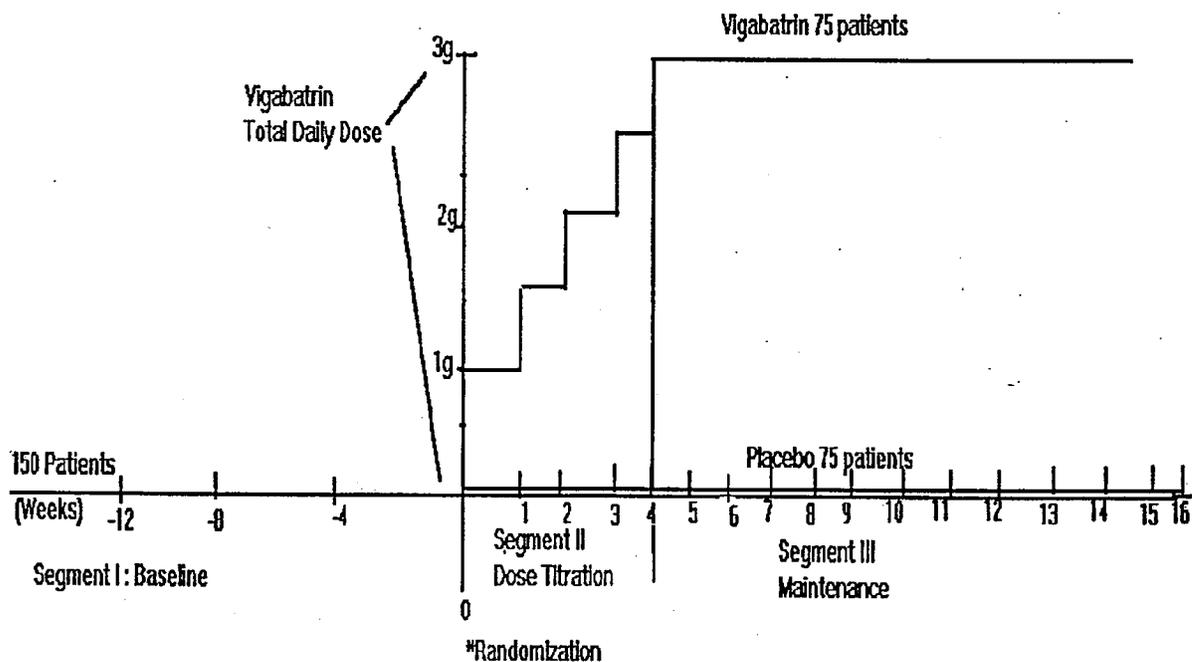
STUDY DESIGN: This is a multicenter , randomized, double-blind, placebo-controlled study with two parallel treatment groups.

- **Initial Evaluation:** Assignment for eligibility for participation in the study where males and nonpregnant females (age 18 to 60 years) with difficult to control complex partial seizures, maintained on one or two concomitant antiepilepsy drugs (AEDs) are the principal inclusion criteria.

- **Segment I:** includes a 12-week evaluation period, where the last 8 weeks of Segment I would be considered Baseline.
- **Segment II:** This phase includes randomization to vigabatrin 3g or placebo followed by a 4-week titration period in which study drug increases from 1 g/day by 0.5 g/day on a weekly basis.
- **Segment III** is a 12-week maintenance period with dosage of vigabatrin 3 g/day or matching placebo. The last 8 weeks of Segment III are considered maintenance.
- **Taper Segment** is restricted to patients discontinuing the study during Segments II or III, or not entering a long-term open-label vigabatrin study. Tapering increments are 1 g TDD on a weekly basis.

Seizure counts would be collected during Segments I, II, and III using patient seizure calendars and used for the calculation of seizure frequencies.

Parallel Study of Safety and Efficacy of Vigabatrin as Add-on Therapy in Patients with Uncontrolled Complex Partial Seizures



ANALYSIS PLAN

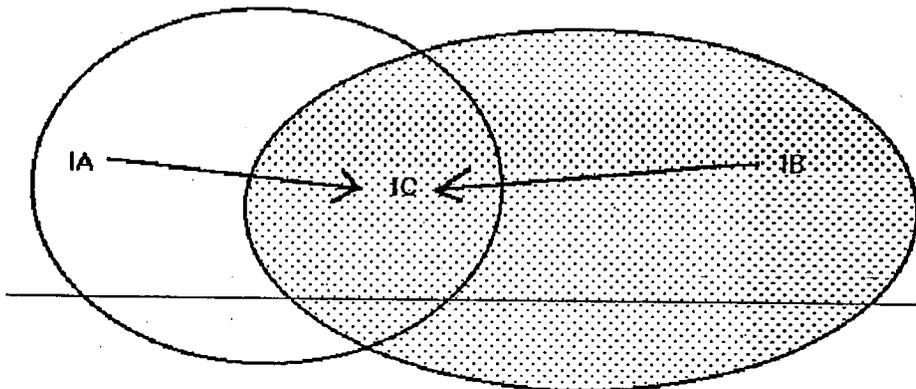
The table below summarizes the 1981 Revised International Classification of the Epilepsies relating specifically to partial seizures. The abbreviations used here will be continued through the remainder of this review in reference to specific seizure types.

| 1981 REVISION OF THE INTERNATIONAL CLASSIFICATION OF EPILEPTIC SEIZURES |
|---|
| <p>I. Partial Seizures (seizures beginning locally)</p> <p>A. Simple Partial Seizures (consciousness not impaired) (IA)</p> <ol style="list-style-type: none"> 1. With motor symptoms 2. With somatosensory or special sensory symptoms 3. With autonomic symptoms 4. With psychic symptoms <p>B. Complex Partial Seizures (with impairment of consciousness) (IB)</p> <ol style="list-style-type: none"> 1. Beginning as simple partial seizures and progressing to impairment of consciousness <ol style="list-style-type: none"> a. With no other features b. With features as in A. 1 through A. 4 c. With automatisms 2. With impairment of consciousness at onset <ol style="list-style-type: none"> a. With no other features b. With features as in A. 1 through A. 4 c. With automatisms <p>C. Partial Seizures Secondarily Generalized (IC)</p> |

PRIMARY EFFICACY MEASURE

The median IB + IC (complex partial plus all partial onset generalized seizures) value and the 95% confidence interval for the median was designated for the primary assessment of efficacy. The schematic on the following page displays the seizures of interest used in the computation of the primary efficacy variable. Note that the efficacy evaluation did not specifically target simple partial seizures with secondary generalization or partial complex seizures with secondary generalization, but rather lumped them together, even though simple partial seizures were excluded from analysis.

Seizures of Interest in calculating the Primary Efficacy Variable :
Types IB+IC, and excluding IA



included
included

not included
included

complex partial seizures (IB)
complex partial seizures----->
secondarily generalized (IC)
simple partial seizures (IA)
simple partial seizures----->
secondarily generalized (IC)

SECONDARY EFFICACY MEASURES are summarized in the table below:

| Efficacy Response Variables | |
|-----------------------------|---|
| Primary | Frequency of Complex Partial Seizures plus Partial Seizures Secondarily Generalized (IB+IC) |
| Secondary | Therapeutic Success ($\geq 50\%$ reduction in IB+IC) |
| | Frequency of Simple Partial Seizures (IA) |
| | Frequency of Complex Partial Seizures (IB) |
| | Frequency of Partial Seizures Secondarily Generalized (IC) |
| | Frequency of Seizure-Free Days |
| | Global Evaluation |
| | Evaluation of Therapeutic Effect |

CONDUCT OF STUDY**INVESTIGATORS/ LOCATION**

There were 15 centers which participated in this trial. The table below shows the distribution of patients and their randomization :

| Distribution of Randomized Patients By Treatment Assignment and Site (N = 183) | | | |
|---|------------------|----------------|--------------|
| Investigative Site | Treatment | | Total |
| | Placebo | 3 g VGB | |
| 005 | 7 | 6 | 13 |
| 054 | 6 | 6 | 12 |
| 055 | 5 | 5 | 10 |
| 056 | 7 | 7 | 14 |
| 057 | 6 | 7 | 13 |
| 058 | 7 | 7 | 14 |
| 059 | 8 | 8 | 16 |
| 060 | 4 | 6† | 10† |
| 061 | 5 | 5 | 10 |
| 062 | 7 | 7 | 14 |
| 063 | 5 | 5 | 10 |
| 064 | 7 | 7 | 14 |
| 065 | 3 | 4 | 7 |
| 066 | 7 | 7 | 14 |
| 067 | 6 | 6 | 12 |
| Total | 90 | 93† | 183† |

NUMBER OF PATIENTS

A total of 203 patients entered Segment I. Patients who met entrance criteria at the end of Segment I were randomized to either vigabatrin or placebo. Of these, 183 patients were randomized to receive study medication (90 placebo; 93 vigabatrin) in Segment II. One patient randomized to vigabatrin discontinued prior to study drug administration.

PATIENT DISPOSITION: 182 patients received study medication (90 placebo; 92 vigabatrin). Of these, 170 completed the study (88 placebo, 82 vigabatrin). A total of 12 patients discontinued from the study prematurely (2 placebo, 10 vigabatrin). Sponsor's Table 8-10 on the following page summarizes this information by study segment.

Ten of the 12 patients who failed to complete the study discontinued because of adverse events (2 placebo, 8 vigabatrin); 10 patients (2 placebo, 8 vigabatrin) because of adverse events. One patient (056-013) became pregnant during the study and was discontinued, and one patient (067-010) committed suicide by taking an overdose of carbamazepine. There were four patients (055-006, 056-007, 056-013, 060-016) randomized to 3 g vigabatrin who discontinued during the Titration Period prior to reaching a dose of 3 g/day. Three of the patients (055-006, 056-013, 060-016) were titrated up to 2.5 g/day vigabatrin and one patient (056-007) was titrated up to 2.0

g/day of vigabatrin. All were included in the 3 g vigabatrin group for all efficacy analyses.

| Sponsor's Table 8-10. Summary of Postrandomization Dropouts (% of Dropouts in Each Treatment Group) | | | |
|---|---------------------|----------------------|---------------|
| Treatment | Segment II Dropouts | Segment III Dropouts | Total |
| Placebo | 1.1% (1/90) | 1.1% (1/89) | 2.2% (2/90) |
| 3 g VGB | 4.3% (4/92) | 6.8% (6/88) | 10.9% (10/92) |
| Total | 2.7% (5/182) | 4.0% (7/177) | 6.6% (12/182) |

The following flowchart shows movement into and out of study C024.

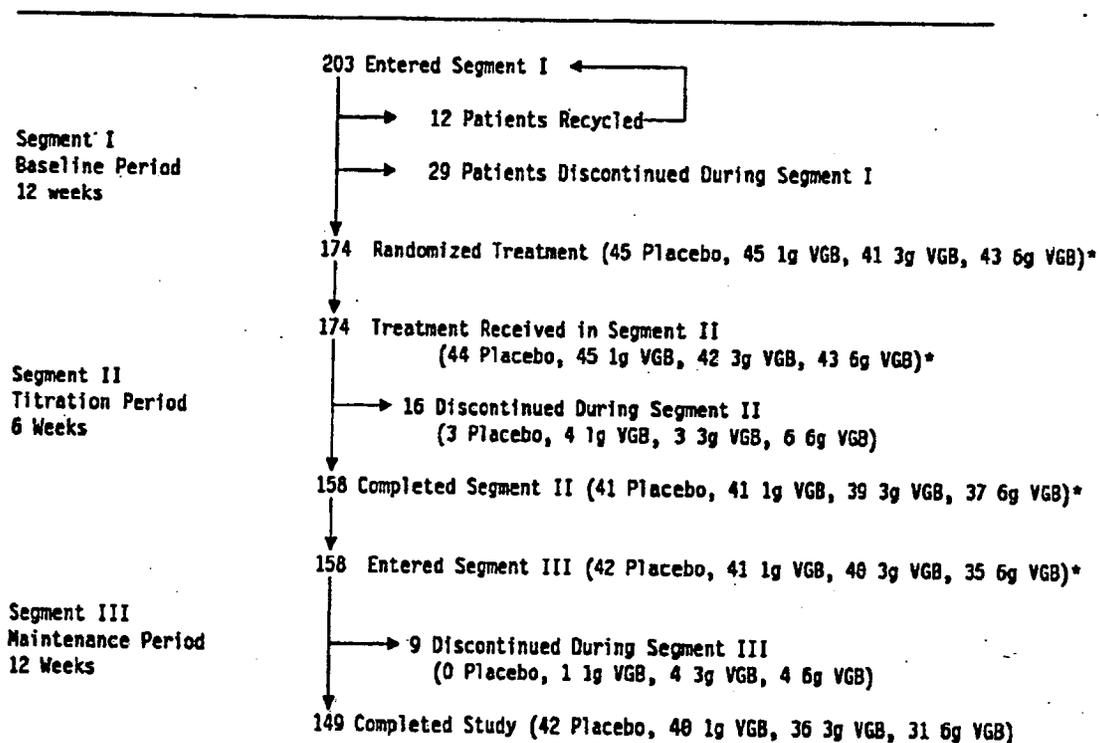


Figure 8-2. Flowchart of Patient Entrance and Exit in Trial.