Div. File

Memorandum

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

DATE: November 18, 1997

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

SUBJECT: Recommendation for Approvable Action, NDA 20-427, Sabril

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

This memorandum conveys my formal recommendation that Hoechst Marion Roussel's (formerly, Marion Merrell Dow's) NDA 20-427, which allows for the use of Sabril (vigabatrin, gamma vinyl GABA, GVG) as an adjunctive treatment for adults with Complex Partial Seizures, be declared approvable.

The PDUFA action date goal for the application is November 29, 1997

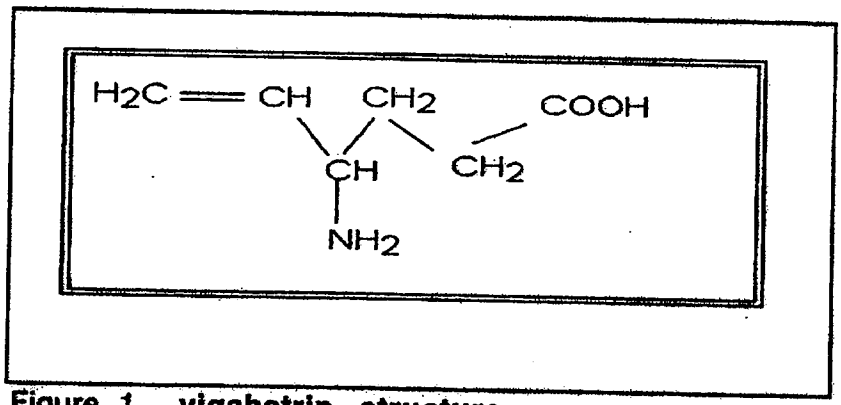


Figure 1 vigabatrin structure

History of GVG's development

In July of 1983, some 2 and a half years after the filing of Merrell-Dow's original IND, domestic clinical investigations of GVG were suspended pending

review and evaluation of reports of intramyelinic edema/vacuolization occurring in the CNS of mice, rats, dogs and arguably monkeys in association with the extended use of this GABA-T inhibitor. In some cases, histological findings suggested that the intramyelinic pathology was irreversible and/or associated with neuronal loss.

These preclinical findings were viewed as alarming, all the more so because they occurred at doses that were considerably lower, on a mg/m^2 basis, than those being administered to humans. In short, there was every reason at the time to be concerned that the extended use of GVG would lead to irreversible CNS damage in humans.

Experience gained to that point in domestic and foreign clinical trials, however, provided no indication (clinical sign or lab test result) that GVG was causing intramyelinic edema/vacuolization in human subjects. Although the lack of adverse reports was somewhat comforting , it was far from reassuring because it was impossible to discern whether it reflected an absence of human pathology, an insensitivity of laboratory tests and medical examinations to detect the pathology, or simply a failure to examine patients appropriately.

Accordingly, the Division, with the endorsement of the PCNS AC (May 1984), demanded that the sponsor withhold further clinical testing until the factors affecting the occurrence of the intramyelinic edema were more thoroughly understood. In November of 1985, after considering arguments made by the firm, the Division, again with the endorsement of the PCNS AC, concluded that, before clinical trials could resume in the United States., the firm would have to develop a non-invasive test capable of detecting signs of intramyelinic edema at an early enough stage to preclude irreversible injury.

Foreign clinical trials continued, however, evidently yielding evidence sufficient to persuade other regulatory agencies that GVG was an effective (and safe enough) anti-epileptic drug (AED). In late 1989, in the face of some evidence indicating that testing with MRI and visual evoked potentials might be able to detect early evidence of intramyelinic edema in dogs, and with knowledge that GVG was about to approved for marketing in the UK, the PCNS AC (November 1989) recommended that domestic clinical trials be permitted to resume.

Clinical testing began anew in the US in September of 1990. Over the ensuing years, GVG was approved for use in an ever increasing number of Western

countries. In 1994, the very year that the Canadian HPB approved the drug for marketing, an NDA was submitted to the FDA.

Original NDA (submitted 4/29/94; declared not approvable 5/28/95)

Although the Division's review of the application led it to conclude that the sponsor probably had two clinical trials that could, if analyzed appropriately, provide substantial evidence of GVG's efficacy as an anti-epileptic drug (AED), it could not conclude, based upon the reports submitted, that Sabril had been shown to be "safe for use."

As discussed in my memorandum of 4/13/95 recommending a not approvable action, this adverse conclusion was not a consequence of affirmative findings of intolerable risks of use, or from a deficiency in the extent of clinical experience[1], but because the application failed to provide, in an organized, reliable (i.e., error free), and reviewable form, the description, detail, and analysis necessary to allow an informed and comprehensive assessment of the untoward clinical and laboratory findings associated with GVG's use.

Following the issuance of the NA letter (5/28/95), the Division assisted the firm in its efforts to correct the deficiencies and errors found in the original application.

Resubmission

The Division review team for the Sabril NDA is headed by Dr. Katz; he recommends that the application be declared approvable (see his supervisory memorandum of 11/9/97) b(4)

Additional reviews of evidence bearing on the product's effectiveness were conducted by Dr. Sahlroot of Biometrics (10/31/97) in consultation with Dr. James Sherry (review of 11/5/97), the neurologist assigned to the

[1] Although the NDA claimed to provide reports on more than 3000 patients who had participated in clinical trials, and GVG was marketed in some 40 or more countries, including those like Canada and the UK, that are generally viewed as setting demanding standards for marketed drug products, the detail provided was sparse.

application following the departure of Dr. McCormick who was the clinical reviewer of the original application.

The safety assessment of the resubmission was conducted by Dr. Gerard Boehm (10/28/97) of the Division's Safety Unit under the supervision of Dr. Greg Burkhart (supervisory memorandum of 11/12/97) .

Also of importance to the recommendations of the Division are the supervisory memorandum of Dr. Fitzgerald (10/17/97) and the Biopharm review by Dr. J.K. Tammara (May 29, 1997).

Effectiveness in Use

Support for the conclusion that Sabril is an effective AED comes from 2 adequate and well controlled clinical investigations, Study 024 and 025.

Study 024

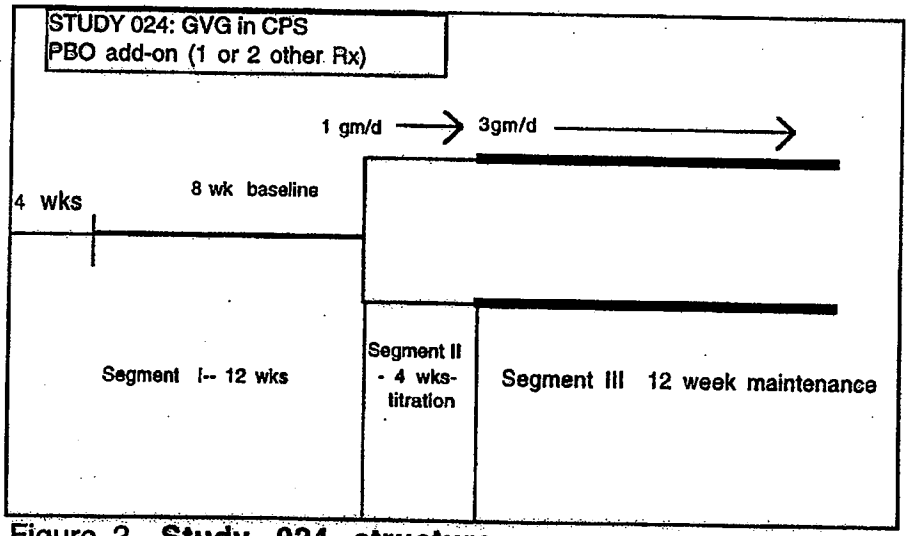
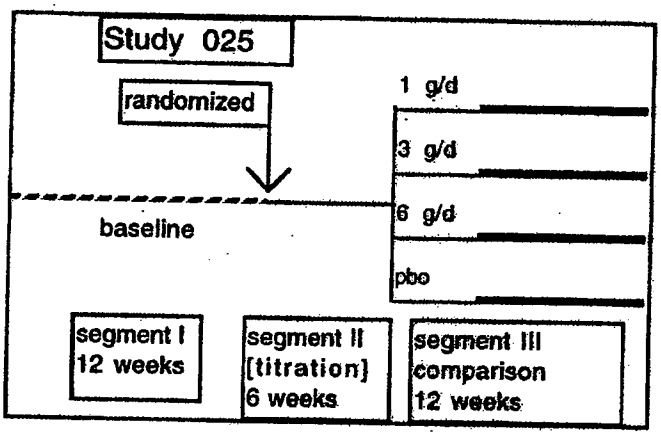


Figure 2 **Study 024 structure**

Study 024, outlined in Figure 2, above, employs what is by now a more or less standard "add-on" parallel design, in this case involving a comparison of 3 gm/day of vigabatrin and placebo in 182 (170 completed) patients with poorly controlled partial complex seizures receiving 1 to 2 concomitant AED's. Unfortunately, the sponsor's original report of the study contained

numerous errors, and required reanalysis. Although there was initially some lack of understanding/agreement about what reanalysis would be most appropriate, the review team is now persuaded that the study provides statistically significant findings supporting (in a proof of principle sense) a conclusion that GVG is effective in adjunctive use as an AED.

Study 025



Study 025 is a parallel, add-on comparison, of 3 fixed daily doses of GVG (1, 3 and 6 grams) and placebo in 174 patients with poorly controlled partial complex seizures. The design allowed for titration to their assigned fixed dose over a period of 6 weeks (Segment II). This study was found to be a source of positive support for the efficacy of GVG upon review of the original NDA.

Treatment	Number entered	Baseline median	End study median
placebo	45	9 [7,10.5]	8.8 [6, 12.1]
1 gm/day	45	8.5 [6, 12.3]	7.7 [4.1, 11.5]
3 gm/day	43	8.0 [7,10.5]	3.7 [2.5, 6.0]
6 gm/day	41	9.0 [7,14.5]	4.5 [3.3, 6.0]

Table of Seizure median frequency as events/28 days, with CLs, from Taneja 3/7/95, (p.18)

A concern about the sponsor's choice of outcome space (which seizure events

to count) has confounded interpretation of the efficacy data. The problem arises because the attributes of the seizure activity exhibited by a patient that allow his/her diagnosis/classification[2] and selection as subject in a clinical investigational do not reflect each and every kind of seizure a patient may experience.

Two Venn Diagrams may help clarify the issue that is discussed in depth in Dr. Katz's memorandum

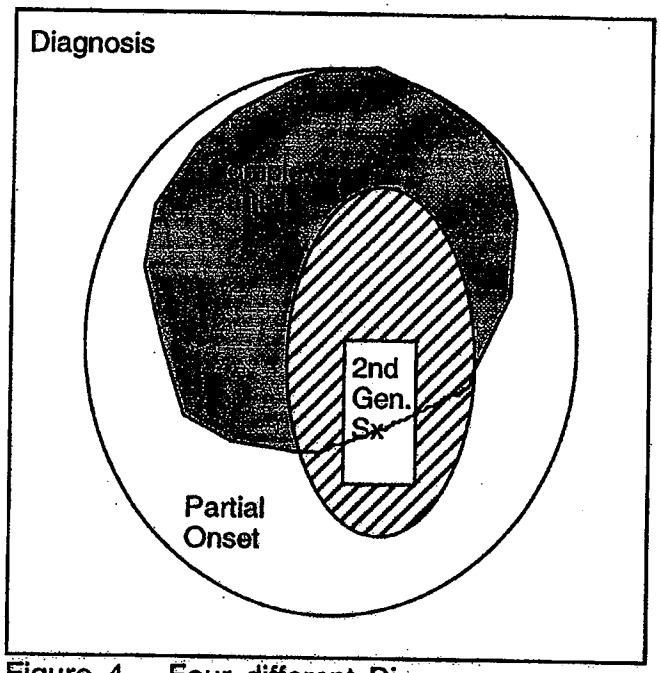


Figure 4 Four different Diagnoses

Basically, There are 4 types of **Partial Onset Seizures.** A patient might be diagnosed as having **Simple Partial Seizures** (i.e., when the onset is local and there is no impairment of consciousness) with or without *secondary generalization* or **Complex Partial Seizures** (local onset with impaired consciousness) with or without *secondary generalization.*

The sponsor elected to admit not only patients with a diagnosis of Partial

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[2] Although not worthy of a lengthy digression here, it is important to take note that the classification of the epilepsies is phenomenologic and taxonomic.

Complex seizures to Study 024 and 025, but those with Simple partial seizures that generalized.)

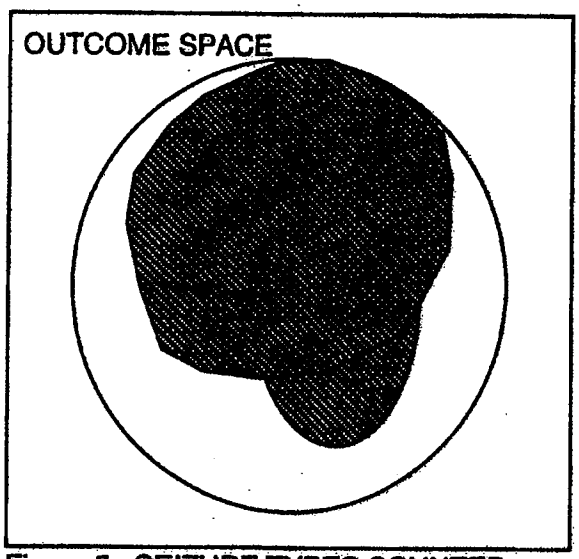

Figure 5 SEIZURE TYPES COUNTED

The outcome space for Studies 024 and 025, therefore, consists of both Complex partial seizures (those that do and do not generalize) and simple partial onset seizures that became secondarily generalized. (i.e., represented by the half moon like protrusion along the lower border of the CPS space in Figure 5 above).

Upon detailed examination of the results of both studies 24 and 25, the review team found that the evidence that speaks to the efficacy of GVG derives almost entirely from the drug's capacity to suppress the frequency of Complex Partial Seizures. (e.g., see page 6 of Dr. Katz's memo). Accordingly, Dr. Katz's argues, and I agree with him, that the evidence adduced may only support a claim for GVG's efficacy as an adjunct in the management of adults with Complex Partial Seizures, not partial onset seizures in general.

Safety for Use

The comprehensive review conducted by Dr. Gerald Boehm and the overview of the safety related findings provided by Dr. Burkhart not only provide a general overall assessment of the risks of GVG, but may be taken to represent the

Division's primary review of the non-US safety data.

Although Dr. McCormick conducted a safety review on reports provided to the original NDA, its value is limited by the fact that the firm's presentation of the safety related information in the original application from sources other than US studies was found upon review to be replete with errors, omissions, and, was deficient in the level of detail provided.

The current resubmission of the NDA provides reports of findings obtained from new databases created using a variety of data sources (e.g., original case reports, (when available), investigator files, etc. by the sponsor and/or its contractors. (see Boehm p 5-7) Also of interest is information obtained from a "Prescription Event Monitoring" [PEM] study conducted in the UK on an observation cohort of some 10,000 patients taking GVG for about 6 months (i.e., about ? 5000 PYs).

Although the newly submitted reports are "improved" compared to those submitted to the original NDA, they still have limitations. (see Dr. Burkhart's 11/12/97 memo, pages 5-6).

Risks considered in the assessment of GVG's safety for use.

No active drug substance is free of risk; in fact, as a class, AEDs seems especially toxic although it must be acknowledged that it is almost impossible to disentangle the specific untoward effects caused by a particular AED from the effects of epilepsy and/or the untoward consequences of previously or concomitantly administered AEDs. Liver injury and SUD are 2 examples of untoward events reported commonly in association with the use of a wide assortment of AEDs that may not actually be caused by drug treatment.

Some untoward events, however, are more than likely directly attributable to the effect of a particular AED; the aplastic anemia that occurs in association with the use of felbatol is a classic example.

The kinds of safety analyses that will most reliably identify the specific risks associated with the use of a new drug are a subject of ongoing review. Whatever the strategy of analysis employed, however, the discovery of drug induced injury is held hostage not only by the amount and quality of the information gathered by a sponsor, but by the nature and qualities of the

untoward injuries caused by a drug.

Unique, easily described, drug caused events that occur shortly after treatment initiation are relatively easy to identify, especially if they occur at high enough frequency to be observed in controlled trials. Events of this kind reported more frequently among patients receiving GVG than among those receiving placebo in the add-on controlled clinical trials include nystagmus, amnesia, confusion, parenthesis, depression, weight gain and edema.

Untoward events occurring at frequencies below 1% or so can also be identified during a typical premarketing drug development program, but for events occurring at this frequency and below, it is rarely clear whether the observed association is causal or accidental, unless, of course, the event is virtually unheard of in the absence of exposure to the drug.

In any case, judged by ordinary NDA standards, the experience gained with GVG would appear reasonably extensive (e.g., over 1800 patients or so/ about 1000 PYs) and reasonably reflective of the conditions under which the drug will be used (regimen, dose, and duration) once marketed.

Unfortunately, the analysis of reports of untoward events are not as extensive as the review team would have preferred. For example, although 1 % of patients on GVG have been reported to exhibit signs/symptoms of a peripheral neuropathy, there is very little detailed information about the defining attributes, if any, of this condition. The issue here, importantly, is not a failure to report adverse events, but a failure to investigate them with sufficient thoroughness.

However, even if the sponsor had been more aggressive in its investigation of adverse reports, a need for caution would persist. Drug associated risks have to be identified as such to be reported and recognized[3] . Drug associated injury developing long after treatment initiation, especially if it lacks a distinctive[4] clinical phenomenology, runs considerable risk of going

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[3] e.g., nomifensine was marketed worldwide for almost 7 years before its association with hemolytic anemia was widely appreciated.

[4] For example, a very dramatic or unusual event (akin to Feinstein's whimsical example of growing feathers) is likely to be identified readily; in contrast, some cognitive disturbance secondary to neuronal injury might not.

undetected and/or unreported. Indeed, the more protean the epiphenomena of a drug induced injury, and the more numerous alternative possible explanations, the less likely the relationship to drug use will be appreciated.

While this concern is generic (i.e., it applies to virtually any new drug), there are good reasons to be especially concerned about GVG given its capacity to cause IME, a lesion that might easily cause any number and kinds of adverse clinical effects depending not only upon its severity, but its location within the CNS, or even PNS.

The risk of IME is central to my concerns about GVG, and is, therefore, worthy of further explication.

Why Intramyelinic edema [IME] is so alarming.

Although there is not even one unequivocally documented example of the lesion in humans, intramyelinic edema must be taken as a potentially serious risk of GVG therapy on no other grounds than the fact that GVG has a documented capacity to cause intramyelinic edema in 3, perhaps 4, animal species at levels of exposures below (based on mg/m^2 dose comparisons) those to which human subjects are exposed.

The fact that IME has not been documented to occur in humans on GVG is not very reassuring.

To begin, the absence of evidence is not evidence of absence, especially when one is dealing with a lesion that may well, especially in mild cases, be clinically silent.

Secondly, it is not in the least clear what the clinical manifestations of the IME lesions might be. There are clinical reports of adverse events referable to the CNS and PNS of "unknown" etiology and pathogenesis associated with the use of GVG. While there is no basis to assert that they are a result of IME, some might well be. All the more reason why I consider the sponsor's failure to investigate these findings in greater depth a serious limitation of the NDA.

In light of this background, the dearth of human brain biopsy and/or autopsy material from patients treated with GVG is very unfortunate; one would have hoped that after 7 years of marketing throughout the world, there would have been an opportunity to collect appropriate tissue samples.

The failure to detect abnormalities with evoked potentials and MRI scans is implicitly taken as being potentially reassuring. Although we are asking the sponsor to include information about the results of these tests and their extent of use in the Warnings Section, I must acknowledge that I am somewhat ambivalent about doing so because there is little, if any, empirical basis to conclude that either test method can detect IME in humans.

Untoward Neurological findings of concern

Given the context, certain clinical reports take on a significance they would not have had if GVG did not cause IME.

Visual Field abnormalities

Reports of constriction of the visual fields and/or field cuts in patients on GVG have only recently been the subject of post-marketing reports in both the UK and Australia. We know very little about these cases. While they may turn out to be spontaneous events only temporally linked to the use of GVG, they may also be the result of injury, perhaps to myelinated nerves. Unfortunately, a systematic assessment of these reports is not available.

Peripheral Neuropathy

Peripheral neuropathy, which occurs at an incidence (1%) several fold that reported among placebo recipients is indicative of injury to the PNS. The pathogenesis of this entity is unknown; the sponsor contends it cannot be linked to IME because the latter involves (in animals) only central myelin. Perhaps the firm is correct, but, if so, one has to wonder why, given its high incidence, we know so little about its properties and course.

Neuropsychiatric disturbances

The neuropsychiatric disturbances (psychotic phenomena, depression), cognitive impairment/mental status changes, and CNS depression (ataxia, nystagmus, etc.) are all neurological functional impairments. Since similar findings are reported with other AEDs, it seem less likely that these phenomena are a manifestation of some GVG specific neuronal injury. On the other hand, that other explanations for their genesis exist, does not exclude the possibility that GVG induced injury to myelin plays a role.

In sum, it would be imprudent to dismiss the potential importance of GVG's capacity to cause IME in animals simply because it has yet to be documented to occur in humans.

Non-neurological putative risks of GVG

Dr. Burkhart points out a number of untoward events and findings that he believes can be interpreted as consequences of GVG use. Among these are cases of liver injury/failure, pancreatitis, and substantive decreases in hematocrit.

Sudden and Unexpected Deaths (SUDs)

The estimated incidence of SUD with GVG is around 3 /1000 PYs, an incidence that is essentially identical to that observed with other recently marketed AEDs. I mention it primarily for sake of completeness.

Recommendations for use (Labeling)

The draft attached to the approvable action letter being forwarded for issuance provides both text and instructions to the sponsor.

Indications

Although I endorse Dr. Katz' conclusion that GVG can be declared approvable for adjunctive use in adults with Complex Partial Seizures, I am troubled by the uncertainties that remain concerning its potential to cause irreversible neuronal injury. Accordingly, I am recommending that GVG be marketed under a claim that asserts that it should not ordinarily be included among the set of AED treatments first chosen for combination use.

Biopharm Section.

This section is comparatively sparse, in part because GVG is largely excreted unchanged in the urine, and in part because the sponsor took a somewhat unconventional approach to developing information on the interaction between GVG and other AEDs. As Dr.Katz notes in his approvable action memo, the agency had asked the sponsor to conduct formal interaction studies, but OCPB now concludes the "population" approach they have taken is

acceptable.

Warnings

[redacted] b(4)

Dosing

The dosing recommendation reflects the Review Team's interpretation of the 2 controlled trials providing support of GVG's effectiveness in use.

Discussion and Conclusions

Dr. Katz recommends that GVG be approved for use as an adjunctive treatment for adults with Complex Partial Seizures (CPS).

Because I still find it difficult, the lack of a specific evidence of the lesion occurring in patients notwithstanding, to conclude that GVG is incapable of causing IME humans, I am unwilling to support an approvable action that endorses GVG's unrestricted adjunctive use as a treatment for CPS.

I am mindful that the imposition of a 'restricted' claim is always an arguable regulatory strategy. Dr. Katz, who shares most of the same concerns that I do about GVG, prefers an unmodified claim, in part because he finds the restriction a potential intrusion into medical practice and also because a restricted claim may be taken to imply that GVG offers a specific advantage in recidivistic patients who fail to respond to AED regimens comprised of other adjunctive treatments. (which it does not.).

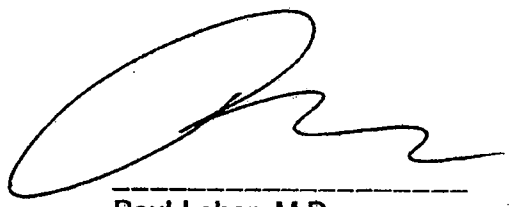
Although his arguments have merit, they are not sufficient to convince me to modify my recommendation. Agency policy basically allows the marketing of any effective drug product, even a potentially dangerous one, provided it is marketed under recommendations for use that render it reasonably "safe for use." A potentially dangerous drug product, accordingly, can be responsibly deemed safe for use in a recidivistic epileptic patient who fails to respond to other AED treatments while being deemed not safe for use in epileptic

patients able to respond to combinations of drug products posing lesser risks of use. This is the reasoning that leads me to condition my approvable recommendation on Sabril's marketing under a restricted claimed indication.

I will acknowledge that I, too, have generic reservations about imposing restrictions on drug product claims in the absence of affirmative evidence of the occurrence of the risk in humans. In this particular set of circumstances, however, my reservations are irrelevant because the failure to find evidence of IME in humans treated with GVG may well be a result of our imperfect methods to detect it and, perhaps, even more likely, a failure to look hard enough for evidence of its presence.

Recommendation

The NDA should be declared approvable under labeling identifying it as one that should not ordinarily be included among the set of AED treatments first chosen for combination use.



Paul Leber, M.D.
November 18, 1997

cc: NDA 20-427
HFD-100
Temple
HFD-120
Katz
Sherry
Burkhart
Boehm
Fitzgerald
Rosloff
Guzewska
Ware
HFD-710
Nevius
Taneja
HFD-426
Baweja
Tammara

MEMORANDUM

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

DATE: November 12, 1997

FROM: Greg Burkhart, Safety Team Leader
Neuropharmacological Drug Products, HFD-120

TO: NDA 20-427

SUBJECT: Review of 5/29/97 Amendment to the Vigabatrin NDA: Safety

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This memorandum provides a summary of the findings from the safety team's review of the vigabatrin amendment to the NDA. Dr. Boehm conducted the primary safety review and Dr. Sherry reviewed the intramyelinic edema (IME) and peripheral neuropathy safety issues. Dr. Katz considers the efficacy findings from HMR's re-analysis of study 024 in his memorandum.

Since the US data contained in the NDA were not re-submitted in the amendment and Dr. McCormick extensively reviewed the US data in the NDA, the safety team did not specifically review these data. However, Dr. McCormick's review was used to both assist with our review of the amendment and to integrate the findings from the US and non-US data.

While the US data contained in the NDA were not re-submitted, the amendment does provide and discuss findings from protocol 253, a North American study of patients with potential neurological and ophthalmological abnormalities. Protocol 253 was conducted as part of the response to the not-approvable (NAE) letter. Both Dr. Boehm and Dr. Sherry have reviewed aspects of these data with both of their memoranda summarizing and discussing protocol 253 findings.

After summarizing the findings from Dr. McCormick's NDA review, the content of the NAE letter and HMR's approach to responding to the NAE letter, I will briefly consider Drs. Boehm's and Sherry's findings. My review will focus on the adequacy of the non-US data and the general findings from the non-US primary database, and then consider specific safety issues such as IME, hepatic toxicity and peripheral neuropathy.

Background

The Not-Approvable Letter

On April 28, 1995 the FDA issued a NAE letter for vigabatrin (NDA 20-427). In short, the agency was unable to reach a conclusion about either vigabatrin's safety or effectiveness because of concerns about the quality and completeness of the data contained in the NDA.

The NAE letter described several problems with the data in the NDA that did not permit a full consideration or description of AEs that could be associated with vigabatrin use. While the US database appeared complete and of reasonable quality except for some concern about the ophthalmological data (discussed below), the non-US database was of uncertain validity. This concern was prompted by the presence of numerous errors in the non-US data discovered when the NDA data was compared to the data on the CRFs that were submitted. To examine the question of data validity in more depth, the review team proposed to review CRFs in non-US patients that were not submitted, but such CRFs were not available. It also appeared that, for many patients in the non-US data, the data on their CRFs were not used for data entry.

Ordinarily, in such a situation, the experience in US patients or the grouping of patients with well documented follow-up may suffice. However, in the vigabatrin NDA, the number of patients in the US data, which was judged to be the only valid data at the time of the NDA, was relatively small. Since the experience in the non-US data was critical towards reaching a conclusion on vigabatrin safety, the FDA review team concluded that there was insufficient experience for which there was adequate documentation and capture of AEs to reach a conclusion on whether vigabatrin was safe for its intended use.

Dr. McCormick, in her review of the US data, also found some problems that required clarification before approval. In her review of the data in study 006, a US study designed to monitor patients for ocular toxicity, she found 36 patients with evidence of at least one ocular symptom or abnormality whereas HMR described 12 such patients.

There were other general problems with HMR's approach to summarizing the safety experience with vigabatrin. HMR did not provide a detailed report of evoked potential (EP) or MRI abnormalities, or autopsy findings for patients who died while on vigabatrin. EP, MRI and autopsy findings may be relevant to examining the potential for vigabatrin to cause IME in humans. IME observed in mice, rats and dogs lead to the concern about human risk and resulted in a prolonged regulatory hold. The hold was lifted after the sponsor conducted animal studies showing that changes on MRI and/or EPs could be used to detect IME.

HMR also did not provide an integrated discussion of serious AEs, examine SUD rates, describe reasons for patient dropout, or discuss the clear excess of hospitalized depression and psychosis that was associated with vigabatrin use in the NDA. Finally, while there were a number of cases of fulminant hepatic failure reported from world wide post-marketing surveillance (PMS) that

were associated with vigabatrin use, there was no discussion of the potential risk in the NDA.

As with the safety data, there were also several problems with the efficacy data for the two RCTs purported to support evidence of efficacy. An agency re-analysis of study 025 was necessary because of concerns about the data quality. Dr. McCormick discovered 32 patients in study 025 who received concomitant AED treatment, a protocol violation, in contrast to the 24 identified by HMR. She also discovered that there were inconsistencies in the assignment of seizure counts for patients with "seizure flurries" seizure counts were not recorded during a patient's hospitalization. Since a similar audit of study 024 was not conducted by the agency, the NAE noted that the data for study 024 would have to be reviewed, verified and possibly re-analyzed if the application was eventually amended by HMR.

Summary of Dr. McCormick's Safety Findings from Review of the NDA

Starting on page 79 of Dr. McCormick's NDA review, she summarizes the safety issues of concern with vigabatrin. In addition to limitations of the autopsy, EP and MRI data to address the IME issue, she raised concerns about a series of literature reports on encephalopathy, confusion, ataxia, psychosis, hallucinations, aggressive behavior, depression and suicide. In the NDA, she observed an excess of hospitalizations and discontinuations in the US controlled data that were associated with psychiatric and CNS AEs. Dr. McCormick also described an excess of relatively commonly occurring (>1%) AEs that were significantly greater on drug than placebo and generally consistent with the occurrence of a peripheral neuropathy.

Ocular abnormalities were also reported more frequently with vigabatrin than placebo in the US controlled data leading Dr. McCormick to review US study 006 in detail. Ophthalmologic exams were conducted prior to and after the start of vigabatrin. She found more patients with poorly described ophthalmologic abnormalities and/or symptoms that had been identified by the sponsor.

Dr. McCormick also described 12 cases of hepatic toxicity that had been reported from post-marketing experience, 7 of which ended in death. Other findings that she noted to be increased with vigabatrin when compared to placebo included weight gain, decreased hematocrit, and decreased WBC counts.

Structure and Content of the Amendment Responding to the Issues Raised in the NAE Letter

On May 29, 1997 HMR responded to the NAE letter amending the application and purportedly addressing the limitations of the data contained in the NDA. In the period between the issue of the NAE letter and the amendment, the sponsor and review team discussed the issues in joint meetings and by teleconference. During these discussions, some general areas of agreement were reached about the form of an amendment to address the issues raised by the review team.

First, HMR agreed to rebuild the non-US database by collecting and translating the CRFs. Part of

the review team's concern about the non-US data originated from HMR's use of what were called "Individual Case Summaries". These patient summaries were completed retrospectively and perhaps unbind to drug assignment. Thus, HMR agreed to use the original CRFs to create new CRFs and to systematically collect data on patient discontinuations and serious AEs at the same time.

Because not all CRFs would be available for all patient exposures in the non-US development program, it was necessary to define three groupings of patient data. The "primary" non-US database would consist of all studies that collected data prospectively where *each* patient in a study had a supporting CRF. Patients who had CRFs but where other patients in the same study were missing CRFs would be placed into the "secondary" database. The secondary database would also contain patients from studies were the CRFs were completed retrospectively or under less rigorous study conditions. Finally, the non-CRF database included patients without formal CRFs sometimes where data had been collected based upon individual case summaries usually completed retrospectively.

In theory, the primary non-US data should be of good quality allowing for risk estimation since, by definition, each patient from a study was to be included. The secondary and non-CRF databases would seem to be most useful for serious AE description.

HMR also recruited clinical specialists to review the neurological, ophthalmological, psychiatric and hepatic safety concerns raised by the FDA. Each specialist or specialist group generated consultant reports on the safety issues in their respective area. HMR provided the reports and a company perspective on each issue in the amendment.

Finally, HMR also designed protocol 253 to address potential abnormal findings on ocular, neurological exams, EPs, and/or MRIs. Patients participating in North American studies who had been included in the NDA data and had potential abnormalities were evaluated with MRI, EPs, ophthalmologic and neurological examinations. These findings were used by the consultants in evaluating safety issues in their area of clinical expertise.

Approach to Reviewing the Amendment

The amendment consisted of 507 volumes that mostly contained information of non-US patients. It included a description of the process used to collect the non-US CRF data; summaries of safety findings; some supporting materials such as CRFs, patient narratives, data tabulations; consultant reports, and an integrated review by HMR. While the US data was not formally resubmitted, they were referred to, and in some cases, included in tables of the integrated review. HMR also provided an integrated database which also included the US data. Findings from study 253 were included as data tabulations and discussed by the consultants and sponsor, but there was no formal study report.

Drs. Boehm and Sherry reviewed NDA amendment for selected safety issues. Dr. Boehm

focused on the overall review of the non-US safety findings in the primary, secondary, non-CRF databases, ophthalmological findings from protocol 253, and considered the consultant reports on ophthalmologic, hepatic, and psychiatric safety. Dr. Sherry, a neurologist with experience in EP interpretation, reviewed the IME and peripheral neuropathy issues focusing on the consultant reports that considered the findings from MRIs, EPs, neurological exams and at autopsy. Dr. Sherry also reviewed the sponsor's efficacy reanalysis of study 024.

Summary of Findings from Review of the Amendment for Safety

Sources of Data in the Amendment

The data cutoff dates for the non-US data and PMS data was December 31, 1995. A non-integrated safety update for serious AEs was provided for events occurring from January 1, 1996 through March 15, 1997. The update included AEs that were reported in patients with ongoing exposure in the development program and from AEs reported from worldwide PMS.

Quality of the Data Contained in the Amendment

Dr. Boehm has cross checked the data on the "new" CRFs with the data in the safety database, examined the coding of investigator verbatims and performed a general audit of the data. He concluded that the data contained in the amendment accurately reflects the data on the CRFs and that the primary non-US data seem of reasonable quality. As in other NDAs, there is no way for the clinical review team to cross check the data in the CRFs with source documents. Dr. Boehm does raise an issue that requires some clarification by HMR. It is unclear in the amendment how often individual case summaries were used as a source of data for patients included in the primary non-US database.

The overall value of the secondary and non-CRF data is questionable because of the absence of CRFs, methods of data collection and uncertain numbers of patients exposed. The non-CRF data, in particular, may be of limited value because of the absence of key information for many events. For example, it was not possible to verify that some AEs of interest even occurred while the patients were on vigabatrin. While the sponsor argues that the secondary non-US data are of sufficient quality to combine with the primary database, I disagree. The secondary database does not include every patient from a study and it also includes patient data collected under less rigorous conditions.

The PMS data provided by the sponsor consists of all serious AEs reported up to the cutoff dates. As with most PMS data, the overall quality and detail provided are limited. HMR also provided findings from a UK PEM study. PEM identifies UK users of a medication and then surveys the primary care physicians for each patient asking about AE occurrence. These data are most useful for identifying uncommon well defined events that may be associated with a drug's use. While the PEM study findings for vigabatrin have been summarized by the sponsor in the amendment, there are limited clinical details for many events of interest. As with most PEM studies, there

was also no comparison cohort to help interpret the event rates observed in the study.

Extent of Exposure

There were 1726 patients contributing an estimated 1039 person-years of vigabatrin use in combined the US and primary non-US data. Of these 1726 patients, 286 were exposed and followed for at least 1 year. HMR did not describe the extent of experience as a function of dose.

While there was substantially more exposure in the secondary and non-CRF databases, these data are of uncertain value.

Review of Deaths

The sponsor estimated all-cause mortality and SUD rates in the US and primary non-US data. As shown in Dr. Boehm's review (page 14 and 20), the rates were similar and consistent with those that we have observed in other AED NDAs. There were no deaths with placebo in the vigabatrin development program.

In calculating the SUDs rate, the sponsor applied Leestma's criteria to classify deaths. While Dr. Boehm does not specifically comment about the accuracy of the classification, there appear to be 1 and maybe 2 additional deaths that could be reasonably classified as sudden and unexpected. However, the vigabatrin SUD rate remains within the range of those observed in other AED NDAs even when counting these two deaths.

Dr. Boehm also examined the clinical characteristics of the deaths and, for the most part, did not find any unusual events that were associated with death. There was one patient reported in the safety update who died with fulminant hepatic failure in a Japanese study. There were no deaths suggestive of the occurrence of aplastic anemia, agranulocytosis, rhabdomyolysis, hemolytic anemia or severe skin rash.

Review of Dropouts and Serious AEs

In Dr. McCormick's review of the US data, she found increased all-cause and AE dropout rates that were greater with vigabatrin use than placebo. As shown in Dr. Boehm's review, all-cause and AE dropouts were also more frequent with vigabatrin in the primary non-US database than placebo.

Most AE dropouts in the US and primary non-US data were attributable to AEs classified in the CNS or psychiatric clinical systems. The most common causes of dropout in US studies were dizziness, seizures and depression, all associated with dropout in about 2% of patients. Leading to dropout somewhat less frequently were fatigue, headache, amnesia, agitation, paranoid reaction and thinking abnormal. The AEs associated with dropout were generally similar in the non-US primary database to those in the US data.

As we have observed in other recent AED NDAs, the apparent mental status changes are poorly described as reflected by the medical terminology used to describe the events (e.g., amnesia and thinking abnormal). Dr. Boehm reviewed some the AEs coded as thinking abnormal and found events described by investigator as decreased calculation skills, decreased cognitive function, poor comprehension, slow mentation , etc. Amnesia was used to code events relating to poor memory, but not actual amnestic events.

In the secondary and non-CRF databases, the clinical nature of AE dropouts were generally similar to that observed in US and primary non-US database. There were no discontinuations that classified by the sponsor as hepatic failure or necrosis, pancreatitis, aplastic anemia, agranulocytosis, rhabdomyolysis, hemolytic anemia or severe skin rash .

The sponsor addressed serious AEs by providing separate presentations of hospitalizations, AEs leading to disability or those associated with cancer occurrence. The purported types of AEs were not any different from those observed with dropouts for the primary, secondary, or non-CRF and US databases. There were no hospitalizations for aplastic anemia, agranulocytosis, rhabdomyolysis, hemolytic anemia or severe skin rash . The one death associated with hepatic failure and noted before was hospitalized.

Common AE Occurrence, Laboratory and Vital Sign Findings

As with AE dropout and serious AE occurrence, the more common events associated with vigabatrin were in the CNS and psychiatric systems. In the controlled data from the US and non-US (using the first period crossover in crossover studies), the AEs that were reported in 2% or more vigabatrin patients and two time greater than placebo were nystagmus (12%), depression (12%), amnesia (9%), weight increased (8%), confusion (7%), paresthesia (6%), concentration impaired (5%), speech disorder (4%), thinking abnormal (4%), dysmenorrhea (at least 4% but males included in the denominator), hyporeflexia (3%), UTI (3%), edema dependent (3%), eye pain (3%), eye abnormality (2%), dyspnea (2%), pruritis (2%), sweating increased (2%), hemorrhoids (2%), personality disorder (2%), and twitching (2%).

The AEs suggestive of peripheral neuropathy, ocular abnormalities, mental status changes and reports of depression are consistent with findings in Dr. McCormick's review and will be discussed in more detail below. The increased rates of dependent edema, UTI, dysmenorrhea and dyspnea, however, appear to be new concerns. I find the increased rates of reported UTIs and dysmenorrhea particularly surprising. In the AE letter, we need to ask HMR to provide a description of these cases. HMR has also included males in the denominator for dysmenorrhea as well as other menstrual disorders.

In the review of the laboratory findings in the controlled studies, there was a dose dependent decrease in the hematocrit compared to placebo without a similar decrease in hemoglobin. On page 41 of Dr. Boehm's review, he describes the percentage of patients with clinically significant

decreases in their hematocrit (females <= 32% and males <= 37%). He found that in the US studies 13% of patients on vigabatrin had at least one clinically significant decrease in hematocrit to 6% of patients on placebo. Two of the patients assigned vigabatrin who had such a decrease in the hematocrit also had clinically significant decreases in hemoglobin.

To address the issue further, Dr. Boehm also reviewed the AEs that were coded as anemia. In the US database, there were 12 patients who had at least one AE coded as anemia. Of these 12 patients, none were hospitalized and none dropped out of the study. For 10 of 12, there was no clinical information. Both of the remaining patients with some clinical information were noted above as having clinically significant decreases of both the hematocrit and hemoglobin. One patient was 31 year old female who had a decrease in hemoglobin from 12.6 at baseline to 10.8 and then 11.9 on the last report. The other patient was a 63 year old female who had a decline in hemoglobin of 12.8 to 8.8. According to the report, the etiology of the anemia was purported to be iron deficiency. Neither patient had any other hematological abnormalities noted and there was no data on RBC indices or reticulocyte counts.

There were 10 patients in the non-US database coded with anemia. As in the US experience, none of the patients were hospitalized or dropped from the study. As before, there was minimal clinical information on the events.

There was also a increase in the percentage of patients who were considered to have had a clinically significant decreases in WBC count. In US controlled data, 10% of patients on vigabatrin had a low WBC compared to 5% of placebo. None of these were classified as serious and no patients discontinued because of a WBC decreases. There were no cases of agranulocytosis or aplastic anemia in the development program. There may have been one pancytopenia although it was not identified as such by the sponsor (patient 30236903 is described on page 42 of Dr. Boehm's review).

For some reason, the sponsor did not analyze either the urinalysis or coagulation laboratory data.

Post-marketing Surveillance and UK PEM Study Findings

The sponsor has estimated that as of December 31, 1995 there have been about 254,597 person-years of worldwide vigabatrin use. They derived this estimate by assuming that the average daily dose was [redacted] and then used the annual sales data in grams to compute the time of use. b(4)

For the most part, PMS really does not identify any new types of events. I will discuss the reports of hepatic failure, the peripheral neuropathy, and abnormal MRIs in the following sections along with Dr. Boehm's and Sherry's review of these reports.

There was one report each for aplastic anemia and agranulocytosis. There were at least 2 spontaneous reports consistent with hemolytic anemia although they were poorly described by the reporter. On page 28 of Dr. Boehm's review he discusses a patient with hemolytic uremic

syndrome who was hospitalized and an 11 month old with hemolysis who continued on vigabatrin.

AEs observed in the PEM data were also mostly consistent with those occurring in the development program. There were no clear cut cases of hemolytic anemia, aplastic anemia, agranulocytosis or hepatic failure. MRI or EP abnormalities were not discussed. There was limited clinical detail provided for ocular or events suggestive of peripheral neuropathy. There were at least 26 patients of the 10,178 in the study who developed a symptom suggestive of peripheral neuropathy. Some patients with ocular abnormalities were noted, but not well described.

Summary of Vigabatirn Safety Issues

IME

Vigabatrin use has been associated with white matter vacuolization (IME) that was apparent as early as 2-4 weeks after first exposure in rats, mice, dogs and possibly in monkeys in studies with relatively high doses. The lowest doses studied, however, were also associated with vacuolization with longer durations of use.

In addition to vacuolization, other changes suggestive of axonal degeneration were also observed after extended exposure at sites where vacuolization have been seen in other studies. These same changes were also observed in discontinuation type study designs where vacuolization was not observed. One interpretation would be that while vacuolization appears to decrease after a period of no exposure following long-term use and may be an acute effect, the axonal changes may represent the consequences of the injury defined as vacuolization and, perhaps, are chronic.

Similar findings were observed in the MRI dog study that showed that MRI could detect both the presence of vacuolization and its resolution. However, the same study also suggested persisting MRI abnormalities even after this resolution. Adding more complexity to the interpretation was the observation in the same study that resolution of EP abnormalities coincided with MRI evidence of the resolution of vacuolization despite the persistent abnormalities.

Both the sponsor and the sponsor's consultants argue that there hasn't been a single confirmed case of IME in humans either in the development program or from spontaneous reporting. Their argument is based upon review of findings from autopsy, MRIs and EPs both in the development program including study 253, and from post-marketing experience. Dr. Sherry has reviewed the same data, and in his memorandum, he describes 6 patients with VEP changes and 5 patients with SEP changes from protocol 253 where the abnormality was not explainable by other pathology. He also discusses several patients with MRI changes that, in his opinion, can not be excluded as IME cases. The most compelling case seems to be the patient with a lesion found by MRI after about 7 weeks of use. Apparently, the lesion decreases in size after vigabatrin is discontinued and her clinical symptoms also resolve. While the case is interesting, it would be

more compelling if the preceding MRI had been done closer to the initiation of vigabatrin and not 2 years before.

While I agree with the sponsor's conclusion that there have been no confirmed cases, I also agree with Dr. Sherry's more agnostic conclusion that we really don't know whether humans are at risk for IME and there really is limited human data to address the issue. In fact, there appears to be very little data in patients with extended use of least 1 year. The exact numbers of patients with pre and post (interim) MRIs by duration of use has not been well described in the NDA. Such description may be useful for labeling.

In my opinion, the labeling should include a warning about IME summarizing the animal toxicology findings and the limited human experience, thus far.

Peripheral Neuropathy

As noted in Dr. McCormick's review of the NDA, there are AEs suggestive of peripheral neuropathy that occur in more than 1% of vigabatrin patients and at rate that is several fold greater than observed with placebo. The sponsor and consultants seem to consider this question as to whether these AEs are suggestive of IME and not whether vigabatrin causes peripheral neuropathy. Their only point was that all AEDs cause these sort of symptoms and seem to consider the difference in AE risk in the controlled data, which are add-on studies, as not relevant. For the most part, these events have not been analyzed in detail. There has been no analysis of dose, time since first use, reversibility on discontinuation and no discussion of nerve conduction studies etc.

There are also spontaneous reports of peripheral neuropathy. However as pointed out by Dr. Sherry there is little clinical data on dose, duration of use or reversibility.

In my opinion, the potential risk for peripheral neuropathy should be discussed in a warning statement particularly given its relatively common occurrence. The sponsor should also develop a case definition and explore the effect of dose, timing, reversibility, etc. Dr. Sherry would also like to review the nerve conduction study findings for those patients that have been so evaluated.

Depression and Psychosis

AEs coded as depression were common (>1%) and also one of the more common causes for vigabatrin discontinuation. Some of these events resulted in hospitalization and there was one suicide in the US data.

The sponsor's consultant developed a case definition of "depression" from the preferred coding terms and then confirmed the apparent increase in depression. He also examined the seriousness of the events in the controlled data and found 6 patients who discontinued because of depression and 3 who were hospitalized for depression. He apparently did not determine and then compare

the incidence of treated depression.

Psychosis, while not as common as the events coded as depression, was one of the more common reasons for drug discontinuation. In the US controlled studies one patient was hospitalized with psychosis. The same consultant who evaluated depression also developed a case definition for psychosis confirming that hospitalization and discontinuations for such events occurred with vigabatrin compared to none on placebo.

In my opinion, some description of both these events should appear in a warning statement perhaps included with the cognitive impairment description. It may also be helpful if the sponsor determines and compares the incidence of treated depression between vigabatrin and placebo examining dose and time since first exposure.

Cognitive Impairment

Like several recent AEDs with GABA activity, mental status changes occurred more frequently with vigabatrin use than placebo and were a common reason for drug discontinuation. However, as in the other NDAs, the terminology used to describe these events was not clinically meaningful (thinking abnormal) and in some cases possibly incorrect (amnesia). In my opinion, we should ask the sponsor to examine some of these events, and in particular their coding for AEs coded as amnesia, thinking abnormal, confusion, etc. The purpose should be develop a more meaningful clinical description of the events. I also think a warning statement describing these events is necessary and the sponsor needs to consider the effect of dose and time since first use on event occurrence.

Hepatic Toxicity

Across the development program, there has been 1 case of fulminant hepatic failure (FHF) reported in a Japanese study in the safety update. From PMS, there have been 21 reports of serious liver injury with 7 of these consistent with FHF. (There was also one other case reported in the safety update which we can include when the sponsor updates use.)

Using the 7 cases for which HMR has estimated global use, we get a reporting rate of about 2.7 per 100,000 PYs of use. The background rate in the general population for unexplained FHF ranges from about 2 cases per million PYs to 1 case per 100,000 PYs. There are no reliable estimates of the rate in a population using multiple AEDs. If we assume that 10% of cases are recognized and reported, then the actual rate would be 3 cases per 10,000 PYs. Most of the cases appear to have occurred more than 9 months of use with the earliest occurring after 4 days. (Pages 19 and 57 of Dr. Boehm's review.)

While it is certainly possible that the AED population has a relatively high background rate of fulminant hepatic failure, we have no experience or data suggesting this to be the case. Thus, given the seriousness of the events, a warning statement seems justified. We should also note that

there is a dose dependent decrease in the hepatic enzymes during vigabatrin use for which a mechanism has not been defined. The impact of such changes on LFT monitoring is unclear. We need a more detailed analysis of the decrease that was observed in the RCTs.

Ophthalmological Abnormalities

Since there were few patients in the US data (28) and non-US primary data that had pre-study and either post or on treatment ophthalmological exams, HMR uses the experience of 331 patients who had pre and post-exposure exams who were in the non-CRF database to argue that there is limited risk. In addition to question of the validity of these data, it is also unclear what type of exam was performed or what the level of training was for the health professionals who conducting them. I am not sure these exams even included visual field checks.

Of the 106 patients in study 253, there were color vision abnormalities in 30 and visual field abnormalities in 16. The field testing and abnormalities were not well described in the amendment. While the sponsor's consultants consider these findings to be more frequent than observed in the general population, they were uncertain as to the clinical significance.

Because protocol 253 selected patients for study on the basis of an existing abnormality from several other study populations, I agree with the sponsor's consultants that the overall rate of findings can not be compared with anything (actual denominator is unknown). However, I think the discussion should focus on very unusual findings, e.g. compelling cases of field cuts, and I don't believe the sponsor or consultants did that.

In considering this issue, I found a published abstract that described the findings from same PEM study of vigabatirn that was included with the amendment. Three patients were listed as having irreversible field cuts out of about the 10,000 patients followed. We could not locate a detailed description of these events in the amendment.

In my opinion, the labeling should include a warning statement summarizing the limited experience on the issue and describing the three patients from the PEM study, if the clinical details for the events can be obtained.

Pancreatitis

There were no cases of pancreatitis in the development program. There were several cases reported in the PMS, but most had pre-existing conditions that are considered to cause pancreatitis.

Hematological Abnormalities

There is a dose-dependent decrease in hematocrit with vigabatrin use. The effect on hemoglobin is less certain although there appeared to more patients on drug that have such decreases. The

mechanism for the decrease is unknown and there were few clinical details for patients identified with anemia. Thus, Dr. Boehm was unable to review reticulocyte counts, RBC indices, or other laboratory data that may be of interest in determining the type and clinical significance of the finding.

Recommendations

Issues for the AE Letter

1. Clarification of the extent of use at doses more than 3 grams per day.

In the amendment, it was not possible to evaluate the extent of use at higher doses. HMR has suggested 6 grams per day as the upper limit.

2. Analysis of AEs by dose, time since first use, age and gender.

For AEs that occur at or more than 1% of patients and 2 fold greater than placebo in the controlled portion of the RCTs, the sponsor needs to consider the effect of dose and time since first use on AE frequency.

While the sponsor described AE occurrence by age and gender there were several problems with that analysis. First, there were no corresponding presentation of the placebo data not allowing for calculation of attributable risk. For gender specific AEs, the sponsor includes males in the denominator.

3. Separate Analysis of the Pediatric Experience.

A separate analysis of the pediatric experience in he development program would be helpful given that there were as many as 200 pediatric exposures.

4. Analysis of Treated Depression.

Comparing the incidence of treated depression between vigabatrin and placebo may be in labeling.

5. Re-analyze the Incidence of Peripheral Neuropathy.

Developing a case definition of peripheral neuropathy and comparing the incidence between vigabatrin and placebo could make the labeling more meaningful. This analysis should examine the effects of dose, duration of use and reversibility upon discontinuation. A good case series that includes the findings nerve conduction studies would also be helpful.

6. Mental Status Changes.

Several codes such as thinking abnormal and amnesia may not be clinically meaningful. The effect of dose and time since first use on event occurrence has not been examined.

7. Laboratory Data.

To evaluate the clinical significance of the change in hematocrit and hemoglobin, HMR needs to examine more clinical data for these cases; reticulocyte counts, RBC indices etc. Since urinalysis and coagulation data were collected, it isn't clear why these data were analyzed. Finally, the description of the decrease in LFTs needs to be expanded by giving the number of patients with 80%, 60%, 40%, 20% declines from baseline for both vigabatrin and placebo.

8. Safety Update.

In the safety update, the findings for the US and primary non-US data can be integrated, but secondary data should not be integrated with the primary data.

9. Role of Individual Case Summaries.

HMR needs to clarify the use of individual case summaries in patients included in the primary non-US database.

G Burkhart 11/12/97

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

cc:HFD-120\Burkhart\Leber\Katz\Boehm\Ware\Sherry
NDA 20-427
HFD-120 Div. File

MEMORANDUM

DATE: November 9, 1997

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

TO: File, NDA 20-427

SUBJECT: Supervisory Review of Response to Not Approvable LEtter for NDA 20-427, for the Use of Vigabatrin as Adjunctive Therapy in Patients with Epilepsy

BACKGROUND

NDA 20-427, for the use of vigabatrin, an irreversible GABA-transaminase inhibitor, in patients with refractory seizures, was submitted by Marion Merrell Dow, Inc., on 4/29/94. The application contained the results of two adequate and well controlled clinical trials as well as experience in several thousand patients.

Unfortunately, the data were inadequately presented in the application, and a Not Approvable letter was sent to the firm on 4/28/95. The letter outlined 2 general areas of deficiencies: 1) there was inadequate collection of safety information deemed critical to an adequate assessment of the safety profile of the drug, and 2) there was inadequate reporting and analysis of critical safety and effectiveness data.

In particular, the initial application contained safety experience from 3 distinct cohorts of patients: 1) a domestic cohort of 537 patients, 2) foreign patients who had data collected on CRFs or other presumably equivalent documents (N=1233), and 3) a cohort for which their data was entered into the database from secondary sources (N=1550). The Agency had determined that the first (domestic) cohort provided reliable, prospectively recorded safety data. At the same time, we concluded that data from the third cohort could not be relied upon to assess the safety of the drug, because it represented data that had not been gathered prospectively, was incompletely recorded, and could not provide

information on the ultimate outcome of many patients. It was on the second (CRF) database that the Agency focused its attention. In the Not Approvable letter, we asked the sponsor to gain access to the CRFs (at the time of our initial review they claimed that they did not have access for many of these, and our initial review of the CRFs that we did have for other studies suggested that the sponsor not infrequently made errors in transcribing data from CRFs into the database), as well as to provide information about the reasons for discontinuations in this cohort, as well as detailed information about incidence and causes of hospitalizations.

Further, the submission was deficient in the reporting of safety data, including inadequately reporting findings that our independent review discovered on CRFs (for the domestic cohort), as well as lacking coherent reports about specific safety concerns (e.g., no discussion of serious adverse events).

Regarding effectiveness, we had concluded that one of the two trials presented supported effectiveness (Study 25), but the second study (Study 24) was inadequately analyzed and reported for us to make an independent assessment.

Specifically, the review team had identified numerous deficiencies in the sponsor's analysis of Study 25, including misclassification of patients with important protocol violations (e.g., took additional concomitant AEDs, misclassification of numbers of seizures experienced, lack of inclusion of seizures during hospitalizations). Extensive efforts by our review team permitted the identification of these flaws in Study 25, and permitted us to re-analyze it appropriately. In the Not Approvable letter, we asked the sponsor to undertake a similar audit of Study 24, and to re-analyze it utilizing the amended data.

In addition, the Not Approvable letter contained several biopharmaceutic and Environmental Assessment comments.

On May 29, 1997, the sponsor responded to the Not Approvable letter; many subsequent amendments were submitted.

These submissions have been reviewed by Dr. Jim Sherry, medical officer

in the division (review dated 11/5/97), Drs. Burkhart and Boehm of the division's Safety Unit (reviews dated 11/7/97, and 10/28/97, respectively), Dr. Todd Sahlroot of the Division of Biometrics (review dated 10/31/97), Dr. Vijay Tammara of the Division of Pharamaceutical Evaluation I (review dated 9/11/97), and Dr. Guzewska, chemist, (reviews dated 12/14/95, and two reviews dated 10/24/97). The environmental assessment was performed by Dr. Berninger and Ms. Sager (two reviews dated 8/7/97).

In this memo, I will summarize the pertinent safety and effectiveness findings, and explicate the basis for my recommendations.

EFFECTIVENESS

The sponsor has proposed that the drug be approved "... as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.".

As noted above, the Agency has previously determined that Study 25, a study comparing the effects of vigabatrin 1, 3, and 6 grams/day to placebo, was considered "positive", but that Study 24 could not at that time be considered so, until it was re-analyzed as requested. In the original NDA, the sponsor proposed that the drug be indicated for the treatment of partial seizures, with and without generalization.

It is critical to note that the protocols prospectively designated the primary outcome to be the effect of the drug on the combination of complex partial seizures (IB) and partial seizures that generalize (IC).

In the Not Approvable letter, though, the Agency noted that the evidence submitted did not permit us to conclude that vigabatrin was effective as a treatment for complex partial seizures that became generalized, (one of the types of seizures that wold have been included in a global claim for partial seizures) because the sponsor had submitted data on all partial seizures combined , but not for the individual types of partial seizures (simple and complex partial). As noted, the current proposal asks only for an effect on partial seizures (the language regarding generalization has been dropped by the sponsor). In addition, the Agency stated that the evidence does not support the conclusion that a daily dose of 6 gms

provides any additional seizure control beyond that afforded by a daily dose of 3 grams.

As both Drs. Sherry and Sahlroot note, the sponsor has audited their data and identified numerous patients whose data had to be amended. Specifically, a total of 54 patients had data that fell into 1 of 4 categories of misclassification as described either by the Agency or as constructed by the sponsor (inappropriate medical treatment for seizures, inaccurate seizure counts, a change in the dose of a concomitant AED, and reaching a protocol specified definition of increased seizure activity). Dr. Sherry has independently determined that 54 patients had data that fell into one of these categories, but he disagrees with the sponsor about into which specific categories a few of these patients' data fall.

According to Dr. Sahlroot, the sponsor's initial response to the NA letter was inadequate, because it excluded a significant amount of information inappropriately. Specifically, once the sponsor "accurately" identified patients who met the protocol violations described above, they excluded data from these patients from the point of the violation forward. Ultimately, based on conversations with Agency reviewers, intent to treat analyses were performed including all data and which used the revised seizure count data in a worst case approach. The following results were obtained:

	Median Baseline Frequency (IB + IC)	Median Frequency on Rx (IB + IC)
Placebo (N=90)	9.0	7.5
Vigabatrin (N=92)	8.3	5.5

The comparison yielded a p=value of 0.0143.

The previous analyses performed by the sponsor (in which data was excluded, as previously described) all yielded significant p-values.

While the overall results were strongly positive, it is of great interest to

examine the effects of treatment on individual seizure types (as discussed, to some extent, in the Not Approvable letter).

This is of critical importance because of the nature of the seizure types designated as primary in the protocol. Specifically, the types included in the primary definition include complex partial seizures that do not generalize (IB) and all partial seizures that generalize (simple partial seizures that generalize, and complex partial seizures that generalize-IC). This combination of seizure types does not lend itself to a meaningful or easily understood Indication section in labeling. It would be helpful, for example if we could conclude something about the effect of the treatment on **all** partial seizures (which the current definition does not include, because simple partial seizures that do not generalize are not included), or alternatively, conclude something about the treatment's effect on all simple partial seizures (which, again, are not all included), or on all complex partial seizures (which are all included, but the data for which are not analyzed separately).

While not all simple partial seizures are included in the primary data analysis, it would be reasonable, in my view, to permit an extrapolation from an effect of the drug on simple (or complex) partial seizures that generalize to an effect on simple (or complex) partial seizures that do not generalize (or vise versa); this is because we are not speaking here about an effect on generalization-a secondary event which is considered to reflect a complex series of neurologic events that differ markedly from the events leading to the initiation of a primary seizure-but an effect on the primary event-the simple (or complex) partial seizure. It is reasonable, in my view, to consider that the primary event is essentially the same, whether it goes on to generalize or not. I believe that this is especially reasonable considering that the drug effect we measure in these trials is the decrease in frequency, or **prevention of onset** of a primary seizure type. For this reason, were an effect shown, for example, on the frequency of simple partial seizures that generalize, I would feel comfortable extrapolating that effect to simple partial seizures that do not generalize, and, hence, to all simple partial seizures.

With these considerations in mind, the following results for individual seizure types of interest have been obtained (based on Dr. Sherry's Table

3, page 11 of his review):

Study 24

Seizure Type	Placebo Baseline	Placebo Endpoint	Vigabatrin (3 gm) Baseline	Vigabatrin (3 gm) Endpoint	P-value
IA	NA	NA	NA	NA	
IB	8.0	7.5	8.5	5.0	0.0006
IC	1.5	1.5	4.0	2.5	0.3881

NA-not enough patients to analyze

Study 25

IA	6.0	4.0	11.0	8.8	0.7511
IB	6.8	8.3	7.0	3.5	0.0014
IC	2.0	1.3	1.5	0.5	0.1828

As can be seen, although the studies were not designed or powered to examine the effects on individual seizure types, there clearly seems to be a differential effect on complex partial seizures that do not generalize (IB) compared to that seen on other seizure types. It is not unreasonable to conclude that the effect seen on the combined seizure types is largely the result of the effect on complex partial seizures. The data do permit serious questions to be raised about the effectiveness of the treatment on simple partial seizures (that do or do not generalize) because 1) any outcome in which these seizures are included (IA and IC) is negative, and 2) in the one study in which there were reasonable numbers of IA seizures (Study 25), there was no demonstrable effect.

While we have little affirmative evidence of vigabatrin's effect on complex partial seizures that generalize (these are a subset of IC seizures that have not been analyzed separately, but the numbers of IC seizures in general were sufficiently small that an analysis that looks at these seizures separately will likely be uninformative). Nonetheless, (reasoning

as I did earlier about extrapolating results from primary events that do not generalize to those that do), it seems reasonable to conclude that vigabatrin has been shown to be effective as adjunctive treatment for adults with complex partial seizures. For the record, I note that the data presented above were taken from the sponsor's analyses, which, as noted earlier, inappropriately excluded a significant amount of data. I recommend that the sponsor be asked to re-analyze the data appropriately, according to the rules applied by Dr. Sahlroot.

SAFETY

Dr. Boehm has conducted a detailed review of the safety data, and Dr. Sherry has provided a review of the neurologic findings, as they relate to any potential concomitant of the intramyelinic vacuolization seen in multiple animal species. In addition, he has reviewed the data that speak to the possible occurrence of a peripheral neuropathy. Dr. Burkhart has written a supervisory memo that summarizes the important safety findings.

Briefly, the sponsor has divided the non US data into several cohorts, depending upon whether or not data from studies were entered into the database from CRFs. Studies in which all patients had data prospectively collected on CRFs were considered to constitute the primary non-US database, and much of the safety review focused on this cohort. The total number of patients included in the US plus non-US primary database was 1726, and there were 3320 patients in the entire database.

The primary adverse events of interest (as well as the primary reasons for discontinuation) were related to the CNS , including dizziness, depression, fatigue, amnesia, paranoid reaction, thinking abnormal, agitation, confusion, psychosis, etc. A number of these terms, as in other NDAs for AEDs, were poorly defined.

Additional findings of interest (noted either in controlled trials, uncontrolled experience in the development program, or from post-marketing reports) included clinical findings consistent with peripheral neuropathy, hepatic failure, and ophthalmologic abnormalities. There were some relatively minimal attempts made to evaluate patients for the

possible occurrence of the vacuolization that was well documented in animals, with the sponsor's conclusion that there were no such occurrences. There were also some indications that vigabatrin use is associated with anemia.

Review of the safety database has revealed no bar to ultimate approval. However, as noted in the reviews by Drs. Sherry, Boehm, and Burkhart, there are still a number of questions that the sponsor must answer before adequate labeling can be written. Those issues are detailed in the attached Approvable letter and/or draft labeling.

BIOPHARMACEUTICS

In the Not Approvable letter, the Agency suggested that the sponsor perform formal interaction studies with vigabatrin and other commonly used AEDs (they had performed population pharmacokinetic analyses of the interactions from the clinical trial data). In addition, we asked that the sponsor study the effects of pH changes in the urine on the excretion of vigabatrin. Finally, the letter asked the sponsor to adopt certain dissolution specifications.

In his review of 9/11/97, Dr. Tammara agrees that the population pharmacokinetic approach to evaluating interactions taken by the sponsor is acceptable, given that vigabatrin does not undergo appreciable metabolism. Further, we are awaiting the results of a formal interaction study with phenytoin. If there is an interaction between vigabatrin and phenytoin, additional formal work may need to be completed. Further, the sponsor and OCPB have come to an agreement about dissolution specifications, which are slightly different (water instead of 0.1N H Cl as the medium) than the one proposed in the Not Approvable letter.

ENVIRONMENTAL ASSESSMENT

There are no outstanding problems.

SUMMARY AND RECOMMENDATIONS

The sponsor has submitted the results of 2 adequate and well controlled

trials that they believe provide substantial evidence that vigabatrin is effective as adjunctive treatment for partial seizures in adults with epilepsy.

Detailed analyses demonstrate that they have presented affirmative evidence of vigabatrin's beneficial effect on complex partial seizures that do not generalize. They have not directly demonstrated that the treatment has an effect on complex partial seizures that do generalize. However, based on reasoning described earlier, I believe it is reasonable to conclude on the basis of the evidence that the treatment has an effect on all complex partial seizures.

The sponsor has not demonstrated an effect on simple partial seizures that either do or do not generalize (indeed, what little evidence they have presented that has the potential to directly speak to the effect of vigabatrin on partial seizures suggests that it has none) . For this reason, I recommend that their proposed indication not be granted, but, instead, should be amended to state that vigabatrin is effective as adjunctive treatment for complex partial seizures in adults with epilepsy.

In addition, there are numerous questions about the safety database that the sponsor should be asked, and these are included in either the Approvable letter and/or the draft labeling.

For these reasons, I recommend that the attached Approvable letter with appended draft labeling be sent to the sponsor.

Russell Katz, M.D.

cc:
NDA 20-427
HFD-120

HFD-120/Katz/Leber/Sherry/Burkhart/Boehm/Ware
HFD-710/Sahlroot

19.1

NOV 5 1997

FDA

Review and Evaluation of Clinical Data

NDA:	**20-427**
Sponsor:	**Hoechst Marion Roussel, Inc.**
Drug:	**Sabril / Vigabatrin**
Proposed Indication:	**Add-on Therapy for Treatment of Complex Partial Seizures with or w/o Secondary Generalization in Adults**
Material Submitted:	**Amendment to a Pending Application**
Serial No.:	**001**
Correspondence Date:	**N (AZ)**
Date Received / Agency:	**05-29-97**
Date Received / Reviewer:	**05-29-97**
Date Review Completed	**11-05-97**
Assignments:	
Project Manager:	**Ware, Jackie**
Clinical Efficacy:	**Sherry, James**
Chemist:	**Guzewska, Maryla**
Pharmacologist:	**Rosloff, Barry**
Statistician:	**Sahlroot, Todd**
Clinical Safety:	**Boehm, Jerry**

1. Introduction:

Vigabatrin is a new molecular entity developed by the sponsor for the treatment of epilepsy. Vigabatrin is an irreversible inhibitor of GABA-transaminase. This inhibition results in the decreased catabolism of GABA, and consequently increased brain GABA levels. This review will focus on two areas: clinical efficacy review of the sponsor's revised analysis of US Study #71754-3-C-024 (C-024) using an ITT analysis with corrected seizure data and a review of the safety issue relative to intramyelinic edema (IME).

1.1 Regulatory History:

A brief review of the regulatory history is provided. A more detailed summary can be found in the Clinical Review of NDA#20-427 (March 5, 1995). The original IND# 17,213 was filed with the FDA in February 1980. In July, 1983, the IND was placed on clinical hold due to animal toxicology findings of intramyelinic edema (IME). In May, 1984, an FDA Advisory Committee concluded that the clinical testing could proceed if the sponsor agreed to perform pre-clinical toxicology studies aimed at detecting IME at early stages. In October, 1985, a FDA Advisory Committee met to discuss findings of IME in a monkey study. The committee recommended that no new human subjects be entered into clinical

trials until the safety issues were resolved. In November 1985, the FDA issued a letter based on the recommendations of the advisory committee. The sponsor was advised that clinical testing could not proceed until a method of detecting the earliest pathological changes in animals could be developed and validated and until it could be demonstrated that these changes were reversible. In December, 1988, the sponsor submitted a proposed US protocol. In November, 1989, a FDA Advisory Committee recommends resumption of US trials with monitoring. The clinical hold was removed in April, 1990. A pre-NDA meeting was held in January, 1993. NDA #20-427 was submitted to the FDA in May, 1994.

1.2 Not Approvable Letter:

A not approvable letter was issued on April 28, 1995. In that letter deficiencies in two general categories were described: "1) Inadequate collection and availability of important safety information, and 2) Inadequate analysis and reporting of information collected relative to both effectiveness and safety. "

The clinical and statistical reviewers performed a complete and independent review of the data submitted for study C-025. In auditing this data, the reviewers noted numerous discrepancies in the following areas: medical intervention for seizures, inaccurate seizure count, changes in concomitant antiepileptic drug (AED) dose and twofold increase in IB or IC seizures, or status epilepticus. Following this reanalysis, the reviewers were persuaded that study C-025 was positive. It was recommended that any resubmission of this NDA should included a similar audit and reanalysis for study C-024.

The information provided in the safety portion of the NDA failed to show that vigabatrin is safe. The deficiencies in the safety database were of two types: 1) Inadequate collection of potentially important safety information, and 2) Inadequate reporting of adverse event data collected.

In addition, the following biopharmaceutics issues were raised. The sponsor should: 1) perform more formal interaction studies to examine the effects of Sabril® on plasma levels of AED drugs, as well as studies to examine the effects of these drugs on Sabril® plasma levels, 2) study the effect of pH changes in urine and its influence on the urinary excretion of vigabatrin, and 3) adopt the following dissolution methodology and specification for vigabatrin 500 mg film-coated tablet:

Medium: 900mb 0.1 N HCl at 37 + 0.5 C
Apparatus: USP Apparatus II (paddle) at 50 rpm
Specification: Not less than [redacted] in 30 minutes. b(4)

Finally, deficiencies in the environmental assessment should be corrected. Specifically, the exact address for the site of disposal of drug substance and drug product should be included in the Freedom of Information (FOI) releasable environmental assessment document.

1.3 Background:

On May 29, 1997, the sponsor submitted a response to the not approvable letter. That response included an amendment to the NDA. An audit and reanalysis of study C-024 was completed. An In-House organizational meeting was held on June 30, 1997. It was decided that in addition to the analysis performed by the sponsor for this amendment, a traditional intent-to-treat analysis should be performed utilizing the audit data. This review will focus on that audit and reanalysis. In addition, the amendment addressed safety, biopharmaceutical and environmental assessment issues. These issues will be reviewed by the respective review teams.

1.4 Chemistry:

1.4.1 Name: SABRIL ® (vigabatrin)

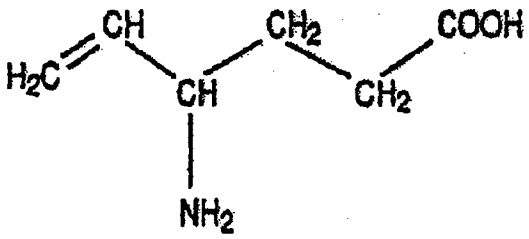
1.4.2 Chemical Name: (±)–4–amino–5–hexenoic acid

1.4.3 Molecular Formula: $C_6H_{11}NO_2$

1.4.4 Molecular Weight: 129.16

1.4.5 Drug Category: oral antiepilepsy drug

Figure 1. Structure



1.5 Pharmacology:

In vitro, vigabatrin is an irreversible inhibitor of GABA-transaminase (GABA-t). *In vivo*, single doses of vigabatrin produce dose-dependent inhibition of GABA-t and increase in brain GABA levels.

2. Efficacy: U.S. Study #71754-3-C-024 (C-024)

2.1 Previous Agency Review(s):

The total, in studies, exposure has been 3320 subjects receiving vigabatrin and 492 subjects receiving placebo. In the US, two placebo controlled efficacy studies have been completed, C024 and C025. An additional four open label extension or primary safety studies (C020, C026, 097-005 and 097-006) have been completed in the US. A total of 443 subjects have been exposed to vigabatrin in these epilepsy trials. In addition, 66 subjects in PK studies and 28 in non-epilepsy studies were exposed to the study drug. The total US exposure under IND is 537 subjects.

Two adequate and well controlled studies have been conducted by the sponsor in support of efficacy in epilepsy. US Studies #71754-3-C-024 (C-024) and #71754-3-C-025 (C-025) were submitted as the pivotal trials in epilepsy. Specifically, these studies were designed to show efficacy of vigabatrin as an adjunctive therapy in subjects with refractory epilepsy. Study #71754-3-C-025 evaluated the dose response across three doses of vigabatrin, lg, 3g, and 6g, and placebo. This study has previously been reviewed by Dr. McCormick and will not be examined in detail for this review. Study C-024 evaluated the efficacy of vigabatrin 3g daily compared to placebo. This audit / reanalysis of this study will be the primary focus of this review. In addition, 13 non-US placebo controlled trials were performed to evaluate the efficacy of vigabatrin in complex partial seizures. The studies have previously been reviewed by Dr. McCormick and will not be discussed in this review.

On March 5, 1995, Dr. Cynthia McCormick completed her clinical review of vigabatrin. The clinical review included the efficacy review of US Studies #71754-3-C-024 (C-024) and #71754-3-C-025 (C-025). Study C-025 utilizes a double blind placebo controlled parallel group design. The study design is similar for C-024 and C-025. The study is divided into three segments. The first segment consists of a 12 week baseline period. The second segment is a 4 week titration period. In study C-024, the subjects are randomized to either vigabatrin 3g daily or placebo. In study C-025, the patients are randomized, 1:1:1:1, to placebo, vigabatrin 1 g / day, vigabatrin 3g / day, or vigabatrin 6 g / day. The third segment is a 12 week maintenance period. In both studies, subjects could enter into an open-label, long-term, 1 year study, designated #71754-3-C-020 (for study C-024) and #71754-3-C-026 (for study C-025). The primary efficacy measure was the frequency of complex partial seizures plus all partial seizures with secondary generalization (see Figure 2 for classification of epileptic seizures). This classification has been employed in Dr. McCormick's review and will also be employed in this review. Secondary efficacy measures included: Therapeutic

Success (≥ 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, and Evaluation of Therapeutic Effect.

Figure 2

1981 REVISION OF THE INTERNATIONAL CLASSIFICATION OF EPILEPTIC SEIZURES

I. Partial Seizures (seizures beginning locally)

A. Simple Partial Seizures (consciousness not impaired) (IA)

1. With motor symptoms
2. With somatosensory or special sensory symptoms
3. With autonomic symptoms
4. With psychic symptoms

B. Complex Partial Seizures (with impairment of consciousness) (IB)

1. Beginning as simple partial seizures and progressing to impairment of consciousness
   a. With no other features
   b. With features as in A. 1 through A.
   c. With automatisms

2. With impairment of consciousness at onset
   a. With no other features
   b. With features as in A. 1 through A. 4
   c. With automatisms

C. Partial Seizures Secondarily Generalized (IC)

In that review Dr. McCormick concluded: "Vigabatrin has been demonstrated to be effective as an adjunctive medication in the treatment of partial complex seizures at doses of 3g/day. No additional efficacy is found at doses of 6g/day or higher. The sponsor has failed to provide adequate affirmative evidence of the drug's safety." She recommended: "that vigabatrin be deemed Not Approvable by virtue of the fact that the sponsor has not met its burden to establish this drug's safety."

2.2 Materials Reviewed:

Integrated Summary of Efficacy, Protocol and Amendments for C-O24, study reports and appendices, and random CRFs in study C-024, Amendments to NDA.

2.3 Title:

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

2.4 Objective:

To evaluate the efficacy of vigabatrin 3g / day compared to placebo, when added to currently prescribed anti-epilepsy therapy in patients with uncontrolled partial complex seizures.

2.5 Design:

This is a multi-center , randomized, double-blind, placebo-controlled study with two parallel treatment groups. The study was conducted in the following five segments:

1. Initial evaluation: Patient were evaluated based on the inclusion / exclusion criteria to determine the eligibility for the study.
2. Segment I: Subjects meeting the entrance criteria were entered into this 12 week segment. The first 4 weeks were considered a training period during which the subjects were instructed on completion of seizure calendars. The last 8 weeks was considered the subjects baseline.
3. Segment II: This segment was a four week titration period. Subjects meeting the entry criteria during segment I were randomized to either placebo or vigabatrin.
4. Segment III: This segment is a 12 week maintenance period during which the subjects were received vigabatrin at 3 g / day or matching placebo. The last 8 weeks are considered maintenance.
5. Taper Segment: Only subjects that discontinue the study during Segments II and III and are not entering into the long-term open-label vigabatrin study are included in this segment. The study drug tapering increments are 1 g TDD on a weekly basis.

2.6 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. It should be noted that IC included all (both simple partial and complex partial) partial seizures with secondary generalization.

2.7 Audit Results:

Following the review of the initial submission of the NDA, the agency requested that the sponsor perform an audit of the data in study C-024 with attention to four categories: medical intervention for seizures, inaccurate seizure counts, change in AED dose, and two-fold increase in seizures or status epilepticus. The sponsor identified 54 subjects that fell in to at least one of these categories. Forty-one of the subjects had corrections in only one category, eleven subjects had corrections in two categories and two subjects had corrections in three categories.

Table 1

Protocol 71754-3-C-024 Audit Results Summary		
Category	Identified by Sponsor	Identified by Reviewer
Medical Intervention for Seizures	19	16
Inaccurate Seizure Counts	13	13
Change in AED Dose	11	13
Twofold Increase in Seizures or Status Epilepticus	11	12
Total	54	54

In reviewing the sponsor's audit results, specifically, the characterization of the audit category, three subjects were classified differently by the sponsor and the reviewer. The three subjects were 61004, 61009, and 65008. Subject 61004 (VGB) was hospitalized to rule out status epilepticus. He was classified as a medical intervention for seizures by the sponsor and as status epilepticus by the reviewer. Both classifications would have been protocol violations and handle similarly. The seizure count was corrected to make a two-fold increase in seizures. Subject 61009 (Placebo) was flagged because he took extra methosuximide due to increase seizures. He was classified as medical intervention by the sponsor, but as change in AED dose by the reviewer. Either classification would be considered a protocol violation. Subject 65008 (VGB) was flagged because the patient took an additional 25 mg of phenytoin. This event was classified as medical intervention by the sponsor and change in AED dose by the reviewer. Again both classifications are protocol violations which would be handled in a similar fashion.

2.8 CRF Review:

The case reports provided by the sponsor were computer generated case report forms. The data from this study was reported to the sponsor utilizing a remote study management system. Please see the complete description in the original NDA, IV. Biostatistical Approaches, A. Data Documentation for additional information. Workbooks were used at each site to collect patient data. This data was entered into a computer at the investigator's site, and subsequently transferred to the sponsor. Several CRFs selected from the placebo subjects with the least improvement in seizure frequency (or worsening seizure frequency) and the vigabatrin subjects with the greatest reduction in seizure frequency were reviewed. This review yielded results consistent with those reported by the sponsor.

2.9 Analysis Results:

The results of the analyses of the primary outcome, the median IB + IC (complex partial plus all partial onset generalized seizures) values are shown in Table 2. The original ITT, all changes, and VGB unfavorable changes analyses have previously been reviewed by Dr. McCormick and will not be repeated in this review. The sponsor was asked by the agency to perform a conventional intent-to-treat analysis using the corrected seizure data (see audit results above). This analysis confirmed a statistically significant reduction in seizure frequency (IB + IC) when 3g vigabatrin was compared to placebo (P=.0143).

Table 2

Efficacy Analysis for Study 71745-3-C-024

			Seizure Frequency (number / 28 days)		
Analysis	**Treatment**	**N**	**Baseline (95% CI)**	**Endstudy (95% CI)**	**p value**
Original Intent-to-Treat	Placebo	90	8.5 (6.5, 10.0)	7.5 (5.5, 9.0)	
	3g VGB	92	8.5 (6.5, 10.0)	5.3 (3.0, 6.0)	.0002
All Changes	Placebo	82	8.0 (6.5, 9.5)	7.3 (5.5, 9.0)	
	3 g VGB	83	8.0 (6.5, 9.5)	5.0 (3.0, 6.0)	.0104
VGB Unfavorable Changes	Placebo	58	8.0 (6.5, 10.0)	7.3 (6.0, 9.0)	
	3g VGB	65	8.5 (6.5, 10.0)	5.5 (3.0, 6.0)	.0098

Intent-to-Treat Corrected Sz. Data	Placebo	90	9.0 (6.5, 11.0)	7.5 (6.0, 9.0)	
	3 g VGB	92	8.3 (6.5, 10.0)	5.5 (3.5, 7.0)	.0143

2.10 Statistical Review and Evaluation

2.10.1 Previous Agency Statistical Review

On March 7, 1995, B. Taneja, Ph.D., completed a statistical review, which concluded: "In the opinion of this reviewer, the sponsor has provided sufficient statistical evidence in the sense of robust results of the effect of VIGABATRIN as an add-on treatment in patients with focal epilepsy with difficult to control complex partial seizures. The optimal dose of vigabatrin based on response appears to be 3g/day."

2.10.2 Statistical Review

Dr. Sahlroot concluded in his review of the Amendment: Response to Request (July 23, 1997) that the ITT re-analyses do not alter the statistical results contained in the original submission.

2.11 Conclusions

US STUDY #71754-3-C-024[1]: The ITT analysis of complex partial seizures (IB) was performed using the 173 patients who had a non-zero Baseline frequency of complex partial seizures. The frequency of complex partial seizures at End study was statistically significantly less for vigabatrin patients than for placebo patients (P= .0006). The ITT analysis of partial seizures secondarily generalized (IC) was performed using the 60 patients who had a nonzero Baseline frequency of partial seizures secondarily generalized. There was no statistically significant difference between the treatment groups (P=.3881). The intent-to-treat analysis, using the corrected seizure data, confirmed a statistically significant reduction in seizure frequency (IB + IC) when 3g vigabatrin was compared to placebo (P=0.143).

US Study #71754-3-C-025 [1]: One hundred and seventy-four (174) patients received study medication and were evaluated for efficacy (45 placebo, 45 lg vigabatrin, 43 3g vigabatrin, 41 6g vigabatrin). The primary endpoint for the evaluation of efficacy was the mean monthly frequency of complex partial seizures (IB) plus partial seizures secondarily generalized (IC) at End study (last 8 weeks of study) compared to Baseline (last 8 weeks of Segment I). A highly significant dose response relationship was observed between increased vigabatrin dose and

[1] C. McCormick; Clinical Review of the Sponsor's Original NDA Submission

decreased seizure frequency (P=.0001). The effect of lg vigabatrin dose was not statistically different from placebo, but the 3g and 6g vigabatrin doses were significantly superior to placebo. There was no statistically significant difference between the 3g and 6g vigabatrin dose groups. The ITT analysis of complex partial seizures (IB) performed using the 171 patients who had a nonzero Baseline frequency of complex partial seizures showed a statistically significant reduction in seizure frequency when placebo was compared to either 3g or 6g vigabatrin (P=.0014 and .0001, respectively). There was no statistically significant difference between placebo and 1 g vigabatrin (P=.1662) or between the 3g and 6g vigabatrin patients (P=.0557). The ITT analysis of simple partial seizures (IA), was performed using 73 patients who had simple partial seizures during baseline (nonzero baseline). None of the treatment comparison contrasts were statistically significant and there was not a statistically significant difference between any group and placebo. ITT Analysis of partial seizures secondarily generalized involved 53 patients who had a nonzero Baseline frequency of partial seizures secondarily generalized failed to show a statistically significant difference between the treatment groups in the End study frequency of partial seizures secondarily generalized (P=.4796), and none of the treatment comparison contrasts were statistically significant (P> .1828). The results of this study support vigabatrin 3g and 6g/day as equally effective adjunctive treatment in those patients with difficult to control complex partial seizures.

Based on this review and the previous review completed by Dr. McCormick, **Vigabatrin has been demonstrated to be effective as an adjunctive medication in the treatment of complex partial seizures at doses of 3g/day. No additional efficacy is found at doses of 6g / day or higher.**

2.12 Recommendations:

Approval is recommended. The indication should be clarified. Specifically, in the sponsor's proposed labeling, SABRIL is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy. The indication of partial seizures is misleading since, SABRIL was not studied in subjects with simple partial seizures. Secondary analysis in subjects with simple partial seizures with secondary generalization failed to demonstrate efficacy. The sponsor should present evidence in support of this claim.

Table 3

Seizure Class	Placebo		Vigabatrin 3 g		
	Baseline [c]	Endstudy	Baseline	Endstudy	P-Value
IB + IC	8.0	7.0	6.5	5.0	.0002
IA	*	*	*	*	*
IB	8.0	7.0	6.5	5.0	.0002
IC	1.5	1.5	4.0	2.5	.3881
Therapeutic Success [d] (IB+IC) [b]	21.1%		39.1%		.008
	Study 025				
	Placebo		Vigabatrin 3 g		
	Baseline	Endstudy	Baseline	Endstudy	P-Value
IB + IC	11.0	9.8	8.0	3.7	.0001
IA	6.0	4.0	11.0	8.8	.7511
IB	6.8	6.3	7.0	3.5	.0014
IC	2.0	1.3	1.5	0.5	.1828
Therapeutic Success [d] (IB+IC)	7%		51%		< .001

[a] from Dr. McCormick's review of the original NDA unless otherwise indicated.

[b] from addendum to NDA utilizing ITT with corrected seizure data.

[c] seizure frequency expressed as number / 28 days (median)

[d] defined as achieving at least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized.

* the sponsor reported not enough subjects to analyze

3. Intramyelinic Edema (IME)

3.1 Pre-clinical

Chronic administration of vigabatrin to animals produces intramyelinic edema (IME; vacuolation). The lesions are characterized by clear vacuoles

resulting from separation of the outer layers of myelin at the intraperiod line. The areas affected are to some extent species specific, but in general involve white matter tracts. There does not appear to be any involvement of the spinal cord or the peripheral nervous system. IME has been observed in the mouse, rat, dog, and monkey.

IME was observed in the mouse at low, medium and high doses. The primary areas effected included the cerebellum, reticular formation and the thalamus. In rats IME was noted at high dose (HD; 300 mg/kg) in the 3 month study and eventually at all doses in the I and 2 year studies. IME was seen primarily in white matter in several areas of brain; most affected were cerebellum, reticular formation, optic tract, anterior commissure, columns of fornix, colliculus, hippocampus, thalamus, cerebral peduncle, and corpus callosum. Although the IME lesions were not noted after a 3 month recovery period, other lesions were observed. These lesions consisted of eosinophilic spheroids (said to be suggestive of swollen or degenerated axons; gave positive response to staining with antibodies to neurofilament protein) and calcium-containing mineralized microbodies were seen (primarily in cerebellum) which were not reversible (and in fact appeared to become more pronounced [regarding incidence and size] during the recovery period).

In the dog, brain vacuolization, IME was seen at the middle dose (MD; 100 mg/kg) and HD (300 mg/kg) in the 3 month study; at MD (100 mg/kg) and HD (200 mg/kg) at 6 months and at all doses (LD = 50 mg/kg) at 1 year. The areas primarily affected included anterior and posterior commissure, hippocampus, median forebrain bundle, stria medullaris, cerebellar periventricular area, lateral geniculate body, mamillothalamic tract, corpus callosum, optic chiasm, habenular nucleus, and pretectal nucleus. The IME appeared to resolve after a 4 - 6 month recovery period.

In the regards to the monkey studies, the sponsor's pathologists and several consultants concluded that there was a possible / slight drug effect in HD monkeys. In these cases, the vacuolization was generally in the optic tract; one consultant also concluded possible effects in corpus callosum, septum, and cerebellum. In the range finding study vacuolization in the corpus callosum was seen in 1 monkey each at 500 and 750 mg/kg but the relation to drug was equivocal in view of the vacuolization seen in some controls.

3.2 Design

At the request of the agency, the sponsor employed independent experts to review the available data with respect to possible IME in human subjects. This evaluation was completed using a two-tiered approach. First, reviewers examined the individual sources of data i.e. MRI, EPs, and neurologic findings. The second tier consisted of an integrated evaluation by three reviewers with expertise in epilepsy and white matter disease. In addition, the sponsor designed Protocol 071754PRO253 for follow-up clinical examination (including EP, MRI, neurological

exam, ophthalmological exam, physical exam) on patients meeting "at risk" criteria for IME (based on EP and MRI data) or having abnormal ophthalmological exam data. Subjects previously enrolled in vigabatrin Protocols 097-005,097-006,71754-3-C-021, 71754-3-C-022.71754-3-C-024, 71754-3-C-020,71754-3-C-025,71754-3-C-026, or 71754-3-C-028 having changes or abnormalities described above were included in this protocol. The summary of subjects in protocol 071754PRO253 is shown in Figure 3.

Figure 3

Summary of Patients Selected for Protocol 071754PR0253

Reason for Selection	*Number of Patients Selected*	*Number of Patients Followed Up*		
		Still on VGB	*Not on VGB*	*Total*
Ophthalmological Abnormality*	57	16	22	38
Unresolved EP Prolongation	77	31	28	59
Both EP and Ocular	12	5	4	9
Total	146	52	54	106

* One patient (009-003), no longer on vigabatrin, was included for MRI changes in addition to EP and ophthalmological abnormalities.

Supporting Data: *Page*
Section G, 071754PR0253 CSR, Appendix D2: Patient Selection *Sg-V132-P227*

3.3 Evoked Potentials

3.3.1 Introduction:

Evoked potentials (EPs) are non-invasive methods to evaluate the functional integrity of sensory pathways i.e. visual pathway (VEP), auditory pathway (BAEP) and the somatosensory pathways (SEP). These test have been extensively used in evaluating patients with suspected central demyelinating diseases such as multiple sclerosis (MS). Assessment of EPs involves examination of the waveform morphology, amplitude, and latencies.

Several studies were conducted in the dog to establish a non-invasive method for monitoring IME. The two methods examined were evoked potentials (visual evoked potentials [VEP] or flash evoked potentials [FEP], somatosensory evoked potentials [SEPs], and brainstem auditory evoked potentials) and MRI. These studies are discussed in greater detail in the pharmacology-toxicology review. Changes in evoked potentials (SEPs and FEPs) were noted beginning at 4-10 weeks of treatment, these changes were correlated with histopathologic findings of IME, and were not seen in the control animals. Both the vacuolation (although in one study microgliosis persisted) and EP changes reversed during the recovery period. Brainstem auditory evoked potentials failed to demonstrate

a consistent correlation with IME. The MRI changes consisted of increased T2 and decreased T1 weighted signal. These changes were most notable in the columns of fornix and "less obvious in discrete areas extending throughout the thalamus and hypothalamus" (sponsor's description from the original NDA submission). The MRI changes occurred at weeks 4-7and correlated with the histopathologic changes. The sponsor reports that following discontinuation of vigabatrin administration in dogs, the MRI demonstrated near complete reversal of microvacuolation, Weiss, et al. [2]

Both the sponsor and the agency concluded that in the dog, EPs (VER and SEPs, but not BAEPs) and MRI were non-invasive techniques capable of early detection of IME.

3.3.2 Previous Agency Review of Evoked Potentials

A clinical review of the evoked potential data was completed on 02-21-95 by Dr. John Feeney. In study C-025, there were 28 patients with a ≥ 15% increase in EP latencies: 12 placebo, 7 low dose, 3 intermediate-dose, and 6 high dose. Review of the six cases observed in the high dose revealed that 3 of the cases were errors in recording or data recording and were subsequently interpreted (by Dr. Feeney) as normal. The remaining three cases were BAEPs. In study C-024, there were 15 patients with a ≥ 15% increase in EP latencies: 9 placebo and 6 vigabatrin. No tracings were reviewed for this study. In studies 020/026, 57 / 280 patients had a ≥ 15% prolongation in at least one EP. 20 / 57 had a continued prolongation and 37 / 57 developed a prolongation during these studies. A large portion of these patients had EP data which, although showed a ≥ 15% prolongation of latency, was still within normal limits. Dr. Feeney also reports that 41 patients who entered these studies with EP prolongations ≥ 15% improved during the studies such that they no longer had a ≥ 15% prolongation at the end of the study.

Dr. Feeney had three main conclusion after his review of these studies. The first concerned the quality of the evoked potentials and the recording of the data. Specifically, he noted that the waveforms were poorly reproducible, repeat studies when requested were not performed, and extreme latency prolongations were reported based on incorrect interpretation or recording of the numeric data. Secondly, the sponsor did not address the clinical significance of prolonged latencies. Finally, EPs were obtained after a relatively short exposure time i.e. 4 months. In dogs, at lower doses, the lesions were not observed until approximately one year. Dr. Feeney suggested that more meaningful results would be obtained from a study in which subjects received vigabatrin for 4-5 years.

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[2] K.L. Weiss, MD; C.E. Schroeder, PhD; S.J. Kastin, MD; J.P. Gibson, DVM, PhD; J.T. Yarrington, PhD; W.E. Heydorn, PhD; R.G. McBride, MD; N.M. Sussman, MD; and J.C. Arezzo, PhD; MRI monitoring of vigabatrin-induced intramyelinic edema in dogs; Neurology 1994; 44; 1944-1949.

3.3.3 Available Data:

Evoked potential measures from seven US and Canadian vigabatrin trials (including protocol 071754PR0253) were reviewed. 9221 evoked potential measurements from 530 patients were used for analysis. Case Report Form information, including all evoked potential tracings and reports, for 58 patients in US trials and 10 patients in Canadian trials with evoked potential increases of 15% at the final EP evaluation in the I-year follow-up studies (71754-3-C-022, 71754-3-C-020,71754-3-C-026) compared to baseline of the well controlled trials 71754-3-C-021,71754-3-C-024, and 71754-3-C-025 were reviewed. The effect of vigabatrin relative to placebo on evoked potential response was evaluated using percent change from baseline. Analyses were done for each of the controlled studies individually (71754-3-C-021, -024, -025) and pooled across all three studies as one. The non-US EP information was not reviewed by a consultant.

3.3.4 Consultant's (Sponsor) Review:

Dr. Brigell concluded the use of a multi-modal EP test battery was well suited for detection of changes in conduction velocity due to intramyelinic edema (IME). The reviewers concluded that "these data corroborate the conclusions reached in the current analysis of the US database in showing no EP evidence of a pervasive IME effect of vigabatrin in humans such as has been reported in dog and rat." In addition, he reported that of the 87 EPs that he reviewed, 9 had firm evidence of latency changes, 14 had had possible EP changes (either the waves were not available for evaluation or the recordings were of poor quality at follow up), 17 were invalid due to protocol violations at the centers (change in equipment, change in recording or amplifier settings), 3 had pre-existing pathology, 36 contained errors in wave identification, and 8 had errors in data entry.

3.3.5 Reviewer's Comments:

Review of the EP data from Protocol 071754PR0253 from subjects currently receiving vigabatrin revealed: 6 subjects with VEP changes not explainable by other pathology (i.e. retinal pathology), and 5 subjects with SEP changes not explained by other pathology (i.e. peripheral neuropathy, previous stroke). A similar review for subjects not currently receiving vigabatrin revealed: 4 subjects with VEP changes not explainable by other pathology (i.e. retinal pathology), and 6 subjects with SEP changes (including improvement from baseline) not explained by other pathology (i.e. peripheral neuropathy, previous stroke). Note BAEPs were not performed in this study even for subjects with abnormal BAEPs in the prior studies. The sponsor attributed this decision to three factors: BAEP data failed to demonstrate consistent correlation with IME in the dog experiments, relatively low number of subjects meeting the EP inclusion

criteria based on BAEPs, and BAEP data was not consistently obtained in other vigabatrin protocols.

The applicability of EPs in monitoring for IME depends on several factors. As stated above, one of the consultants concluded that EPs are well suited for detection of changes in conduction velocity due to IME. This statement is true only if the areas affected by IME in humans involve structures in the particular sensory pathway being evaluated. The animals studies have demonstrated that the location of IME lesions tend to be variable depending on the animal studied, although there is a significant amount of overlap in the distribution of the lesions. SEPs were useful in monitoring for IME in the dog, since the thalamus was an area affected by vigabatrin. Likewise, the VEPs were useful since structures in the visual pathway were affected. However, if the IME lesions in humans involve other areas i.e. cerebellum, pons, and corpus callosum, EPs would not be a useful tool for monitoring of IME. Another potential problem with EPs is the quality of the recordings. SEPs, in particular, can be technically difficult to perform and the results extremely variable between labs / technicians. In the dog studies, the animals were sedated for the studies. Sedation has the tendency to reduce muscle activity artifact and changes in the baseline due to movement. Human subjects were not sedated for EPs. Dr. Feeney, in reviewing the EP data (see evoked potential section above), concluded: that the waveforms were poorly reproducible, repeat studies when requested were not performed, and extreme latency prolongations were reported based on incorrect interpretation or recording of the numeric data. Similar observations were made by one of the sponsor's consultant, Dr. Brigell. Finally, as Dr. Feeney noted in his review, many of the EPs were obtained after a relatively short exposure time i.e. 4 months, during which time IME lesions may have not developed. One criteria for enrollment in protocol 071754PRO253 was a prolonged EP; the longest duration of exposure to vigabatrin at this enrollment was approximately 1 year. Subjects with normal EPs would not have been restudied.

3.4 Magnetic Resonance Imaging

3.4.1 Previous Agency Review of MRI Data:

On March 22, 1995, [redacted] b(4)

[redacted], completed a review of the clinical study report guide, the canine data, and the available MRI images (studies C-024, C-025, C-020, and C-026). He concluded that there were no cases in which the drug study images differed from the baseline images. However, he noted that there were a number of cases with poor image quality, motion artifact, or missing images.

3.4.2 Available Data:

The sponsor reports that MRIs were not routinely performed for non-US (except Canada) clinical trials, and the database rarely contains more than an indication of an MRI being performed. Therefore, MRI results were primarily collected from publications and internal reports and occasionally from Case Report Forms. MRI films from non-US (except Canada) clinical trials are not part of the patients' case records and, therefore, could not be reviewed by the consultants. MRI evaluations were completed for the US protocols as follows:

71 754-3-C-024	Baseline and Endstudy
71 754-3-C-020	Endstudy
71 754-3-C-025	Baseline and Endstudy
71 754-3-C-026	Endstudy
71 754-3-C-028	Within 6 months of entry and yearly thereafter
071 754PR0253	One MRI evaluation on this follow-up exam

Robert Peyster, MD, Chief of Neuroradiology at Stoney Brook Medical Center, and Gordon Sze, MD, Chief of Neuroradiology at Yale University School of Medicine reviewed MRI films from US and Canadian vigabatrin studies specifically for changes potentially indicative of IME. In addition, Dr. Peyster reviewed the films obtained on patients in the follow-up Protocol 071754PRO253. Dr. Peyster reviewed 388 subjects' MRIs and Dr. Sze reviewed 412 subjects' MRIs. Dr. Sze's review included 24 of 36 subjects for which no baseline MRI was available for review. A summary of the MRI information is provided in Figure 4.

Figure 4

Summary of MRI Information from US and Canadian Controlled Trials

Protocol Number Report Number (NDA Location)	*Number of Patients with Complete Sets of MRIs Reviewed*	*VGB Dose (Duration) Study Design*	*Results*
71754-3-C-024 K-93-0810-CS (NDA 9-1282, v1.04)	Placebo=74/90 3 g VGB=72/92	VGB 3 g/day (4 months) DBPC-parallel; add-on.	No changes suggestive of intramyelinic edema on any scan in either treatment group.
71754-3-C-025 K-93-0808-CS (NDA 8-8384; v1.114)	Placebo=36/48 VGB=109/129	VGB 1-6 g/day (4-6 months) DBPC-parallel; add-on.	No changes suggestive of intramyelinic edema on any scan in either treatment group.
71754-3-C-026 71754-3-C-028 K-94-0102-CS (120-Day Update, 36-V3.26-P6913)	VGB=228/324	Open label (12 months)	No changes suggestive of intramyelinic edema.
71754-3-C-021 Report in progress	Placebo=31/53 VGB=36/58	VGB 1-4 g/day (9 months) DBPC-parallel	No evidence of white matter changes suggestive of intramyelinic edema in either treatment group.
71754-3-C-022 Report in progress	VGB=57/87	Open Label (12 months)	No changes suggestive of intramyelinic edema.
A patient may have more than one MRI; therefore, counts cannot be summed to get the total number of patients with MRIs.			
Supporting Data: *Appendix A4, Listing 1: MRI's in US and Canadian Trials Reviewed by Dr Peyster (Dates of Review)*			*Page* Sg-V149-P365

Dr. Peyster identified 10 subjects in whom there was a difference in the follow-up MRI when compared to the baseline MRI. He concluded that the changes were not consistent with IME and were primarily interval surgical changes or artifacts. In addition, he concluded that there were no changes consistent with IME. Likewise Dr. Sze concluded that no MRI changes consistent with IME were seen. Three (3) subjects discontinued vigabatrin administration due to MRI changes considered by the investigators to be possibly related to vigabatrin. In two of the three cases no baseline MRI was available for review. The cases are summarized (from the sponsor's submission) below.

Patient 009-003 (Protocols 097-005,097.006,71754-3.C-028,071754PRO253): This 58-year-old postmenopausal female discontinued vigabatrin after 11 years because of ataxia, diplopia, dizziness, nystagmus, visual abnormality ("blurred vision"), and "brain atrophy." She titrated to 4 g/day in Protocol 097-005, was on 1.5-5 g/day in Protocol 097-006, then entered Protocol 71754-3-C-028 and was maintained on 5 g/day. At baseline in Protocol 005, the patient was taking 1600 *g/day carbamazepine and 1000 *g/day primidone and reported no baseline adverse events. Nystagmus was reported after 6.5 years of vigabatrin therapy. Ataxia, diplopia, dizziness, and blurred vision began after 10 years of vigabatrin therapy, while on 5 g/day. The investigator assessed these adverse events as possibly related to vigabatrin and reduced the vigabatrin dose to 4.5 g/day. The ataxia, dizziness, and diplopia worsened and the investigator assessed this worsening as possibly related to vigabatrin, when the dose was 2.5 g/day. The vigabatrin dose was tapered to discontinuation. The duration of the ataxia, diplopia, dizziness, and blurred vision was 14.4 months: these AEs resolved 1 month after vigabatrin was discontinued. The outcome of the nystagmus was not established at endstudy in Protocol 71754-3-C-028. Vigabatrin was discontinued because of worsening dizziness and ataxia on 12/04/92, and because of the results of an MRI conducted on 12/07/92. Supplementary information on the Case Report Form states that vigabatrin was "also discontinued due to MRI results" showing a "small area of demyelination in the white matter; cerebellar and cerebrocortical atrophy." No baseline MRIs were available on this patient because she participated in Protocols 097-005 and 097-006, during which MRIs were not performed. Review of this patient's MRI scans (the first at entry to Protocol 71754 3-C-028, a second at the time of discontinuation. and the third in Protocol 071754PRO253) did not reveal notable differences. No IME related abnormalities were observed on this patient's MRI studies. (* divided doses)

Patient 1194-0010 (Protocol VGPR0098): This 53-year-old postmenopausal female was discontinued from vigabatrin in Protocol VGPR0098 on 2/13/96. Vigabatrin was discontinued when a fairly large discrete demyelinated lesion in the corpus callosum was identified by MRI on 2/5/96. The MRI was conducted because of increased seizure frequency. The radiologists, [redacted], raised the possibility of multiple sclerosis. Dr. Eun-Kyu Lee, principal investigator for Site VGST1194 (Sacramento, California), assessed the adverse event as possibly related to the patient's vigabatrin therapy. The patient had been taking vigabatrin up to a maximum of 4 g/day for a total exposure of 46 days (12/18/95 to 2/l/96) at the time of the adverse event.

b(4)

Patient GADERS ID 96002420 (Spontaneous UK): A spontaneous report from the UK described a 56.year-old female epilepsy patient who experienced severe visual field defects during therapy with vigabatrin 3 g/day (therapy duration not provided, approximately 6 years) that was considered to be medically serious. During evaluation of the visual abnormalities, an abnormal brain MRI consistent with possible demyelination was observed that was also considered medically serious; however, baseline MRI data prior to vigabatrin therapy was not provided.

3.4.3 Consultant's (Sponsor) Review:

In case Patient 009-003, the reviewers concluded that this was not consistent with IME. In the case of Patient 1194-0010, there was disagreement among the consultants as to whether this case was consistent with IME and whether or not it was related to vigabatrin. The case of Patient 1194-0010 will be discussed in more detail below, in the section review of safety reports. One reviewer concluded that this case is "suspicious for IME". In the case of Patient GADERS ID 96002420, the reviewers concluded that this case was not consistent with IME. An additional two cases of lesions with increased signal on T2 weighted images (subject 010-118 in the pons and subject 066-005 in the inferior temporal lobe) were noted by Dr. Peyster. He conclude that these were most likely artifact, since the areas were not seen on the two different images i.e. axial vs. coronal.

3.4.4 Reviewer's Comments:

Several of these cases, based on the available information, can not be excluded as possible cases of IME. Probably the most compelling cases is Patient 1194-0010 (Protocol VGPR0098). This case will be discussed in detail later in this review. The case of Patient 009-003 (Protocols 097-005,097.006,71754-3.C-028,071754PRO253) is not inconsistent with IME. The rapid resolution of the symptoms is difficult to interpret. In the animal studies, the symptoms were usually emesis and diarrhea, the resolution of which was not well characterized. Rats treated with vigabatrin developed seizures. The seizures persisted in some animals for up to 12 months after discontinuing the vigabatrin. It is conceivable that this patient's symptoms were due to "acute" effects of vigabatrin (as can be seen with other anticonvulsants), but it would be unusual to develop after 11 years. I am not convinced based on review of the MRI data that IME does not (has not) occurred in humans.

3.5 Autopsy / Neuropathology

3.5.1 Available Data:

The sponsor reports that as of 12/31/95, autopsy information was available on 42 / 123 deaths reported in patients taking vigabatrin. Of those subjects, nine patients had no brain evaluation. Thirty-three (33) subjects had autopsy evaluations which included the brain. Of the autopsies with brain evaluations, only 23 had histologic evaluations. Nineteen of the 23 cases were reviewed by a consultant and 4 by the medical examiner. Treatment duration for these subjects ranged from 0.6 months to 9.6 years. In 12 of 23 autopsies, the duration of exposure to vigabatrin was less than 12 months. The sponsor has suggested that immunocytochemical methods were utilized to allow differentiation of antimortem histological lesions, in which gliosis is present, from postmortem lesions, in which

a glial cellular response is not seen. Specifically, the sponsor states "vacuolation in the absence of gliosis was considered to be artifactual". However, the sponsor reports in the section Animal Histopathology Using Immunocytochemical Staining Procedures (Sa-V1-P167) that astrocytosis was not consistently associated with vacuolation i.e. some areas of vacuolation were not associated with gliosis and areas of reactive astrocytosis were not associated with vacuolation. Immunocytochemical methods (GFAP for astrocytes and NFP for axonal neurofilament) were applied to tissues of 14 vigabatrin-treated patients. Five (5) of the 14 autopsies with immunocytochemical analysis involved durations of exposure longer than 12 months. Only 1 / 5 included examination of the thalamus, and none specifically examined the corpus callosum. Vacuolization was observed in 4 cases, but utilizing the above criteria was considered artifactual. Three cases of gliosis were reported. Autopsies performed in 11 subjects with epilepsy, but not treated with vigabatrin, revealed 3 reports of vacuolization and 7 reports of gliosis.

3.5.2 Consultant's (Sponsor) Review:

The reviewers concluded that there was no evidence of IME in human brain.

3.5.3 Reviewer's Comments:

The sponsor defined any vacuolation not associated with gliosis as artifactual. The sponsor has not provided specific data to support this statement. In addition, the sponsor has suggested that vacuolation occurs in epilepsy patients not treated with vigabatrin and sited the results of autopsies performed as part of their study on this patient population. The sponsor does not quantify this background vacuolation.

On reviewing the autopsy reports, several cases are worthy of discussion. For Patient No. 21202, the pathologist reports that "the myelin splitting although variable appears to be greater than might be expected by hypoxia alone." He goes on to state " the possibility that epileptic therapy may have been a contributing factor cannot be excluded. Several cases of vacuolation are reported in autopsy cases of subjects with epilepsy receiving vigabatrin and also, to a lesser degree, in subjects with epilepsy not treated with vigabatrin. For patient 533300024, with a 6 month exposure to vigabatrin at 4 g / day, the pathologist reports diffuse vacuolation throughout which he summarizes as probably artifactual, and in the body of his report he states" it can not be determined whether this is artifactual or not." For patient VGZ-9400-6444, with a 11 month exposure to vigabatrin, the pathologist concludes "widespread myelin vacuolation which is not specifically associated with reactive astrocytosis or microglial activation and should therefore be considered as an artifact". Areas effected by this vacuolation included: temporal lobe ("extensive"), pons, thalamus,

optic tracts and chiasm, and cerebellum. A similar case is reported for patient N107-90, without exposure to vigabatrin.

The sponsor has concluded that there is no evidence of IME in the autopsy cases. Without validation of the sponsor's definition for artifactual vacuolation and without quantification of the background vacuolation, it is difficult to make any conclusions about the available autopsy data. The ability to draw conclusions is further limited by the small sample size, limited exposure to vigabatrin, and limited evaluation of potentially involved CNS areas. I can not conclude from this data that IME does not occur in subjects receiving vigabatrin.

3.6 Neurologic Findings

3.6.1 Available Data:

In response to concerns expressed by the agency, the sponsor employed two consultants (neurologists / epileptologists) to review the available safety data for evidence of neurologic changes potentially related to vigabatrin. Two areas were of specific concern, IME and peripheral neuropathy. Four sets of data were reviewed.

3.6.1.1 Incidence Tables for Changes in Neurological Examinations: Short-term, Placebo-Controlled Studies (protocols 71754-3-C-021,71754-3-C-024, and 71754-3-C-025):

Please see Table 5 (from the sponsor's submission).

3.6.1.2 Neurological Examination Results, Adverse Events, and Case Report Forms: Follow-up Studies (71754-3-C-024,71754-3-C-025, 71754-3-C-021, 71754-3-C-020, 71754-3-C-026, 71754-3-C-022, and 71754-3-C-028).

Please see Table 6 (from the sponsor's submission). Patient 059-003 was noted to have the onset of hypertonia after administration of vigabatrin, hypertonia was not noted on the entrance evaluation. The vigabatrin was withdrawn due to lack of efficacy. Subsequent follow-up as part of protocol 071754PRO253, revealed normal tone.

3.6.1.3 Neurological Examination Findings from Protocol 071754PR0253

Patients from protocol 071754PR0253 with findings on their neurologic examination are summarized in Table 4 and Table 7 (from the sponsor's submission).

Table 4

[redacted]

Status of Vigabatrin Therapy	Worsened	No Change	Improved
Still on Vigabatrin Therapy	7	28	11
Vigabatrin Discontinued	16	34	4
Total	23	62	15

Of the 23 patients with worsening of their neurologic examination, the components showing deterioration included mental status, memory, reflexes, position, vibratory sense, nystagmus, spasticy, and overall neurological status. In the 7 patients still on vigabatrin therapy with worsening of their neurologic examinations, the changes included diminished reflexes (patient 054-004 and patient 061-008); pain, touch, vibratory sense decreased, and diminished biceps and triceps (patient 061-003); decreased concentration (patient 061-006); reflexes increased, nerve head abnormal bilaterally (patient 079-006); decreased reflexes, questionable changes in mental status (patient 006-012); and hearing loss (patient 005-006).

3.6.1.4 Adverse Events from the Global Adverse Event Reporting System (GADERS) Database.

Please see Table 8 (from the sponsor's submission). Seven patients were flagged by the reviewers for neurologic adverse events. Two of these patients were diagnosed with multiple sclerosis following administration of vigabatrin. In one patient the duration of treatment was 1.5 years. The sponsor notes A third patient (VGZ-9016-701) with pulmonary embolism, cerebral vein thrombosis, and increased intracranial pressure was noted to have axonal spheroids in the white matter at autopsy. Four patients (VGZ-9203.445, VGZ-9206-635, VGZ-9400-0407, VGZ-9400-6450) were diagnosed with polyneuropathy.

3.6.2 Consultant's (Sponsor) Review:

3.6.2.1 IME

The following were considered by the reviewers to be the Anticipated Clinical Signs and Symptoms Suggestive of White Matter Injury: weakness, numbness, hyperreflexia, increased muscle tone and spasticity, Babinski signs, incoordination, tremor on pointing, inability to walk in a straight line, and loss of perception in some portions of the visual field. In addition, they concluded that in animals, IME is always bilateral and symmetrical, which would result in symmetric signs and symptoms. In summary, the reviewers concluded that there were no patients with a definitive neurological examination finding or event that was consistent with white matter lesions that have been described in animals with IME.

3.6.2.2 Peripheral Neuropathy

In reviewing the incidence tables for neurologic changes in the double-blind placebo-controlled trials, the consultants concluded the following:

- Vibratory: No apparent difference from placebo were observed in protocol 717543-C-021 for "vibratory." In protocols 71754-3-C-024 and 71754-3-C-025, slightly more patients on VGB had worsening "vibratory" than on placebo.
- Touch: The frequency of changes from baseline in "touch" were few and similar on placebo and on VGB.
- Position: No apparent differences between VGB and placebo for "position" were observed in protocols 71754-3-C- 021 or 71754-3-C-025. In protocol 71754-3-C-024, 4% (4/91) of patients on 3 gm VGB compared to 0% (0/90) of patients on placebo had worsening "position".
- Muscle Strength and Tone: Based on review of the listings of neurological examination changes in muscle strength and tone, no clinically significant motor changes were observed in any of the three protocols with the possible exception of one patient, 011-101 in the 6 gm dose group of protocol 71754-3-C-025, reported as hypertonic in all extremities.
- Reflexes: Slightly more decreases in knee and ankle reflexes occurred in VGB patients as compared to placebo patients in protocols 71754-3-C-024 and 71754 3-C-025.

The sponsor's consultants concluded that in the review of 467 patients (from US and Canadian trials) confirmed 13 (3%) cases of peripheral nervous system changes(decreased reflexes and/or decreased vibratory sense) possibly consistent with peripheral neuropathy. The consultants concluded that this incidence is consistent with that expected in patients treated with chronic AEDs. They note that all thirteen of theses patient's were exposed to at least one other AED.

The consultants concluded, based on their review of 071754PR0253, that there were 11 / 100 patients on vigabatrin with improvement in their neurologic examination compared to their previous examination. This cases received no additional review. A second group described by the consultants consisted of 16 / 100 patients with a deterioration of their neurological examination as compared to their last evaluation. They concluded that these changes were not due to vigabatrin, but rather due to age, disease progression, or long-term AED therapy. A third group consisted of 11 /100 patients with a change in neurologic examination, that the consultant's concluded may be related to vigabatrin. Seven of those patients had a worsening of and 4 had improvement in their neurologic examination. Four of the seven patients with worsening and one of the patients with improvement of their neurologic examinations had findings which would be consistent with a peripheral neuropathy. The consultants concluded that these findings were not likely due to IME (either central or peripheral).

In their review of the GADERS database, the consultants identified four patients diagnosed with polyneuropathy without clear etiology. In two of these patients, the symptoms abated after discontinuing the vigabatrin. An additional case of possible Guillian-Barre syndrome (GBS) was excluded by EMG / NCS. The consultants concluded that these cases could possibly be due to vigabatrin, but determination of demyelination or IME is not possible. Finally, they concluded "none of the possible neuropathies observed in this review appear clinically significant or demyelinating in nature."

3.6.3 Reviewer's Comments:

3.6.3.1 IME

The consultants' criteria for relationship of neurologic findings to IME is based on the results from animal studies. Their criteria assumes that the location of the lesions in humans is similar to animals, this may not be the case. In three of the four data sets reviewed, additional evaluations included MRI and EPs. Presumably, the MRI would have been abnormal in the subjects with abnormal neurologic examinations secondary to IME, however, the temporal relationship of the MRI evaluation to the neurologic examinations is not clear. With respect to the GADERS Database, no conclusions can be drawn concerning IME, although at least two cases, VGZ-9205 337 and VGZ-9500-5680 were diagnosed with multiple sclerosis. The sponsor should provide additional information on these two cases, specifically, how the diagnosis of MS was made. Based on the available data, it is not possible to exclude these patients as a possible cases of IME.

3.6.3.2 Peripheral Neuropathy

It is clear that the sponsor's consultant's reviewed the cases of possible peripheral neuropathy on the basis of their association with demyelination / IME rather than as a separate process. The conclusion that none of the cases of possible peripheral neuropathy are demyelinating has not be substantiated. The consultant's basis for establishing clinical significance has not been described.

In reviewing the data from the placebo controlled trials, the following could be considered signals for possible peripheral neuropathies. A larger percentage of vigabatrin treated patients in study C-024 had diminished position and touch sense. This pattern was not seen in the studies C-021 and C-025. In studies C-024 and C-025 (not in C-021), a greater percentage of vigabatrin treated patients had diminished vibratory sense. Ankle reflexes were diminished in a larger percentage of vigabatrin treated patients in studies C-021 and C-025 (not C-024).

In reviewing follow-up studies (71754-3-C-024,71754-3-C-025, 71754-3-C-021, 71754-3-C-020, 71754-3-C-026, 71754-3-C-022, and 71754-3-C-028), 39 / 467 patients were identified with "peripheral neuropathy-like" neurological

examination results. Nine of these patients had the findings at baseline. The remaining 30 patients had signs consistent with a peripheral neuropathy.

Eighteen of 96 patients in examined in protocol 071754PR0253 had abnormal neurological examinations with signs that could be attributed to a peripheral neuropathy. Ten of 18 were not on vigabatrin treatment at the time of evaluation.

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

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

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

3.7 Review of Safety Report:

Patient 1194-0010 discontinued from ongoing Protocol VGPR0096 when a fairly large discrete demyelinating lesion in the corpus callosum was identified on MRI. She had been receiving up to 4 g/day vigabatrin for 46 days.

The following is from the initial IND safety report. Treatment with vigabatrin was initiated on December 18, 1995. The patient was also taking carbamazepine and phenytoin. The carbamazepine was tapered and discontinued on January 2, 1996. By February 1, 1996, the phenytoin had been tapered from 350 mg /day to 200 mg / day. On February 1 , 1996 (after approximately 6 weeks on vigabatrin 2 g / day), the subject complained of increased seizure frequency and a change in her auras. Her phenytoin dose was increased to 350 mg / day. An MRI was obtained on February 5, 1996, which showed "a fairly large discrete demyelinating lesion" in the corpus callosum. The MRI report for the MRI examination of February 5, 1996 stated: 1) well defined 1.2 cm non-enhancing area of T2 prolongation and low T1 signal in the splenium of the corpus callosum, which might be a new finding. Differential diagnosis for this would include MS or other demyelinating process, low grade glioma, lymphoma, and though unlikely, gliosis from an old shear injury; 2) encephalomalacia left temporal lobe, related to prior surgery, with small extra-axial fluid collection in the middle cranial fossa. Based upon this information the event description was changed from "demyelination of the corpus callosum" to "abnormal MRI - lesion in

corpus callosum". Vigabatrin was discontinued and the subject was dropped form the trial. A previous MRI obtained in October 1994, following a left temporal lobectomy was negative for any lesion in the corpus callosum. The patient's medical history was positive for alcoholism 8 years prior to the event; according to the investigator the patient had not been drinking. In OCT 94, the patient underwent a left temporal lobectomy. The patient lived abroad for approximately 22 years including India, the Philippines, Ecuador, Panama, and Argentina. The investigator noted the following additional symptoms prior to entering the study: 1) clumsiness; 2) loss of right visual field for approximately 30 minutes without loss of consciousness; symptoms recurred for about 24 hours; 3) intermittent blurred vision for 1 year; 4) tingling in the feet and hands for 4-5 months.

Subsequent EPs (VER and SEPs median and posterior tibial) were normal. An ophthalmology examination on February 13, 1996 did not reveal any abnormalities of the optic nerve. Analysis of CSF obtained on February 14,1996 revealed protein 54 mg/dl (normal 15-45), glucose 50 mg/dL (normal 45-80), RBC 0 (normal 0), WBC 2 (normal 0-5), VDRL negative, normal IgG index, no oligoclonal bands, negative PCR for EBV, negative cultures, and no malignant cells. On February 20, 1996, the patient informed the investigator that she felt much better overall since being withdrawn from vigabatrin; she had experienced only two small auras since discontinuation of vigabatrin.

3.7.1 Consultant's (Sponsor) Review:

A consultant neuroradiologist reviewed the MRIs (1-Jul-94, 24-Oct-94, 5-Feb-96). He concluded that the lesion was unlikely related to vigabatrin because of its location and its sharp demarcation. He noted that the lesions observed in dogs receiving vigabatrin had ill-defined margins when they occurred in the thalamus and hypothalamus, or involved these structures diffusely. With the exception of the corpus callosum lesion, there was no evidence of pathology in the areas that had been known to be affected in dogs receiving vigabatrin. He would not expect that intramyelinic edema would present with sharply defined margins. The consultant suggested that follow-up MRI studies be performed to evaluate the progress of the lesion and to determine whether other lesions develop. A follow-up MRI on October 30, 1996 revealed the lesion greatly diminished in prominence from previous MRIs.

3.7.2 Reviewer's Comments:

The corpus callosum, interhemispheric commissure, is composed of myelinating fibers which reciprocally interconnect nearly all cortical regions of the two hemispheres[3]. Complete surgical section of the corpus callosum does not produce obvious neurologic deficits, but these patients show a striking functional

[3] M.B. Carpenter; Core Text of Neuroanatomy; Third Edition; Williams and Wilkins; 1985; Pages 26, 32.

independence of the two hemispheres with respect to perceptual, cognitive, mnemonic, learned and volitional activities [3]. As described above in section 12.1, IME lesions involving the corpus callosum have been reported in rats, dog, and monkey. In addition, at least some of the lesions of IME have been described as discrete. Given the temporal relationship of this lesion to treatment with vigabatrin, and the subsequent partial resolution of the lesion with discontinuation of vigabatrin, this case is consistent with IME.

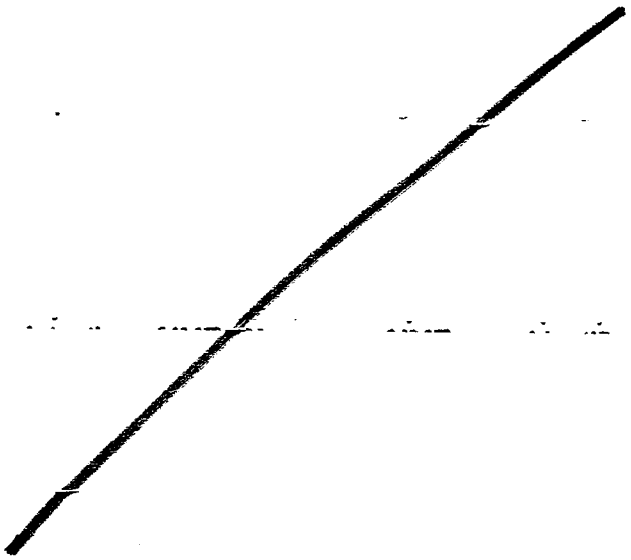
3.8 Conclusion:

I am not reassured by the sponsor's claim of lack of evidence of IME in humans. Several of the case reviewed above are consistent with IME. The most compelling case is Patient 1194-0010. Please see section 3.7 for additional details. The most prudent course would be to include a description of this case in the labeling (see recommendations below).

3.9 Recommendations:

3.9.1 Labeling:

The following statement should be added to labeling:



b(4)

[redacted]

b(4)

[redacted]

3.9.2 Additional Information:

3.9.2.1 IME

3.9.2.1.1 Histopathology:

The sponsor should provide support for their conclusions that vacuolation without gliosis is artifact. In addition, the sponsor should quantify the background incidence of vacuolation in epilepsy patients not administered vigabatrin.

3.9.2.1.2 GADERS Database:

The sponsor should provide additional information on the two cases (VGZ-9205 337 and VGZ-9500-5680 diagnosed with multiple sclerosis) specifically, how the diagnosis of MS was made.

3.9.2.2 Peripheral Neuropathy:

The sponsor should provide additional information about the course of the vigabatrin associated peripheral neuropathies, e.g. onset, duration of exposure, resolution. In addition, the sponsor should provide any additional information concerning characterization of the peripheral neuropathy e.g. electroneuromyography evaluations and nerve biopsies.

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

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

Table 5

Best Possible Copy

Table 1. Incidence of Worsening of Neurological Evaluation, Protocols 71754-3-C-021, -024, and -025

	Protocol -021		Protocol -024		Protocol -025				Total	
Test*	Placebo (N=53)	4 G VGB (N=58)	Placebo (N=90)	4 G VGB (N=92)	Placebo (N=45)	1 G VGB (N=45)	3 G VGB (N=43)	6 G VGB (N=41)	Placebo (N=188)	VGB (N=279)
Mental Status										
Calculation	1.9%	3.4%	0.0%	3.3%	2.2%	0.0%	2.4%	5.3%	1.1%	2.9%
Concentration	0.0%	3.4%	1.1%	5.5%	0.0%	0.0%	7.0%	2.6%	0.5%	4.0%
Language	3.8%	3.4%	0.0%	1.1%	0.0%	0.0%	0.0%	0.0%	1.1%	1.1%
Memory recent	1.9%	5.2%	1.1%	7.7%	4.4%	6.8%	9.3%	10.5%	2.1%	7.7%
Memory remote	1.9%	1.7%	1.1%	3.3%	0.0%	2.3%	4.7%	0.0%	1.1%	2.8%
Mood	0.0%	5.2%	2.2%	1.1%	2.2%	2.3%	11.6%	7.9%	1.6%	4.7%
Orientation	0.0%	1.7%	0.0%	0.0%	0.0%	0.0%	2.3%	2.6%	0.0%	1.1%
Speech	3.8%	1.7%	0.0%	1.1%	0.0%	0.0%	0.0%	0.0%	1.1%	0.7%
Thought	0.0%	1.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%
Fundoscopy/Visual Acuity										
L Funduscopy Ves	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
L Macula	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.3%	0.0%	0.0%	0.4%
L Nerve Head	0.0%	0.0%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%
R Funduscopy Ves	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
R Macula	0.0%	1.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%
R Nerve Head	0.0%	0.0%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%
Cranial Nerves										
Accessory	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Confrontation	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%	4.7%	0.0%	0.5%	0.7%
Extraocc. mvmnt	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Facial motor	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%	2.3%	0.0%	0.5%	0.4%
Glossopharyngeal	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Hearing	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%	2.3%	2.6%	0.5%	0.7%
Hypoglossus	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Table 5

Table 1. Incidence of Worsening of Neurological Evaluation, Protocols 71754-3-C-021, -024, and -025										
	Protocol -021		Protocol -024		Protocol -025				Total	
Test*	Placebo (N=53)	4 G VGB (N=58)	Placebo (N=90)	4 G VGB (N=92)	Placebo (N=45)	1 G VGB (N=45)	3 G VGB (N=43)	6 G VGB (N=41)	Placebo (N=188)	VGB (N=279)
Trigem motor	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Trigem sensory	0.0%	0.0%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	0.0%
Vagus	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Visual Acuity	0.0%	3.5%	1.1%	2.2%	0.0%	6.8%	0.0%	0.0%	0.5%	2.6%
Nystagmus										
Nystagmus	3.8%	8.6%	10.0%	8.6%	4.4%	9.1%	9.3%	10.5%	6.9%	9.1%
Muscle Strength and Tone										
Strength L lower ex	0.0%	5.2%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	1.1%
Strength L upper ex	0.0%	3.4%	0.0%	1.1%	0.0%	0.0%	2.3%	0.0%	0.0%	1.5%
Strength R lower ex	0.0%	3.4%	2.2%	0.0%	0.0%	0.0%	0.0%	0.0%	1.1%	0.7%
Strength R upper ex	0.0%	3.4%	0.0%	1.1%	0.0%	0.0%	2.3%	0.0%	0.0%	1.5%
Tone L lower ext	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.6%	0.0%	0.4%
Tone L upper ext	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.6%	0.5%	0.4%
Tone R lower ext	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.6%	0.0%	0.4%
Tone R upper ext	0.0%	0.0%	0.0%	0.0%	2.2%	0.0%	0.0%	2.6%	0.5%	0.4%
Sensation, Cerebellar Function and Gait										
Coordination	0.0%	1.7%	0.0%	3.3%	0.0%	2.3%	2.3%	0.0%	0.0%	2.2%
Finger-Nose	3.8%	1.7%	3.3%	5.5%	2.2%	0.0%	2.3%	2.6%	3.2%	2.9%
Gait	0.0%	1.7%	3.3%	3.3%	2.2%	0.0%	0.0%	2.6%	2.1%	1.8%
Heel shin	1.9%	1.7%	0.0%	2.2%	0.0%	0.0%	2.3%	2.6%	0.5%	1.8%
Pain	0.0%	0.0%	2.2%	2.2%	0.0%	0.0%	2.3%	0.0%	1.1%	1.1%
Position	1.9%	0.0%	0.0%	4.4%	2.2%	0.0%	2.4%	2.6%	1.1%	2.2%
Rapid alter mvmnt	0.0%	0.0%	0.0%	2.2%	0.0%	2.3%	2.3%	2.6%	0.0%	1.8%
Tandem gait	3.8%	3.4%	8.9%	4.4%	0.0%	2.4%	2.3%	10.5%	5.3%	4.4%
Touch	0.0%	0.0%	1.1%	2.2%	0.0%	0.0%	0.0%	0.0%	0.5%	0.7%

Table 5

Table 1. Incidence of Worsening of Neurological Evaluation, Protocols 71754-3-C-021, -024, and -025

	Protocol -021		Protocol -024		Protocol -025				Total	
Test*	Placebo (N=53)	4 G VGB (N=58)	Placebo (N=90)	4 G VGB (N=92)	Placebo (N=45)	1 G VGB (N=45)	3 G VGB (N=43)	6 G VGB (N=41)	Placebo (N=188)	VGB (N=279)
Vibratory	0.0%	0.0%	5.6%	7.7%	2.2%	4.5%	2.4%	5.3%	3.2%	4.4%
Reflexes										
Ankle L	0.0%	5.2%	6.7%	5.5%	4.4%	9.1%	11.6%	10.5%	4.3%	7.7%
Ankle R	0.0%	3.4%	5.6%	6.6%	4.4%	6.8%	11.6%	7.9%	3.7%	6.9%
Babinski L	0.0%	0.0%	0.0%	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%
Babinski R	0.0%	0.0%	0.0%	3.3%	2.2%	0.0%	0.0%	2.6%	0.5%	1.5%
Biceps L	1.9%	1.7%	6.7%	3.3%	4.4%	2.3%	9.3%	0.0%	4.8%	3.3%
Biceps R	0.0%	1.7%	7.8%	3.3%	4.4%	2.3%	9.3%	2.6%	4.8%	3.6%
Knee L	1.9%	1.7%	7.8%	5.5%	4.4%	9.1%	11.6%	2.6%	5.3%	5.8%
Knee R	0.0%	1.7%	7.8%	6.6%	4.4%	9.1%	11.6%	2.6%	4.8%	6.2%
Triceps L	1.9%	1.7%	7.8%	4.4%	2.2%	2.3%	11.6%	2.6%	4.8%	4.4%
Triceps R	0.0%	1.7%	7.8%	4.4%	2.2%	2.3%	11.6%	5.3%	4.3%	4.7%
Neurological Status										
Neurological Status	5.7%	8.6%	4.4%	4.4%	6.8%	6.8%	14.0%	13.2%	5.3%	8.4%

* Patients with missing test results are not included in denominator.

Table 6

TABLE A

Assessment Code:

1 = Recorded change within normal expected variability from one exam to another - &/or recorded change noted by investigator as due to a difference in individual examiners - not relevant

2 = CRF review indicates abnormality was present at baseline - not relevant

3 = CRF review confirms abnormality, explanation unknown (possible relationship to VGB).

4 = Other

Table A. Patients with peripheral neuropathy-like neurological exam results which, based on the listings, appeared to worsen from baseline and were not resolved by study exit; dataset from Protocols: 71754-3-C-020, 71754-3-C-024, 71754-3-C-025, 71754-3-C-026, 71754-3-C-021, 71754-3-C-022, 71754-3-C-028.

Master Patient Number	*Protocol Sequence*	*Exposure VGB Weeks*	*Non-normal Neurologic Exam Finding**	*Reviewer's Assessment/Comments*
006-106	25/26/28	147	dec ankle	1
010-106	25/26/28	179	dec ankle	1
010-114	25/26/28	149	dec bicep, tricep & knees	4**
011-107	25/26	39	dec ankle jerks	3
012-115	25/26/28	112	dec biceps, triceps, ankle jerks	1
013-003	25/26/28	167	absent ankle, biceps, triceps, dec knees	4**
013-009	25/26/28	141	dec L&R ankle jerks	1
054-002	24/20/28	165	dec ankle ref, dec serial 7s	1
054-011	24/20/28	130	dec reflexes	3
055-003	24/20/28	101	dec reflexes, dec distal 7s	4**
055-008	24/20	29	dec reflexes, dec vib	3
058-005	24/20/28	151	left calf atrophy	2

Table 6

Table A. Patients with peripheral neuropathy-like neurological exam results which, based on the listings, appeared to worsen from baseline and were not resolved by study exit; dataset from Protocols: 71754-3-C-020, 71754-3-C-024, 71754-3-C-025, 71754-3-C-026, 71754-3-C-021, 71754-3-C-022, 71754-3-C-028.

Master Patient Number	*Protocol Sequence*	*Exposure VGB Weeks*	*Non-normal Neurologic Exam Finding**	*Reviewer's Assessment/Comments*
059-001	24/20/28	172	dec vibration	3
059-002	24/20/28	152	dec vibration	1
059-004	24/20/28	147	dec reflexes	1
059-006	24/20/28	160	dec vibratory sense	3
059-012	24/20	69	dec ankle jerks	2
059-014	24/20	35	dec reflexes	2
060-004	24/20/28	115	dec vibratory sense	3
060-007	24	15	dec vibratory sense	3
061-002	24/20/28	141	dec reflexes, dec vib	2
061-004	24/20	34	dec reflexes, dec vib	3
061-008	24/20/28	122	dec vib/position	2
063-002	24/20	38	dec vibratory	3
065-004	24/20/28	141	dec reflexes	1
066-005	24/20/28	105	dec reflexes	4**
066-007	24/20	14	dec reflex, dec touch sensation	3
066-008	24/20/28	149	dec reflex, dec vib	3
067-005	24/20	30	dec reflex, dec vib	3
069-005	25/26/28	128	dec biceps, triceps, knee & ankle jerks	1
071-005	25/26/28	162	dec ankle jerks, biceps, triceps & knees	1
072-008	25/26/28	116	dec biceps, triceps & knee jerks	2

Table 6

Table A. Patients with peripheral neuropathy-like neurological exam results which, based on the listings, appeared to worsen from baseline and were not resolved by study exit; dataset from Protocols: 71754-3-C-020, 71754-3-C-024, 71754-3-C-025, 71754-3-C-026, 71754-3-C-021, 71754-3-C-022, 71754-3-C-028.

Master Patient Number	*Protocol Sequence*	*Exposure VGB Weeks*	*Non-normal Neurologic Exam Finding**	*Reviewer's Assessment/Comments*
075-001	25/26	25	dec biceps, tricep dec ankles & knees	1 (dec biceps/triceps only)
075-005	25/28/28	133	absent ankles, dec biceps, knees (diffusely)	2
075-006	25/26/28	160	ankles, biceps, knees, triceps, went from dec to absent	2
077-003	21/22	89	dec ankles & knees	2
082-004	21/22/28	121	dec ankle jerks bilaterally	1
089-008	25/26/28	147	absent R ankle, dec biceps, knee, triceps	1
093-009	25/26/28	69	dec ankles, biceps, knees, triceps	3

* The description of the "non-normal neurological exam finding" reflects the reviewer's clinical description of the exam findings and is not a verbatim from the listing.
** Compatibility of Case Report Forms make interpretation difficult, however, expert opinion is that no change has occurred.
Abbreviations: dec=decreased; ref=reflex(es); vib=vibratory

Table 7

TABLE B

Assessment Codes:

1 - Change within expected variability or secondary to different examiner- no significant

2 - No significant change from previous exam to protocol 71753PR0253

3 - CRF review indicates change present at baseline - not significant

4 - Abnormality confirmed by CRF review, explanation unknown

4A) abnormal exam on drug went to normal off drug

4B) normal on drug went to abnormal while still on drug

5 - Other

6 - Improvement in neurological exam while on VGB - uncertain significance

7 - Deterioration in neurological exam while off VGB - uncertain significance

Table B. Protocol 71754PR0253 Patient Review

Master Patient Number	*VGB (Y or N)*	*Abnormal Neuro Exam and Comment(s)*	*Assessment*
005-001	Y	without significant change	2
005-005	N	off drug - therefore without change, decreased reflexes, tremor (13.6 years exposure)	7
005-006	Y	hearing loss	4B
005-010	Y	without significant change	2
005-011	N	off drug - therefore without change, distonic posturing, (13 years exposure)	7
005-015	Y	without neuro change	2
005-111	N	without significant change	2

Table 7

Table B. Protocol 71754PR0253 Patient Review			
Master Patient Number	*VGB (Y or N)*	*Abnormal Neuro Exam and Comment(s)*	*Assessment*
006-012	Y	dec reflexes - questionable changes mental status (13.1 years exposure)	4B
006-017	Y	without neuro change	2
006-111	N	without change	2
009-003	N	dec reflexes, but off drug without change	7
009-004	N	dec vibratory sense, poor memory	7
009-014	Y	decreased pin/vibratory sens, but reflexes absent pre-253	2
009-015	Y	without significant change	2
010-004	Y	existing neuropathy	2 assessment is that severity of the neuropathy has not increased, therefore without significant change
010-006	Y	without significant change	2
010-012	N	without change in longstanding neuropathy- investigator comment: peripheral neuropathy for approx 15-16 yrs before VGB, probably phenytoin induced	3
010-015	N	worsened off drug - without change	7
010-107	N	tandem gait improved off drug may be due to ataxia, an expected SE of drug rather than AE	1
010-110	N	without change, reflexes dec off drug	7
010-120	N	without change	2
011-002	N	worsened off drug	7
011-003	N	okay off drug	2
011-005	N	worsened off drug	7

Table 7

Table B. Protocol 71754PR0253 Patient Review			
Master Patient Number	*VGB (Y or N)*	*Abnormal Neuro Exam and Comment(s)*	*Assessment*
013-010	N	no change in 253	2
054-004	Y	peripheral - reflexes "diminished" at 253 exam but normal pre-253	4B
054-006	Y	while patient still on drug, elements of exam went from abnormal to normal	6
054-008	N	no change	2
054-009	Y	mood went from abnl to nl on VGB	6
058-002	N	L upper quadrantanopsia secondary to temporal lobectomy	5*
058-005	N	L upper quadrantopsia, secondary to temporal lobectomy; change in reflexes - PI says "not an AE, due to change in examiner" L Babinski present prior to 253, disappears at 253, but predates VGB	5*
058-014	N	memory worsened, reflexes improved at ankles, diminished elsewhere as compared to prior to 253, probably normal exam variation	1
058-003	Y	memory worse at 253, noted to be "due to bitemporal seizures"	5*
058-011	N	tone "hypertonic" pre253 on VGB, normal at 253 off VGB	4A
059-003	N	dec coord & inc reflex pre 253, normal at 253. Baseline exam indicates inc reflex and ataxia on tandem gait - exam variability	1
059-004	Y	vibratory and pain sense improved from pre-253 to 253. Ankle jerks diminished slightly, rest of reflexes unchanged	6
059-009	N	reflexes from diminished pre 253 to nl at 253, but dec reflex at baseline - exam variability	reflexes, 1

Table 7

Table B. Protocol 71754PR0253 Patient Review			
Master Patient Number	*VGB (Y or N)*	*Abnormal Neuro Exam and Comment(s)*	*Assessment*
059-014	N	memory & speech abnl at initial exam, changes in reflexes reflect exam variability.	1
061-003	Y	pain, touch, vibratory decreased at 253, ankles, biceps, triceps normal to diminished	4B
061-004	N	coordination worse, DTR's went from decreased to normal, but reflexes dec at baseline also.	reflex, 1
061-006	Y	decreased concentration, serial 7's poor	4B
061-007	Y	decreased pin face, not clearly significant	1
061-008	Y	peripheral at 253 - findings consistent with $L5/S_1$ radiculopathy. Reflexes from normal to diminished	4B
064-004	Y	overall neuro status exam pre-253 "mildly abnl," at 253 "normal"	1
066-008	Y	minor changes in both directions (nl to abnormal and abnl to nl) overall, status mildly abnl to nl	1
066-013	N	pt developed scotoma in R eye off drug	7
067-006	N	cognitive deficits improved - exam from mildly abnl to normal	4A
067-011	N	vibratory mildly abnl to nl	4A
069-004	Y	tandem gait slightly worse	1
070-004	Y	no change noted	2
070-006	Y	no change noted	2
070-007	Y	no change noted	2
070-008	Y	RAM's slightly slow, otherwise ok	1
071-003	N	memory improved slightly; reflexes from nl to diminished or absent	7

Table 7

Table B. Protocol 71754PR0253 Patient Review			
Master Patient Number	*VGB (Y or N)*	*Abnormal Neuro Exam and Comment(s)*	*Assessment*
075-006	Y	mental status improved, some reflexes from absent to diminished	6
076-001	N	coord slightly worse	1
076-006	N	no change, visual acuity improved with refraction	1
077-001	N	no change noted	2
077-003	N	pre-253, reflexes rated as "reduced, not significant, normal." At 253-nl	1
077-013	N	mental status from nl to abnl, but "longstanding borderline to MR"	3
078-004	Y	refractive change only	2
078-011	Y	all changes related to congenital hemiparesis	3
079-001	N	mild nystagmus at 253	1
079-002	N	abnl tandem gait secondary sore R ankle	5*
079-006	Y	nerve head described at 253 as abnl bilaterally ms improved at 253, reflexes nl throughout to increased throughout	4B
080-002	Y	change in nystagmus only	1
080-009	N	change in nystagmus only	1
082-002	Y	change in nystagmus only	1
089-004	N	worsening sensation off drug-questionable diabetes	7
089-010	N	questionable diminished reflexes off drug, but discrepancy between exam summary and individual reflex findings	7
089-012	Y	no change in exam	2
089-014	Y	questionable improvement on drug	6

Table 7

Table B. Protocol 71754PR0253 Patient Review			
Master Patient Number	*VGB (Y or N)*	*Abnormal Neuro Exam and Comment(s)*	*Assessment*
090-007	N	slight improved mental status off drug	1
090-010	N	without change, old brain injury	3
091-001	Y	probably without change, overall summary from moderately abnormal to mildly abnormal on drug	6
091-011	N	no change in exam	2
091-006	N	increase in spasticity off drug	7
091-007	Y	L facial weakness reported as new, but there was longstanding L hemiparesis, so likely okay	1

** indicates neurological exam change related to change in medical condition unrelated to VGB
Abbreviations: sign=significant ni=normal, abni=abnormal, dec=decreased, sens=sensory or sensation, PI=primary investigator, pt=patient, vib=vibratory, RAM=rapid alternating movement, coord=coordination, ms=mental status, MR=mental retardation, 253=protocol 71754PR0253, VGB=vigabatrin, DTR=deep tendon reflexes.

Table 8

Table C. Patients Identified from GADERS Review

CF File	Age (yrs)	Sex	Concomitant Medications	Adverse Event*	VGB Dur of Therapy	Outcome	Additional Information	Reviewer Comments
VGZ-9301-1266	48	F	Barbexaclone Phenobarbital	Aphasia	1/92-?	Unk	Increased existing motor aphasia	symptoms resolved; has history of brain tumor with radiation therapy; like VGB side effect.
VGZ-9500-3904	9	M	Phenytoin Lorazepam	Aphasia	4 days	Result in Disability	choreoathetosis	history of gangliosidosis which antedated VGB therapy
VGZ-9016-704	30	M	Phenytoin CRB	Ataxia	3/90-?	Unk	Also Balance Difficulty	unknown relationship to VGB
VGZ-9016-710	43	M	CRB	Ataxia	3/90-?	Unk	Also Coordination Abnormal	unknown relationship to VGB
VGZ-9211-345	54	F	CRB Clobazam Atenolol	Ataxia	2/91-?	Unk		unknown relationship to VGB
302333124 (VGST-C333-196)	27	F	CRB Clonazepam	Ataxia	3/88-?/89	Unk		unknown relationship to VGB
30233398 (VGST-C333-197)	25	F	CRB Clonazepam VAL	Ataxia	5/89-7/89	Unk		unknown relationship to VGB
VGST-MUMF-104	48	F	CRB Phenobarbitol Phenytoin	Ataxia	6/83-?/89	Unk	Also Diplopia	unknown relationship to VGB
VGST-MUMF-114	52	M	Phenytoin CRB	Ataxia	6/87-?/89	Unk	Also Diplopia, Sleepy	unknown relationship to VGB
VGST-MUMF-211	5	M	Clonazepam VAL	Ataxia	?/89-?/89	Resolved	Also Transient Hyperkinesia	unknown relationship to VGB
VGZ-9106-612	28	M	CRB Clobazam	Balance Difficulty	5/86-8/91	Unk	history of mental retardation	unknown relationship to VGB
VGZ-9500-0255	2.5	F	Diphenhydramin Septra	Chorea	?/92-cont	Not Resolved	s/p brain surgery on ketogenic diet	unknown relationship to VGB

Table 8

Table C. Patients Identified from GADERS Review

CF File	Age (yrs)	Sex	Concomitant Medications	Adverse Event*	VGB Dur of Therapy	Outcome	Additional Information	Reviewer Comments
VGZ-9500-3895	10	F	CLB Levonorgesterol	Fecal Incontinence	9/94-cont	Not Resolved	Also Urinary Incontinence	under etiology; unknown relationship to VGB
VGST-AU20-0632	?	F	Albuterol Paracetamol	Guillain Barre Syndrome	7/29-8/5/94	Resolved		unknown relationship to VGB but Guillian-Barre not by NCVs
VGST-MUMF-129	42	M	Clonazepam	Hemiparesis	?/85-?/88	Unk		unknown relationship to VGB
VGST-9213-516	27	M	VAL CRB	Hemiplegia	12/19/91-?	Unk		unknown relationship to VGB
VGZ-9205-337	48	F	Phenytoin Estrogen Progesterone	Multiple Sclerosis	11/90-7/92	Not resolved	may have been inflammatory myelitis	unlikely related to VGB
VGZ-9210-048	35	F	Phenobarbitol CRB	Myoclonus	1/91-?	Unk		unknown relationship to VGB
VGST-1193-0006	43	F	PRIM Levothyroxine	Neuropathy	8/15/91-10/95	Not Resolved		unknown relationship to VGB
VGZ-9400-6450	30	M	CRB PRIM	Neuropathy	2/22/92-cont.	Unk		unknown relationship to VGB

* included term
Abbreviations: CRB=carbamazepine; PRIM=primidone; VAL=valproate