CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-427

OTHER ACTION LETTER(s)

DEPARTMENT OF HEAL . & HUMAN SERVICES

Public Health Service

NDA 20-427

Food and Drug Administration
Rockville MD 20857

OCT 27 1998

Hoechst Marion Roussel
Attention: M. Lorie Stewart
Mail Station H4-M2110
Kahsas City, Missouri 64134-0627

Dear Ms. Stewart:

Please refer to your new drug application (NDA) and to your amendment dated April 24, 1998, received April 27, 1998 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril® (vigabatrin) Tablets, 500mg.

Reference is also made to the Agency's Approvable Letter dated November 26, 1997.

We acknowledge receipt of your submissions dated:

May 21, 1998	August 25, 1998
June 4, 1998	September 11, 1998
July 29, 1998	September 23, 1998

We also acknowledge receipt of your submission dated October 20, 1998. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

The user fee goal date for this application is October 27, 1998.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act. Our review reveals that there is insufficient information to determine whether Sabril® is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling [21 CFR 314.125(b)]. The deficiencies may be summarized as follows:

Vigabatrin Associated Visual Field Defects

As you know, our review of your most recent submissions has revealed that Sabril appears to have the capacity to induce a number of adverse clinical phenomena referable to the visual system. Of most concern is the occurrence of a relatively stereotypical visual field defect, characterized by bilateral concentric constriction of the visual fields, with a

propensity to affect the nasal fields. While a number of sources of evidence strongly suggest that the finding is related to treatment with Sabril (including the results of epidemiological studies, spontaneous reports, and reports in the literature), the most compelling evidence derives from perimetry data obtained in the Finnish and Japanese patients. In this cohort, 38/136 patients (28%) had visual field defects of the type described, with 82% of these defects judged to be moderate or severe. Of particular concern is the fact that these patients were asymptomatic. This finding appears to be of sufficient severity and frequency to warrant the accrual of additional data prior to any consideration of marketing. Many of the most basic facts necessary to characterize the finding are still unknown, including the true incidence, the anatomic location of the lesion(s) underlying the finding, its relation to the dose and/or the duration of treatment, the course of the finding once it occurs, the sensitivity of any method of surveillance for the lesion, and the potential reversibility of the lesion.

Your 9/23/98 submission proposes that Sabril be marketed as a last resort agent under extremely restrictive conditions. We do not believe this is acceptable at this time because the risk is not yet adequately characterized and Sabril's effectiveness in last resort situations has not yet been documented. This may require additional effectiveness trials showing superiority of Sabril to other available AED(s) in a suitable population.

While we cannot at this time offer detailed guidance about the nature and amount of safety data that would be considered sufficient to support the approval of this application, it is likely that a study in large numbers of patients followed forward prospectively for a sufficient duration and monitored appropriately and that is designed to collect the data necessary to characterize the elements described above will be required. Of course, members of the Division of Neuropharmacological Drug Products will be happy to discuss these issues with you.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Melina Malandrucco, R. Ph., Regulatory Management Officer, at (301) 594-5526.

Sincerely,

Robert Temple 10/26/98

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

fax 10/26/98

Archival NDA 20-427
HFD-120/Div. Files 10/26/98
HFD-120/Leber/Katz/Burkhart/Boehm/Oliva/Fitzgerald/Rosloff/Malandrucco
HFD-860/Tammara 6 RM 10/26/98
HFD-002/ORM
HFD-101/ADRA
HFD-95/DDMS
HFD-810/DNDC Division Director
DISTRICT OFFICE

NOT APPROVABLE (NA)

NDA 20-427

NOV 26 1997

Hoechst Marion Roussel
Attention: M. Lorie Stewart
Mail Station H4-M2110
P.O. Box 9627
Kansas City, Missouri 64134-0627

Dear Ms. Stewart:

Please refer to your new drug application dated April 29, 1994, received May 2, 1994, and to your amendment dated May 29, 1997, received May 29, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril® (vigabatrin) tablets, 500mg.

Reference is also made to the Agency's Not Approvable Letter dated April 28, 1995.

We acknowledge receipt of your additional correspondence and amendments dated:

May 5, 1995	July 17, 1995	September 12, 1996	July 23, 1997
May 15, 1995	August 1, 1995	March 11, 1997	July 28, 1997
June 5, 1995	August 2, 1995	April 1, 1997	July 31, 1997
June 12, 1995	August 9, 1995	April 28, 1997	August 13, 1997
June 13, 1995	September 26, 1995	May 22, 1997	September 16, 1997
June 30, 1995	January 3, 1996	May 29, 1997	September 26, 1997
July 10, 1995	January 4, 1996	May 30, 1997	September 29, 1997

The User Fee goal date for this application is November 29, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following requests or comments.

Labeling

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Sabril® tablets upon its approval. Although sections of this proposal are taken verbatim from the labeling proposed by you in the NDA, other sections have been extensively revised and/or expanded to include new subsections. Please note that we have embedded throughout the text of the attached draft labeling, "Notes to Sponsor:", requesting further revisions or clarification of the label, as well as blank spaces requiring a numeric value which you must provide.

We have the following specific comments and requests for the following sections of labeling. Again, this comprises a relatively small subset of the changes in labeling that we are requesting, but we felt that these deserved special attention.

1. Indication Section

   a. You have proposed that vigabatrin be indicated as adjunctive treatment for partial seizures in adults with epilepsy. In support of this claim, you have submitted the results of two adequate and well controlled trials that demonstrate the beneficial effects of vigabatrin on the combination of IB seizures (complex partial seizures that do not generalize) and IC seizures (partial seizures secondarily generalized).

      Because this combination of seizures does not support a claim in labeling that would be easily understood by prescribers, analyses were undertaken to examine the effects of vigabatrin on the various relevant seizure types. These analyses demonstrate that vigabatrin has a robust effect on IB seizures, but not on other seizure types. In particular, no significant effects were seen between treatments on IA (simple partial seizures) or IC seizure types. While it is true that in general there were likely too few seizures of these types to detect a statistically significant between treatment difference, inspection of the data reveals that at least in one study (Study 25), there were a sufficient number of IA seizures to detect a between treatment difference; indeed, in that study, the median number of IA seizures in both treatment groups at baseline was either essentially equal to or greater than the analogous number of IB seizures. In this study, the p-value for the between treatment difference for IA seizures was 0.75, compared to a p-value for IB seizures of 0.0014. We note that you have not demonstrated an independent effect of the treatment on complex partial seizures that do generalize (a subset of IC seizures that you have not examined). Nonetheless, we believe it is reasonable to extrapolate from the finding in IB seizures and conclude that vigabatrin is effective adjunct therapy in the treatment of complex partial seizures.

   b. Because of unresolved concerns about the potential of Sabril to cause intramyelinic vacuolization in humans, we have concluded that it should not be recommended as first line adjunctive therapy.

      Intramyelinic vacuolization (IMV) develops in the CNS of dogs, rats, mice, and arguably monkeys exposed for extended periods to vigabatrin. It is of considerable concern, therefore, that these lesions occur in these species at levels of vigabatrin exposure below those that will be recommended for the management of complex partial seizures if vigabatrin is approved for marketing.

Although the Agency is mindful that there is some evidence that IMV developing in dogs exposed to vigabatrin can be detected by following changes in the latency of visual (VEP) and/or somatosensory (SEP) evoked potentials, the kind (type, size) of lesion that must develop before detection is reliably achieved is unknown. Even more important, there is no evidence that speaks to the degree, if at all, that either VEP or SEP would be sensitive to lesions developing in humans. An identical observation can be made about the capacity of MRI to detect lesions in both dogs and humans.

Our assessment of the risk posed to humans is further confounded by the fact that we cannot be certain about the nature of clinical signs and symptoms that would result from intramyelinic vacuolization. This is of some concern because we know, arguing by extension from experience gained in patients with multiple sclerosis, that relatively extensive white matter injury can occur in the absence of obvious clinical defect.

Accordingly, histopathological examination of brain tissue constitutes the only fully reliable and valid means to assess whether or not chronic exposure to vigabatrin causes IMV in humans. Moreover, it is not sufficient to study any area of brain. To the contrary, it is critical that tissue be taken from regions of white matter likely (based on animal study results) to be at risk of vacuolar pathology. Finally, numbers count. As in any situation where the goal is to exclude a risk not seen, the size of the population examined and found to be free of injury is critical to the warrant of safety.

It should not be surprising, therefore, that we find the citation of a lack of lesions in 11 patients treated for over a year who underwent autopsy insufficient to support a conclusion that vigabatrin poses no risk of IMV to humans. While a considerably larger number of samples of brain tissue taken from neurosurgical cases were also examined and found to be free of IMV, the source of these samples as you acknowledge, was primarily from the temporal lobe, a region found to be free of IMV in animals with white matter lesions elsewhere in their brains.

In sum, the absence of reports of IMV in human tissue is not reassuring given the kind of tissue and the number of samples examined. In light of this, especially in the absence of any documented compensating advantage of vigabatrin among the drugs available for the management of CPS, we believe it prudent to require that the product not be the first AED chosen for adjunctive use in the management of patients with CPS.

2. Cognitive/Neuropsychiatric Adverse Events Section

Alterations in mental status, some so severe as to require discontinuation of vigabatrin treatment, have been reported in association with its use. Our efforts to understand and describe the full panoply of untoward mental status and behavioral changes reported in association with the use of vigabatrin has been severely hampered by the terminology employed. Terms such as confusion, thinking abnormal, even psychosis, convey little in the way of clinically useful information. To some degree, the problem is a generic one arising from the general limitations of COSTART as a dictionary for neuropsychiatric untoward events and phenomena.

Beyond the limitations of COSTART, however, are problems that arise because the strategy you employed for grouping and distributing untoward events among the various named categories of adverse events is unclear. In fact, we are concerned that events may have been misclassified. To illustrate, the differential diagnosis of altered mental status includes absences and absence status. This distinction is important because the treatment of the latter involves withdrawal, not increment, of vigabatrin treatment.

Accordingly, a new analysis must be performed, and any review and analysis of events characterized by complex changes in behavior or mental status must make clear why one particular diagnostic assignment was made in preference to another including an enumeration of the empirical findings supporting that choice (e.g., that an EEG done while the behavior was manifest showed a classic spike and wave configuration, etc.),

Clearly, extensive guidance regarding this effort cannot be provided in this letter. Staff of the Division of Neuropharmacological Drug Products , however, will be happy to meet with your staff to develop an appropriate strategy for the requested analysis.

3. Adverse Reactions Section

In your analyses of the effects of age and gender, you have only included rates for vigabatrin. Please reanalyze your controlled trial data including placebo experience. Please also compare frequency of adverse events for vigabatrin (1g, 3g, 6g) with placebo in the controlled trial data. Additionally, compare the frequency of adverse events by time since treatment initiation. For these analyses, please examine adverse events associated with discontinuation, as well as the more commonly occurring adverse events.

4. Clinical Trials Section

An analysis of the effects of age, gender and race on the estimates of treatment effect obtained in the controlled clinical trials is required. If, upon analysis, these factors are found to have had no effect on these estimates, labeling should make a statement to that effect. Contrawise, if an effect of one or more of these covariates is found, it must be described in labeling.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Safety Issues

1. Although Sabril is not being indicated for use in the pediatric population, it would nonetheless be useful for us to examine the pediatric safety database separately to determine if there are any serious adverse events in this population. Therefore, please submit an analysis of any adverse event resulting in discontinuation or considered serious in this group.

2. Please describe the extent of use for vigabatrin at doses of 4-5g and 5-6g. Please categorize the patients by duration of use (e.g., 1 week, 2 weeks, etc.) for each dose group. Patients can appear in both dose group analyses, if appropriate.

3. We note that in several places in your application, you refer to the use of individual case summaries as a source of safety data, despite your prior assurances that these summaries would not serve as primary source documents. Please summarize the extent to which these case summaries were substituted for primary data.

4. Please provide comprehensive analyses of your urinalysis and coagulation data.

5. Please provide comprehensive clinical descriptions of cases of dyspnea, dependent edema, dysmenorrhea, and urinary tract infections. These events occurred with significantly increased frequency compared to placebo in controlled trials. In your submission, please consider the data from controlled trials and uncontrolled trials separately.

Safety Update

In your May 22, 1997 correspondence, you provided a proposal for the content of the safety update (referred to as final safety update by you) to be submitted in response to an FDA action letter. We find the proposal acceptable with one exception. Your proposal states that you will be presenting U.S. and non-U.S. (i.e. primary and secondary non-U.S.) data combined. We, however, request that you only combine the U.S. and primary non-U.S. databases. For the secondary non-U.S. and non-CRF databases, please submit data only for deaths, discontinuations due to adverse events, and serious adverse events.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Submit U.S. and primary non-U.S. safety data including results of trials that were still ongoing at the time of NDA submission. The presentation of this data can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will facilitate review.

2. Submit U.S. and primary non-U.S. drop-out data with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study. Your request for a waiver of the requirement for submission of CRFs for patients who did not complete a study because of an adverse event is granted, but these CRFs should be available for submission, if requested.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Nomenclature

Concerns have been raised regarding the potential for medication errors related to similarities between the names Sabril (vigabatrin) and Gabitril (tiagabine). Please address this issue.

Biopharmaceutics

1. Please submit for our review the results of your ongoing phenytoin-vigabatrin interaction study in order that appropriate language regarding this potential interaction may be incorporated into drug product labeling.

2. We ask that the following final dissolution methodology and specification be adopted for Sabril® tablets:

Apparatus:	USP Apparatus II (paddle)
Agitation:	50 rpm
Medium:	Water, 900mL, 37± 0.5°C
Specification:	NLT [redacted] in 30 minutes

b(4)

Chemistry, Manufacturing, and Controls

The expiration dating period for Sabril tablets is extended to 36 months when packaged and stored as per the original NDA submission.

Phase IV Commitments

Because uncertainties remain about vigabatrin's capacity to cause neuronal injury, and because the mechanism of its link to visual field abnormalities and peripheral neuropathy is unclear, future investigations in these areas are warranted. Accordingly, we expect you to commit prior to the approval of vigabatrin to performing appropriately designed studies which will address these concerns. The Division will be happy to discuss the designs of these studies.

Pregnancy Registry

We recognize that you intend to collect information about the use vigabatrin in pregnant women. Please submit your plan to conduct such a registry.

Promotional Material

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Melina Malandrucco, R.Ph., Regulatory Management Officer, at (301) 594-5526.

Sincerely yours,

Robert Temple 11/26/97

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA 20-427
HFD-120/Div. Files
HFD-002/ORM
HFD-92/DDM-DIAB
HFD-120/M.Malandrucco/Ware
HFD-120/Leber/Katz/Sherry/Burkhart/Boehm/Fitzgerald/Rosloff/Guzewska
HFD-710/Chi/Sahlroot
HFD-860/~~Baweja~~/Tammarra/Chandra Sahajwallal
HFD-101/Office Director
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-560/OTC (with labeling - for OTC Drug Products Only)

Drafted by: JHW/MNMOctober 21, 1997/20427ae.ltr
Initialed by:
Final:

APPROVABLE (AE)

SABRIL® Tablets
(vigabatrin) 500 mg

DESCRIPTION

SABRIL (vigabatrin) is available as white, film–coated tablets for oral administration. Each tablet contains 500 mg vigabatrin. Tablets also contain as inactive ingredients: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycols, povidone, sodium starch glycolate, and titanium dioxide. Vigabatrin is an oral antiepilepsy drug with the chemical name (±) 4–amino–5–hexenoic acid. It is a racemate consisting of two enantiomers. The molecular formula is $C_6H_{11}NO_2$ and the molecular weight is 129.16. It has the following chemical structure:

[Insert Structure Here.]

Vigabatrin is a white to off–white powder which is freely soluble in water, slightly soluble in methyl alcohol, very slightly soluble in ethyl alcohol and chloroform, and insoluble in toluene and hexane. The pH of a 1% aqueous solution is about 6.9. The n–octanol/water partition coefficient of vigabatrin is about 0.011 (log *P*=–1.96) at physiologic pH. Vigabatrin melts with decomposition in a 3–degree range within the temperature interval of 171°C to 176°C. The dissociation constants (pK_a) of vigabatrin are 4.02 and 9.74 at room temperature (25°C).

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is believed to be the result of its action as a preferential and irreversible inhibitor of γ–aminobutyric acid transaminase (GABA–T), which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter γ–aminobutyric acid (GABA). This action results in increased levels of GABA in the CNS.

No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to be dependent on the rate of enzyme resynthesis rather than on the plasma concentration of drug.

Pharmacokinectics: Following oral administration, vigabatrin is essentially completely absorbed from SABRIL 500 mg film-coated tablets. Food increases Cmax by about 33% and delays Tmax, but the extent of absorption is not affected. The half-life of vigabatrin is about 7 ½ hours.

Vigabatrin is widely distributed throughout the body; mean steady state volume of distribution is 1.1 L/Kg (CV = 20%). Vigabatrin does not bind to plasma proteins. CSF vigabatrin concentrations represent approximately 10% of the corresponding blood concentrations.

Following administration of ^{14}C-vigabatrin to healthy male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing most of this. Vigabatrin is thus excreted essentially unchanged in humans.

Following multiple dosing of vigabatrin 1.5 g bid to epileptic patients, peak plasma concentration occurred in one hour. There was little accumulation on multiple dosing. Vigabatrin displayed linear pharmacokinetics over a single dose range of 0.5 - 4 g, and a repeated dose range of 0.5 to 2.0 g bid, and in a treated population given a 4 -6 g daily dose. Oral administration of vigabatrin resulted in a linear increase in the suboccipital CSF concentration of vigabatrin at 1.5 to 4.5 g doses.

Special Populations

Age Effects: No specific pharmacokinetic study was conducted to investigate the effect of age. Population analysis of patient data indicated that the elderly cleared the drug 25% slower than the young (See Precautions Section).

Gender Effects: No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients.

Race Effects: No specific pharmacokinetic study was conducted to investigate race effects. A cross study comparison between 23 Caucasians and 7 Japanese subjects who were administered 1, 2, and 4 g of vigabatrin indicated that the AUC, Cmax, and half-life were similar for the two populations, but the mean renal clearance of Caucasians is about 25% higher than that of the Japanese.

Renal Impairment: Mean AUC increased by about 30%, 100%, and 450%, and terminal half-lives rose to 12 hours, 16 hours, and 28 hours in patients with mild (CL_{cr} > 50-70 mL/min), moderate (CL_{cr} > 30-50 mL/min), and severe (CL_{cr} > 10-30 mL/min) renal impairment, respectively.

Accumulation of vigabatrin can occur in patients with moderate or severe renal impairment. Patients with moderate and severe renal impairment should be started with a lower dose of vigabatrin and monitored closely for any side effects considered dose related (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

CLINICAL STUDIES

The effectiveness of SABRIL as adjunctive therapy was established in two multicenter placebo–controlled, double–blind, parallel–group clinical trials in 357 adults with refractory complex partial seizures, with or without generalization, or partial seizures that generalized. The patients (aged 18 to 60 years) had a history of at least six partial seizures per month in spite of receiving one or more antiepilepsy drugs dosed to therapeutic concentrations.

The primary measure of effectiveness was the change from baseline in the frequency ofthe seizures described above. Additional analyses were performed to assess the effect of vigabatrin on individual seizure types. Therapeutic success, a protocol-specified secondary outcome measure, was defined as ≥ 50% reduction in mean monthly combined seizure frequency.

One study (n=174) was a randomized, double–blind, placebo–controlled, dose–response trial consisting of an 8–week baseline period and an 18–week treatment period. After establishing baseline, the patients were randomized to receive placebo or 1, 3, or 6 g/day SABRIL administered as twice a day dose. During the first 6 weeks following randomization, the dose of study medication was titrated upward beginning with 1 g/day and increased by 0.5 g/day on days 1 and 5 of each subsequent week in the 3g/day and 6g/day groups untill the assigned dose was reached. Results are shown in Table 1. The 3g/day and 6g/day doses produced significant reductions in seizure rates. The 6g/day dose was not significantly superior to 3g/day dose.

[Note to Sponsor: In the tables that follow, please fill in the cells with numbers (N's, seizure medians, p-values, etc.), that correspond to the analyses reported in your 6/24 and 6/30 submissions; that is, the results of intent to treat analyses of all patients that incorporate revised (worst case) seizure rates only for patients with revised seizure counts.]

Table 1 **Seizure Frequency (Number/28 Days)**

Treatment	*n*	*Baseline Median*[a]	*End Study Median*	*Change in Median From Baseline to End Study*	*p value for Median Change from Baseline*	*Therapeutic Success Patients at End Study*[b]
Placebo	45	9	9	0		8%
1 g SABRIL®	39	7.5	7.5	0	0.079	26%
3 g SABRIL®	39	8	4.5	–3.5	0.0012	44%
6 g SABRIL®	38	8.3	4.3	–4.0	0.0001	53%

[a] seizure frequency expressed as number / 28 days (median)
[b] defined as achieving as least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized.

In this study, the following results were seen for individual seizure types; most of the seizure reduction seen resulted from the effect on complex partial seizures.

Analysis of Efficacy Results by Seizure Class					
Seizure Class	Study 25				
	Placebo		Vigabatrin 3 g		
	Baseline[a]	Endstudy	Baseline	Endstudy	P-value
IA (partial seizures)	6.5	4.5	11.0	8.8	.7511
IB (complex partial seizures that do not generalize)	8.8	8.3	17.0	3.5	.0014
IC (partial seizures secondarily generalized)	2.0	1.3	1.5	0.5	.1828
IB+IC	9.0	8.8	8.0	3.7	.0001
Therapeutic Success[b] (IB+IC)	7%		51%		<.001

[a] seizure frequency expressed as number / 28 days (median)
[b] defined as achieving as least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized.

The second study (n=183) was a randomized, double–blind, placebo–controlled, parallel trial consisting of an 8–week baseline period and a 16–week treatment period. During the first 4 weeks following randomization, the dose of study medication was titrated upward beginning with 1 g/day and increased by 0.5 g/day on a weekly basis to the maintenance dose of 3 g/day. SABRIL 3 g/day was superior to placebo in reducing the median seizure frequency. The percentage of patients achieving therapeutic success was greater for the SABRIL group compared to placebo.

Table 2 **Seizure Frequency (Number/28 Days)**						
Treatment	*n*	*Baseline Median*[a]	*End Study Median*	*Change in Median From Baseline to End Study*	*p value for Median Change from Baseline*	*Therapeutic Success Patients at End Study*[b]
Placebo	90	9	7.5	-1.5		21.1%
3 g SABRIL®	92	8.3	5.5	-2.8	0.0143	39.1%

[a] seizure frequency expressed as number / 28 days (median)
[b] defined as achieving as least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized.

In this study, the following results were seen for individual seizure types:

Analysis of Efficacy Results by Seizure Class					
Seizure Class	Study 24				
	Placebo		Vigabatrin 3 g		
	Baseline[a]	Endstudy	Baseline	Endstudy	P-value
IA (partial seizures)	*	*	*	*	*
IB (complex partial seizures that do not generalize)	8.0	7.0	8.5	5.0	0.0006
IC (partial seizures secondarily generalized)	1.5	1.5	4.0	2.5	0.3881
IB+IC[b]	9.0	7.5	8.3	5.5	0.0143
Therapeutic Success[b,c] (IB+IC)	21.1%		39.1%		.008

[a] seizure frequency expressed as number / 28 days (median)
[b] utilizes ITT with corrected seizure data
[c] defined as achieving as least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized.
* not enough subjects to analyze

[Note to Sponsor: For these studies, please provide analyses of the effects of age, race, or gender on the realized drug treatment effect, and describe the results of these analyses at this point in the labeling text.]

INDICATIONS AND USAGE

SABRIL is indicated as adjunctive therapy in the treatment of complex partial seizures in adults with epilepsy. Because of its potential to cause intramyelinic vacuolization in mammalian species, SABRIL should not ordinarily be included among the AED treatments first chosen for combination use.

CONTRAINDICATIONS

SABRIL is contraindicated in patients with a known hypersensitivity to vigabatrin or any of the other components of the tablet.

WARNINGS

General

As occurs with other antiepilepsy drugs, abrupt discontinuation may lead to increased seizure frequency, including status epilepticus; therefore, discontinuation of SABRIL should occur by gradual dose reduction over a 2– to 4–week period if possible.

Potential Risk of Irreversible Neural Injury

[Note to Sponsor: The entire following section should be bolded.]

Vacuolization, characterized by a separation of the outer lamellar sheath of myelinated fibers, has been observed in brain white matter tracts in rats, mice, dogs, and possibly monkeys. The lesion, in appearance consistent with what has been called intramyelinic edema (IME) in other settings, was seen in rats given daily oral doses of 30 mg/kg and greater, and in mice and dogs given daily oral doses of 50 mg/kg and greater. Vacuoles were seen at the higher doses as early as 4 weeks and were seen at lower doses with longer duration of treatment. A no-effect dose was not established in these species. The doses at which vacuolization occurred are within the human therapeutic range. On a body surface area basis, these doses are equivalent to 1/10 to ½ of the maximum recommended daily human dose of 3 grams.

In both the rat and dog, vacuolization was not detectable after variable periods following discontinuation of vigabatrin treatment, but changes consisting of swollen or degenerated axons, mineralization, and gliosis have been seen in some of the areas in which vacuolization had been previously observed. The possibility that vigabatrin may

interfere with myelination in the developing brain has not been fully studied (see **PRECAUTIONS, Nursing Mothers** and **PRECAUTIONS, Pediatric Use**).

In the monkey, neither vacuolization nor other changes were seen after 6 years of treatment at 50 and 100 mg/kg/day. In monkeys receiving 300 mg/kg for 16 months, however, minimal vacuolization was noted with equivocal differences between treated and control animals.

In the dog, electrophysiological studies indicated that vacuolization was associated with increased latencies of the somatosensory–evoked potentials (SEP) and visual–evoked potentials (VEP); these changes were reversible when the drug was withdrawn. Vacuolization was also correlated with increased magnetic resonance imaging (MRI) signals in the dog.

Although there has been no clear finding of intramyelinic vacuolization in humans, whether this can occur is unknown, and it is difficult to rule out the possibility. First, it is not clear what clinical manifestations would be associated with intramyelinic vacuolization. Second, although there is a hope that MRI and EP would be able to detect the lesions before they are clinically manifest, there is no evidence in humans that they can do so. This limitation noted, the following sections describe available human data.

Of the 3320 patients exposed to vigabatrin during the development program, __ **[Note to Sponsor: Please state the total number of individual patients who have received at least 1 evaluable MRI or evoked potential test while on treatment with vigabatrin. Do not include in this number those patient who had an MRI or evoked potential, but whose test was not retrievable.]** were evaluated for the occurrence of intramyelinic vacuolation utilizing the techniques shown to be sensitive to this finding in animals. Of these __ patients, __ patients **[Note to Sponsor: Please state the total number of individual patients who meet the criteria described in this sentence.]** received at least 1 evaluation prior to initiation of treatment with vigabatrin and at least 1 evaluation while receiving vigabatrin.

MRI Findings: [Note to Sponsor: Please fill in the blanks contained within this paragraph with the appropriate numbers of patients as described in each sentence.] Of these patients, __ had on-treatment MRIs performed at least 12 months after the initiation of treatment, and __ had on-treatment MRIs done at least 3 years after beginning treatment. An additional __ patients had an evaluation prior to initiation of treatment and a subsequent evaluation after having been off vigabatrin treatment for periods ranging from __ to __ (time period, i.e., days or months). An additional __ patients had an MRI after initiation of treatment but no pre-treatment evaluation; __ of these patients had their MRI while still receiving treatment, while __ patients were evaluated after having discontinued treatment.

In the two controlled clinical trials, 0/181 vigabatrin treated patients and 0/112 placebo treated patients developed any unexplained MRI abnormalities at 4-5 months. In the uncontrolled experience, there were 3 cases which were consistent with intramyelinic vacuolization.

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

Evoked Potential Findings: [Note to Sponsor: Please fill in the blanks contained within this paragraph with the appropriate numbers of patients as described in each sentence.] Of these patients, __ had on-treatment EPs performed at least 12 months after the initiation of treatment, and __ had on-treatment EPs done at least 3 years after beginning treatment. An additional __ patients had an evaluation prior to initiation of treatment and a subsequent evaluation after having been off vigabatrin treatment for periods ranging from __ to __ (time period, e.g., days or months). An additional __ patients had an EP after initiation of treatment but no pre-treatment evaluation; __ of these patients had their EP while still receiving treatment, while __ patients were evaluated after having discontinued treatment.

In the two controlled clinical trials, there were no significant changes in VEPs and SEPs seen in either vigabatrin treated or placebo treated patients **[Note to Sponsor: Please confirm and document that this statement is true for both VEPs and SEPs. Further please submit all EP tracings for patients in Study 024.]**. In uncontrolled experience, there were 10 patients who had VEP changes compared to baseline that were unexplained by other pathologies. Of these 10, 6 were being treated with vigabatrin at the time of the abnormality (duration of treatment ranged from __ to __), and 4 had been discontinued from treatment (length of time since last exposure ranged from __ to __). In these 10 patients, MRIs done at approximately the same time as the post-treatment VEPs did not demonstrate findings consistent with vacuolization.
In the uncontrolled experience, there were 11 patients who had SEP changes compared to baseline that were unexplained by other pathologies. Of these 11, 5 were being treated with vigabatrin at the time of the abnormality (duration of treatment ranged from __ to __), and 6 had been discontinued from treatment (length of time since last exposure ranged from __ to __). In these 11 patients, MRIs done at approximately the same time as the post-treatment SEPs did not demonstrate findings consistent with vacuolization.

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

Ophthalmologic Signs and Symptoms: [Note to Sponsor: Please provide a detailed accounting of all cases of visual field defects and retinal abnormalities, as well as all cases of optic neuritis and/or atrophy. Please describe the number of cases of these abnormalities seen in the database.] Whether or not these abnormalities are related to treatment, and if they are related to white matter vacuolization and/or other changes previously described (see WARNINGS: White Matter Neuropathology), is unknown.

Clinical studies in the development program were not designed to systematically identify ocular abnormalities; only 28/537 patients in the U.S. epilepsy trials had pre-treatment ophthalmologic exams. In one study, patients who were previously identified as having MRI and/or EP abnormalities, or visual and/or ocular complaints had confrontational visual field testing and indirect ophthalmoscopy. In this study, __ patients were found to have visual field defects and/or retinal abnormalities. **[Note to Sponsor: Please submit all additional data referable to these cases. Specifically, we are interested in formal visual field and/or retinal tests , follow-up data on these cases, etc...]**

During the routine prescription event monitoring (PEM) performed in the United Kingdom following vigabatrin approval, in cohort of 10,178 patients, there were 3 cases of bilateral, irreversible peripheral field defects. **[Note to Sponsor: Please describe these defects in more detail.]** In similar PEM studies of lamotrigine (11,316 patients) and gabapentin (3,100 patients), no similar cases were reported.

The value of baseline and periodic ophthalmologic examinations has not been systematically evaluated but should be considered.

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

as well as from open and post-marketing experience. Examine the effects of dose, duration, and vigabatrin discontinuation on the symptoms and signs of peripheral neuropathy.]

Retinal Toxicity

Animal Finding: Disruption of the rod and cone layer of the retina was seen in albino rats (at 3 months) and mice at doses within the human therapeutic range. Reversibility was not examined. The lesion was not seen in dogs or monkeys.

Cognitive/Neuropsychiatric Adverse Events

[Note to the Sponsor: As requested in the FDA approvable letter, we anticipate a full revisitation of these events and an attempt to describe them in clinically meaningful terms. This reanalysis should cover all the relevant terms that now appear in various parts of the adverse events section. Additionally, please examine dose response for the events described in this section and draft appropriate statements, and analyze the time to onset of these events from start of treatment.] Adverse events most often associated with the use of SABRIL were central-nervous system related. The most significant of these can be classified into three general categories: 1) psychiatric symptoms including depression and psychosis, 2) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties, and 3) somnolence or fatigue.

In the studies with the most reliably recorded data, _/_ (_%) of patients discontinued vigabatrin and _/_ (__%) were hospitalized because of reported depression. **[Note to Sponsor: Please calculate these numbers for the combined U.S. and primary non-U.S. studies.]** In North American controlled trials, __ % of patients discontinued vigabatrin and/or were hospitalized and/or received medical treatment due to depression compared to __ % of placebo patients. In North American controlled trials 2/280 (1%) of vigabatrin patients attempted suicide compared to 0/188 of placebo patients.

In the studies with the most reliably recorded data, _/_ (_%) of patients discontinued vigabatrin and _/_ (__%) were hospitalized because of reported psychosis (hallucination, schizophrenic reaction, and/or paranoid reaction) **[Note to Sponsor: Please calculate these numbers for the combined U.S. and primary non-U.S. studies based on those cases conforming to your consultants definition of psychosis.]** In North American controlled trials, __ % of patients discontinued vigabatrin and/or were hospitalized and/or received medical treatment due to psychosis compared to __ % of placebo patients.

Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common. Although in some cases these events were of mild to moderate severity, they at times led to withdrawal from treatment. **[Note to Sponsor: Please insert statements about dose response and time to onset here.]**

Somnolence and fatigue were the most frequently reported CNS adverse events during clinical trials with SABRIL. Although in some cases these events were of mild to moderate severity, they led to withdrawal from treatment in __ % of the patients enrolled in North American controlled trials. **[Note to Sponsor: Please calculate this proportion from studies 024, 025, and 021. Additionally, insert statements about dose response and time to onset here.].**

Liver Failure

A total of seven cases of fulminant hepatic failure resulting in six deaths and one transplant have been reported in post-marketing experience from _____ to December 31, 1995. **[Note to Sponsor: Please insert the date range covered by this post-marketing experience.]** Based on an estimated exposure of _____ and an estimated rate of _____ in an untreated population, the estimated rate of fulminant hepatic failure appears to be up to 10 times that of the background rate, without considering under-reporting.

Assuming a 10% reporting rate gives a rate of 3 per 10,000 patient-years. In the development program, there was 1 case of hepatic failure in __ patient-years of vigabatrin use. **[Note to Sponsor: Derive a person-year estimate from the all U.S., primary non-U.S., and ongoing clinical studies that meet the criteria of the primary non-U.S. database.]**

For six of the seven cases, the onset of illness was approximately 270 or more days after initiation of vigabatrin. **[Note to Sponsor: Please describe, to the extent possible, the clinical characteristics of the illness including prodromal symptoms and laboratory findings.]** It is not known whether discontinuing vigabatrin at the first sign of laboratory and/or clinical abnormalities can prevent the occurrence of hepatic failure.

PRECAUTIONS

General

Drowsiness is commonly reported at the start of SABRIL treatment (see WARNINGS: Cognitive/Neuropsychiatric Adverse Events). Patients should be cautioned about this possibility at the start of treatment. Special care should be taken by patients if they drive, operate machinery, or perform any hazardous task.

Vigabatrin is eliminated via the kidneys, and therefore, caution should be exercised when administering SABRIL to patients with a creatinine clearance less than 60 mL/min. These patients should be monitored for adverse events such as drowsiness and confusion (see **DOSAGE AND ADMINISTRATION**).

Anemia

In North American controlled trials, __% of vigabatrin patients experienced an abnormally low hematocrit (females ≤ 32; males ≤ 37) compared to ___% of placebo patients. **[Note to Sponsor: Please describe here the course of these patients; e.g., __% of patients continued on treatment with resolution of the anemia, __% of patients continued on treatment with persistent anemia. Additionally, please submit a description, for our review, of all cases of serious anemia, by the usual definition, occurring in the entire development program. Included in this description should be all relevant information, including time to onset, other hematologic parameters (i.e., RBC indices, Reticulocyte count), other relevant laboratory tests (e.g., Coombs' test, ferritin, etc.), time course of the anemia. Please also provide this information for patients in whom the anemia resulted in treatment discontinuation. Please draft an appropriate description of the relevant findings in this section of labeling.]**

Sudden and Unexplained Deaths in Epilepsy Patients (SUDEP)

[Note to Sponsor: Please revise this section to reflect only the data for the US and non US primary database.] During the course of premarketing development of SABRIL, __sudden and unexplained deaths were recorded among a cohort of__ patients (one patient randomized to SABRIL in a US study never received medication and is not included in the total here) with epilepsy (__ patient–years of exposure). This represents an incidence of __ deaths per patient–year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving SABRIL (ranging from 5/10,000 for the general population of epileptics, to 4/1,000 for recently studied clinical trial populations similar to the population in the clinical development program for SABRIL, to 5/1,000 for patients with refractory epilepsy). The estimated SUDEP rate in patients receiving SABRIL was similar to that observed in patients receiving other antiepilepsy drugs who underwent clinical testing in a similar population at about the same time.

Status Epilepticus

In placebo–controlled studies, the incidence of status epilepticus in epilepsy patients receiving SABRIL was 1.5% (6/406) vs 1.3% in patients receiving placebo (4/311). Across all controlled and uncontrolled epilepsy studies, the overall incidence of status epilepticus in patients receiving SABRIL was 2.6% (51/1942).

[Note to Sponsor: Please include a statement about the risk of absence seizures and absence status and vigabatrin. Please also provide the references in support of such statement.]

SABRIL® Tablets
(vigabatrin) 500 mg

Information for Patients

Patients should be cautioned that SABRIL may cause drowsiness. Special care should be taken by patients if they drive, operate machinery, or perform any hazardous task. Patients should be advised to notify their physician immediately if they develop any worsening of seizures.

Patients should be questioned about pregnancy or lactation before starting SABRIL therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to the fetus.

Patients or their families should be advised to notify the treating physician immediately if they experience any mental or behavioral changes.

Laboratory Tests: Vigabatrin decreases alanine transaminase (ALT) and, to a lesser extent, aspartate transaminase (AST) plasma activity. The magnitude of suppressions for ALT has been reported to vary between 30% and 100% **[Note to Sponsor: Please submit data from the controlled trials examining the extent of LFT decreases. Specifically, please examine the proportion of patients who had LFT decreases in the following ranges; 80%-100%, 60%-80%, etc.. Also please examine the range of time to onset of the first abnormality and the relation to dose]**. Treatment with vigabatrin may be associated with decreases in hematocrit (see **PRECAUTIONS**).

Drug Interactions

Formal interaction studies with vigabatrin and commonly used anti-epilepsy drugs have not been performed Based on population pharmacokinetics, carbamazepine, clorazepate, phenobarbital, phenytoin, primidone, and sodium valproate appear to have had no effect on plasma concentrations of vigabatrin.

SABRIL had no effect on plasma concentrations of carbamazepine, clorazepate, and primidone during controlled clinical trials. During concurrent SABRIL treatment, phenobarbital plasma concentrations were reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of less than 10% in some multicenter trials but not in others. These reductions did not appear to be clinically relevant.

Phenytoin: A 16% to 33% average reduction in total phenytoin plasma levels has been reported in controlled clinical trials. In a pharmacokinetic study, levels returned to baseline in 7 weeks. The exact nature of this interaction with SABRIL is not understood; in these studies the interaction did not appear to be clinically relevant. Therefore, during concurrent therapy with SABRIL, phenytoin dose adjustment should be considered only in those cases in which both plasma levels of phenytoin decrease and seizures worsen.

Clonazepam: Clonazepam (0.5 mg) co-administration has no influence on the pharmacokinetics of vigabatrin (1.5 g bid). Vigabatrin increased the mean Cmax of clonazepam by about 30 % and decrease the mean Tmax by 45 %.

Alcohol: Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g bid) indicated that neither drug influences the pharmacokinetics of the other.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Vigabatrin showed no carcinogenic potential when given in the diet to the CD_1 mouse at doses up to 150 mg/kg/day for 18 months or to the Long–Evans rat at doses up to 150 mg/kg/day for 2 years (approximately 1/4 and ½ of the maximum recommended human daily dose of 3 grams on a mg/m^2 basis, respectively).

Vigabatrin was not mutagenic in the *in vitro* Ames assay in Salmonella or the CHO/HGPRT mammalian cell forward gene mutation assay. It was not clastogenic in the *in vitro* chromosomal aberration assay in rat lymphocytes or the *in vivo* mouse bone marrow micronucleus assay.

Reproduction and fertility studies using doses up to 150 mg/kg/day, which corresponds to approximately ½ of the maximum recommended human daily dose on a mg/m^2 basis, have shown no effect on male or female fertility in rats.

Pregnancy

Pregnancy Category C: Administration of vigabatrin to pregnant mice and rabbits was associated with embryolethality and teratogenic effects. When rabbits were dosed orally during the period of organogenesis at 150 and 200 mg/kg/day (approximately equal to or slightly greater than the maximum human daily dose of 3 grams on a mg/m^2 basis) the fetal incidence of cleft palate was 2% and 9%, respectively, and the litter incidence was 12% and 24%, respectively. Cleft palate did not occur in the control group. At 200 mg/kg/day vigabatrin was associated with an increase in resorptions. These doses were maternally toxic as evidenced by decreased food consumption and transient body weight loss. A no-effect dose for these effects was 100 mg/kg/day (2/3 of the human daily dose of 3 grams on a mg/m^2 basis). When mice were dosed by the intraperitoneal route at 300 or 450 mg/kg on a single day during the period of organogenesis (days 7,8,9,10,11 or 12), cranio-facial and skeletal malformations occurred at both doses and exomphalos occurred at 450 mg/kg. There were also increased resorptions and decreased fetal body weights. A no-effect dose for these effects was not determined (Abdulrazzaq Y.M., et al., *Teratology* 55: 165-176 [1997]). Vigabatrin was not teratogenic in rats dosed during the period of organogenesis at oral doses up to 150 mg/kg/day (½ of the human daily dose of 3 grams on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women, and SABRIL should be used during pregnancy only when the potential benefit justifies the potential risk to the fetus.

Pregnancy Exposure Registry: To monitor fetal outcome of pregnant women exposed to SABRIL, Hoechst Marion Roussel supports the Antiepilepsy Drug Pregnancy Registry. Physicians are encouraged to register patients **before fetal outcome (e.g., ultrasound, results of amniocentesis, birth, etc.) is known,** by calling toll–free 1–888–233–2334.

Nursing Mothers

Vigabatrin is excreted in breast milk in low concentrations. Therefore, a decision should be made on whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Because SABRIL causes vacuolization in myelin in rats, mice, and dogs, nursing mothers should be advised that the possibility that it will interfere with myelination in the developing nervous system should be considered.

Pediatric Use

The safety and effectiveness of SABRIL have not been established in the pediatric population.

Because SABRIL causes vacuolization in myelin in rats, mice, and dogs, the possibility of interference with myelination in the developing nervous system should be considered.

Use in Elderly
[Note to Sponsor: Please develop this section of labeling as described in the final rule for the addition of a "geriatric use" subsection. This final rule was recently published in the Federal Register #45313, on August 27, 1997.]

SABRIL tablets should be used with caution in elderly patients due to a decrease in the clearance of vigabatrin.

Use in Renally Impaired Patients

SABRIL tablets should be used with caution in moderately (Cl_{cr} >30-50 mL/min) and severely (Cl_{cr} > 10-30 mL/min) renally impaired patients due to a decrease in the clearance of vigabatrin. These renally impaired patients should be started with a lower dose of vigabatrin and they should be monitored for any side effects (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

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ADVERSE REACTIONS

The most commonly observed adverse events in placebo-controlled epilepsy studies associated with the use of SABRIL in combination with other AEDs, not seen at an equivalent frequency among placebo–treated patients, were nystagmus, amnesia, confusion, paresthesia, depression, weight increase, and peripheral edema.

Approximately 12.9% of the 1942 individuals who received SABRIL in controlled and uncontrolled epilepsy clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with discontinuation were drowsiness (1.5%) and depression (1.4%) **[Note to Sponsor: Please expand this list in decreasing order of frequency of individual events associated with discontinuation, and provide placebo values. The frequency of each event should be included. Please also include a statement about which events are dose related. Make cut at the 1%.].**

In Studies 024 and 025 (U.S. studies), the double-blind, placebo-controlled, parallel-group, add-on studies, the proportion of patients that discontinued treatment because of adverse events was __% for the group treated with SABRIL and __% for the placebo group. The most common adverse events considered the primary reason for discontinuation were [Note to Sponsor: Please create a list in decreasing order of frequency of individual events associated with discontinuation.].

<u>Adverse Event Incidence in Controlled Clinical Trials</u>
Table __ lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with SABRIL in placebo-controlled, add-on epilepsy trials and that were numerically more common in the SABRIL group. In these studies, either SABRIL or placebo was added to the patient's current AED therapy.

The prescriber should be aware that these figures, obtained when SABRIL was added to concurrent AED therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

[Note to Sponsor: Please switch the order of the placebo and SABRIL columns in the following Table, and within systems, list events in order of decreasing frequency based on SABRIL. Also, please note that comments regarding certain terms are contained within the table and listings, and are located in brackets after the specific term. A response to these comments is necessary.]

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Table __ Treatment-Emergent Adverse Event[1] Incidence in Placebo-Controlled, Add-On Trials (events in at least 2% of patients treated with SABRIL and numerically more frequent than in the placebo group)		
Body System/Event	*Placebo (n=311) %*	SABRIL (n=406) %
Neurologic		
Headache	26	28
Drowsiness	15	26
Dizziness	14	19
Nystagmus	5	12
Tremor	8	11
Amnesia	4	9
Ataxia	5	8
Confusion	3	7
Paresthesia	2	6
Coordination Abnormal	3	5
Gait Abnormal	4	5
Concentration Impaired	2	5
Speech Disorder [not clinically meaningful]	1	4
Vertigo	2	4
Hypoesthesia	2	3
Hyporeflexia	0	3
Hyperreflexia	1	2
Tinnitus	1	2
Convulsions Grand Mal	1	2
Twitching	0	2
Psychiatric		
Depression/psychotic depression	4	12
Agitation	8	11
Anxiety	4	7
Emotional Lability	3	5
Thinking Abnormal [not clinically meaningful]	2	4
Aggressive Reaction	2	3
Personality Disorder	1	2
Gastrointestinal System		
Nausea	8	9
Diarrhea	6	7
Abdominal Pain	4	6
Constipation	4	6
Vomiting	5	6
Tooth Disorder [define further]	2	3

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Body as a Whole		
Fatigue	16	26
Fever	3	4
Malaise	1	2
Generalized Edema (including edema) [evaluate & combine with peripheral edema]	1	2
Face Edema	0	2
Respiratory System		
Throat Irritation	6	7
Upper Respiratory Tract Infection	3	5
Dyspnea	0	2
Infectious Disease		
Infection Viral	12	14
Infection Fungal	1	2
Dermatologic		
Pruritus	0	2
Sweating Increased	1	2
Musculoskeletal System		
Arthralgia	4	7
Back Pain	4	6
Arthrosis	2	3
Metabolic & Nutritional		
Weight Increase	4	8
Reproductive, Female		
Dysmenorrhea	1	4
Menstrual Disorder [vague]	1	2
Urinary System		
Urinary Tract Infection	0	3
Cardiovascular		
Peripheral Edema (including dependent and leg) [evaluate & combine with generalized edema]	1	6
Ophthalmologic		
Vision Abnormal [vague]	6	10
Diplopia	6	8
Eye Pain	1	3
Eye Abnormality [vague]	1	2
Hematologic		
Anemia/hypochromic anemia	1	2
Ear, Nose & Throat		
Earache	1	2

[1]Patients in these epilepsy studies were receiving concomitant therapy with other AEDs in addition to SABRIL or placebo. Patients may have experienced multiple adverse events during the study; therefore, patients may be included in more than one category.

Adverse events reported in 1 - <2% and numerically more frequent than in the placebo group were: hearing impaired, myopathy, neuropathy, dreaming abnormal, nightmare, paranoid reaction, euphoria, suicide attempt [vague], hemorrhoids, vaginitis, rigors, urination disorder [vague], urinary retention, lymphadenopathy, and allergy.

Other adverse events reported in ≥1% of patients but equally or more frequent in the placebo group included convulsions (including condition aggravated), aphasia, hypokinesia, hypertonia, insomnia, depersonalization, apathy, dyspepsia, anorexia, abdominal distention, pain, trauma injury, hot flushes, congestion, coughing, rhinorrhea, bronchitis, epistaxis, rhinitis, influenza–like symptoms, infection, herpes simplex,- rash, acne, alopecia, eczema, erythema, urticaria, furunculosis, weight decrease, phosphatase alkaline increased, urinary frequency, urinary incontinence, GGT increased, leukopenia, conjunctivitis.

[Note to Sponsor: Please examine dose-response in the safety database. In particular, examine the relationship between dose and discontinuations, serious adverse events, and commonly occurring events. Please describe the results of these analyses at this point in the labeling text. Use a table to display results that show dose response.]

[Note to Sponsor: Current FDA regulations require that you analyze clinical studies to determine whether or not, and if so to what extent, age, race, and/or gender affected the incidence of these events. Please describe the results of these analyses at this point in the labeling text. Reanalyze dysmenorrhea and other menstrual disorders to only include females in the denominator; see FDA approvable letter.]

Other Adverse Events Observed During All Epilepsy Clinical Trials

SABRIL has been administered to 1942 individuals during all phase 2/3 clinical trials, only some of which were placebo controlled. During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHO dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 1942 individuals exposed to SABRIL who experienced an event of the type cited while receiving SABRIL. All reported events are included except those already listed in the previous table, events seen only three times or fewer (unless potentially important), events very

unlikely to be drug-related, and those too general to be informative. Events are included without regard to determination of a causal relationship to vigabatrin.

Events are classified within system organ class categories and enumerated in order of decreasing frequency using the following definitions: *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *Rare* events are those occurring in fewer than 1/1000 patients.

Neurologic: *Infrequent:* dyskinesia, EEG abnormal, muscle weakness, sleep disorder, stupor, migraine headache, dysphonia, dystonia, hypotonia, labyrinthine disorder, mental deficiency, upper motor neuron lesion (positive Babinski), dementia, hemiparesis, taste perversion, dryness of mucous membranes, ptosis, cerebellar syndrome, choreoathetosis, delirium, extrapyramidal disorder, paralysis, psychomotor hyperactivity. *Rare:* ataxia vestibular, cerebral infarction, cerebrovascular accident, coma, convulsions petit mal, deafness nerve, encephalopathy, hyperesthesia, opisthotonos, paraplegia, paresis, parosmia, taste loss.

Psychiatric: *Infrequent:* hallucination, libido decreased, crying abnormal, bulimia, delusion, hysteria, lalorrhea, teeth–grinding. *Rare:* cyclothymic reaction, libido increased, schizophrenic reaction.

Gastrointestinal: *Infrequent:* saliva increased, dry mouth, gingivitis, gastroenteritis, stomatitis aphthous, gingival hyperplasia, colitis, gastritis, melena, stomatitis, glossitis, hiccup, stomatitis ulcerative, gastrointestinal hemorrhage, hemorrhage rectum, eructation, gastric ulcer, gingival bleeding. *Rare:* cheilitis, duodenal ulcer, dysphagia, enteritis, esophagitis, fecal incontinence, gastroesophageal reflux, hemorrhoids thrombosed, salivary gland enlargement, tongue edema.

Body as a Whole: *Infrequent:* edema periorbital, pallor, chest pain substernal, abscess, ESR increased, halitosis. *Rare:* perineal pain male.

Respiratory System: *Infrequent:* pneumonia, bronchospasm, apnea, hyperventilation, pulmonary edema, wheezing. *Rare:* hemoptysis, laryngitis, nasal polyp, pleural effusion, pleural fibrosis.

Dermatologic: *Infrequent:* dermatitis, photosensitivity reaction, dry skin, hypertrichosis, rash maculopapular, pruritus genital, hair texture abnormal, seborrhea, chloasma, hair discoloration, psoriasis, skin discoloration, skin hypertrophy, skin ulceration. *Rare:* angioedema, bullous eruption, dermatitis exfoliative, vitiligo.

Musculoskeletal System: *Infrequent:* tendonitis, arthritis. *Rare:* arthritis rheumatoid aggravated, Dupuytren's contracture, hernia, osteoporosis, temporomandibular joint dislocation.

Metabolic and Nutritional: *Infrequent:* thirst, hyponatremia, amylase increased, hypocalcemia, hypokalemia. *Rare:* acidosis, calcinosis, gout, gamma–globulins increased, hypercholesterolemia, hyperlipemia, hypoglycemia, ketosis.

Urinary System: *Infrequent:* dysuria, cystitis, hematuria, pyelonephritis. *Rare:* albuminuria, nocturia, pyuria, renal calculus.

Cardiovascular: *Infrequent:* hypertension, hypotension, tachycardia, bradycardia, syncope, arrhythmia atrial, AV block, extrasystoles, fibrillation atrial, hypotension orthostatic. *Rare:* arrhythmia nodal, cardiomyopathy, mitral insufficiency, pericardial effusion.

Ophthalmologic: *Infrequent:* cataract, dry eyes, photophobia, retinal pigmentation, visual field defect, corneal deposits, lacrimation abnormal, accommodation abnormal, strabismus, blepharitis, blepharospasm, myopia, photopsia, corneal ulceration, scotoma, vitreous detachment. *Rare:* anisocoria, hemianopia, hemorrhage anterior chamber eye, mydriasis, optic atrophy, optic neuritis, pupillary reflex impaired.

Reproductive, Female: *Infrequent:* menorrhagia, breast pain female, vaginal hemorrhage, leukorrhea, pelvic inflammation, premenstrual symptoms. *Rare:* breast enlargement, cervical uterine polyp, endometriosis, endometritis.

Hematologic: *Infrequent:* granulocytopenia, thrombocytopenia, lymphoma–like disorder, macrocytosis, granulocytosis, leukocytosis. *Rare:* anemia pernicious, bleeding time increased, eosinophilia, hemolysis, lymphadenopathy cervical, lymphocytosis, monocytosis, prothrombin decreased, thrombocytosis.

Ear, Nose and Throat: *Infrequent:* otitis media, otitis externa.

Vascular (extracardiac): *Infrequent:* flushing, peripheral ischemia, vein varicose. *Rare:* aneurysm, hemangioma acquired, thrombophlebitis arm.

Endocrine: *Infrequent:* goiter, hypothyroidism. *Rare:* gynecomastia, inappropriate ADH.secretion syndrome, lipidosis.

Reproductive, Male: *Infrequent:* impotence, prostatic disorder, epididymitis. *Rare:* priapism.

Immunologic: *Infrequent:* allergic reaction. *Rare:* lupus erythematosus syndrome, polymyalgia rheumatica, vasculitis.

Postmarketing Surveillance

In addition to the adverse experiences reported during clinical testing of SABRIL, the following adverse events have been reported in patients receiving SABRIL in an estimated 125,000 patients during worldwide use. Data are insufficient to establish a causal association.

Hypomania and mania have been rarely reported.

Rare instances of marked sedation, stupor, and confusion associated with nonspecific slow wave activity on electroencephalogram have been described soon after the introduction of SABRIL therapy. These events have been reversible following dose reduction or discontinuation of SABRIL.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of SABRIL has not been evaluated in human studies.

OVERDOSAGE

Confirmed and/or suspected SABRIL overdoses have been reported during clinical trials and postmarketing surveillance; many of the cases involved possible suicide attempts. None of the SABRIL overdoses resulted in death. When reported, the SABRIL dose ingested ranged from 3 g to 90 g, but most were between 7.5 and 30 g. Nearly half of the cases involved multiple drug ingestions including carbamazepine, barbiturates, benzodiazepines, lamotrigine, valproic acid, acetaminophen, and/or chlorpheniramine.

Coma, unconsciousness, and/or drowsiness were described in the majority of cases of SABRIL overdose. Other less commonly reported symptoms included vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation, irritability, confusion, and increased seizure activity or status epilepticus. These symptoms resolved with supportive care.

There is no specific antidote for SABRIL overdose. Supportive measures should be employed and standard measures to remove unabsorbed drug should be considered. In an in vitro study, activated charcoal did not significantly adsorb vigabatrin. The effectiveness of hemodialysis in the treatment of SABRIL overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of SABRIL, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

SABRIL® Tablets
(vigabatrin) 500 mg

DOSAGE AND ADMINISTRATION

SABRIL is intended for oral administration twice daily and is given orally with or without food.

The effective dose of SABRIL in adults is 3 g/day given in two divided doses using 500 mg tablets. The starting dose is 1 g given in two divided doses with titration in 500 mg increments at weekly intervals depending on response. Most patients will need 3 g/day for an optimal response and tolerance. Larger doses, up to 6 g/day, are associated with an increased incidence of side effects, and there is no evidence that such doses provide additional benefit.

Patients With Renal Function Impairment
SABRIL is eliminated via the kidney, and therefore, caution should be exercised when administering the drug to patients with decreased creatinine clearance. In moderately renally impaired patients (Cl_{cr}>30-50 mL/min), vigabatrin should be started with a lower dose. As clearance is known to decrease by two-fold in these patients, it is recommended that the starting dose be 500 mg qd and that the maintenance dose be 750 mg bid. In severely renally impaired patients (Cl_{cr} > 10-30 mL/min), vigabatrin should also be started with a lower dose. As clearance is known to decrease by 4.5-fold in these patients, it is recommended that the starting dose be 250 mg qd and maintenance be 750 mg qd.

General Dosing Considerations

It is not necessary to monitor SABRIL plasma concentrations to optimize therapy. If a decision is made to discontinue SABRIL, the dose should be gradually reduced over a 2– to 4–week period.

HOW SUPPLIED

SABRIL film–coated tablets containing 500 mg vigabatrin are supplied as follows:
- NDC 0088–0900–47: Bottles of 100 tablets
- NDC 0088–0900–55: Bottles of 500 tablets
- NDC 0088–0900–49: 100–ct UDIP®

Tablets are white, film–coated, oval, biconvex, scored, and debossed "SABRIL" on one side .

Store at Controlled Room Temperature, 20°C to 25°C (68°F to 77°F) and protect from light .

SABRIL® Tablets
(vigabatrin) 500 mg

Prescribing Information as of April 1997.

Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-427

Food and Drug Administration
Rockville MD 20857

Marion Merrell Dow Inc.
Attention: Gregory A. Hileman, Ph.D.
US Regulatory
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

APR 28 1995

Dear Dr. Hileman:

Please refer to your pending April 29, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Sabril® (vigabatrin) 500mg tablets.

We acknowledge receipt of your amendments dated:

05-05-95	05-23-94	06-06-94	06-08-94	06-10-94	06-14-94
06-20-94	06-27-94	07-11-94	07-19-94	07-26-94	08-03-94
08-04-94	08-09-94	08-29-94	09-21-94	09-22-94	10-07-94
10-18-94	10-27-94	11-09-94	11-10-94	01-16-95	01-17-95
01-25-95	02-01-95	02-08-95	02-09-95	02-10-95	02-15-95
02-22-95	02-23-95	02-27-95	03-02-95	03-03-95	03-06-95
03-08-95	03-14-95	03-24-95	03-27-95	03-22-95	03-23-95
03-31-95	04-14-95				

Reference is also made to an Agency letter dated January 31, 1995, requesting additional Chemistry and Manufacturing Control information.

We have completed our review of your application, and have determined that it is not approvable under section 505(d) of the Act. Our review reveals that there is insufficient information to determine whether Sabril® is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling [21 CFR 314.125(b)(4)]. We also cannot reach a final conclusion as to the effectiveness of Sabril®.

GENERAL COMMENTS

Deficiencies in the organization, analysis and content of the new drug application have made it impossible to adequately assess the safety and effectiveness of the drug. Some of these deficiencies may be remedied by further analysis on your part, but some may reflect an irreparable lack of critical data.

The deficiencies in the application can be considered to fall into 2 general categories: 1) Inadequate collection and availability of important safety information, and 2) Inadequate analysis and reporting of information collected relative to both effectiveness and safety. Because of these

deficiencies it has been impossible for us to rely upon your reports of the studies you have performed. In the remainder of this letter, we will enumerate specific problems that we have been able to identify in these 2 categories. Because the flaws in the application are so serious, however, we cannot be certain that we have identified all the relevant problems with the application or the drug itself.

Safety concerns are most critical, particularly given the long history of a concern with findings of intramyelinic edema in multiple animal species at doses close to those used clinically. Many of our concerns arise from the unavailability of the primary Case Report Forms (CRFs) for European patients in the CRF database. Without secure knowledge of results in at least a portion of the patients exposed to Sabril® in European trials, the available safety data base that can be fully assessed is the domestic data base of somewhat over 500 patients, not, we believe, an adequate-sized exposure. The unavailability of European CRFs is perplexing to us, given that the studies from which the data in the CRFs was generated were conducted by your European affiliate. Although regulations require that you submit with the initial application only those CRFs for patients who died or discontinued treatment due to adverse events, regulations also require (21 CFR 314.50(f)(3)) that a sponsor submit additional CRFs needed to conduct a proper review as requested by the Agency.

Access to these primary records for our review is particularly critical in this case, because in our review of CRFs that have been submitted we have discovered important data that have not been reported in study reports. Because of these findings (examples of which are detailed below), we cannot be confident that your study reports accurately reflect the data as collected. Without the ability to review these primary records, we are unable to confirm your conclusions about the safety of the drug that derive from studies for which CRFs are not available. Although we also detected similar serious discrepancies between the data recorded in CRFs and reported in study reports for the 2 domestic effectiveness trials (Studies 024 and 025), which contributed to our view that your study reports were potentially unreliable, because we did have access to the CRFs, we were able to re-analyze the studies using all the relevant data.

EFFECTIVENESS

You have submitted the results of two adequate and well-controlled clinical investigations that appear (but note reservations below) to provide evidence to support your claim that Sabril® is effective as adjunctive treatment for patients with partial seizures, with and without generalization. These trials do not provide evidence that doses of Sabril® greater than 3 grams/day provide any greater therapeutic benefit than that obtained at a maximum daily dose of 3 grams.

We were not able to conclude from the evidence submitted, however, that Sabril® is effective as a treatment for complex partial seizures that become generalized. As you know, you have submitted data on the effects of Sabril® on **all** partial seizures that generalize, but have not

submitted data for each individual type of partial seizure (complex partial seizures or simple partial seizures) that can generalize. As a result, we are unable to conclude that complex partial seizures that generalize, specifically, are successfully treated by Sabril®.

Our tentative positive interpretation of the evidence adduced in these two clinical trials has been possible only because of the extraordinary efforts of our medical and statistical review staff. Because their initial audit of the documents in the NDA file bearing on the efficacy of Sabril® revealed numerous troubling, and unexplained, discrepancies between the evidence presented in the summary reports you compiled and the evidence recorded in primary data sources (individual case reports and other primary records), our staff undertook a complete and independent analysis of the evidence using primary data for one of the two trials (Study 025). It is this analysis that persuades us that Study 025 is positive; given time and resource constraints, however, we have not yet conducted an independent audit of Study 024 records. If you intend to resubmit the NDA, you will need to carry out a similar audit/re-review of study 024. We believe it important to illustrate the kind of discrepancies that we found and why we consider them so disconcerting.

Our review of individual CRFs from Study 025, for example, detected a total of 32 patients who were inappropriate recipients of concomitant anti-epileptic treatment for inadequately controlled seizures **(an explicit protocol violation).** Your summary report identified only 24 patients with this protocol violation; a misclassification rate of 25% for so critical a factor unacceptable and difficult to explain if the process of data tabulation, transfer, and auditing that you employed in the construction of your NDA was reliable.

Another troubling finding of our review involved your attempts to quantify the number of seizures that occurred during those episodes originally described in the CRFs as "seizure flurries", "clusters", etc. As you have acknowledged, in these cases, the assignment of a specific number of seizures to these episodes were made by company monitors, on some occasions years after the trial was completed, based on discussions with the patients, families, and/or investigators. On a number of occasions, however, the number of seizures assigned were inconsistent with previously recorded data for a given patient (e.g., the number "4" was assigned as a score for a seizure flurry 1 1/2 years after the trial was completed for a patient whose mother had been able to record up to 11 seizures/day on other occasions.). Admittedly, your summaries described the "assignment" procedure in a generic way, but specific examples of the kind of data re-expression just cited are inconsistent with the generic depiction of the process and require further specific explanation. Your study report summaries, unfortunately, had no detailed discussion of these numerical assignments made retrospectively by the company monitor.

Our review of Study 025 case reports also led to the discovery of individual records in which seizure counts for subjects were not recorded during hospitalizations. This omission has the potential to introduce significant bias, yet it was not noted in your study reports.

In sum, although we are reasonably confident that the NDA provides evidence from more than a single controlled trial to support a claim that Sabril® is an effective treatment for partial complex seizures, the review that supports this judgment also shows serious and pervasive

deficiencies in the reports submitted to the NDA. These will have to be addressed in any resubmission of the NDA; specifically, a full re-review of study 024 will be needed.

SAFETY

The information provided in the NDA fails to show that Sabril® is safe for use.

While you have ostensibly provided safety data for a cohort of greater than 3000 patients who have received Sabril®, close inspection reveals that you have not adequately recorded and/or reported important information required to establish the safety and characterize the toxic potential of Sabril®.

Deficiencies in the safety data base can be characterized as falling into one of 2 types; 1) Inadequate collection of potentially important safety information, and 2) Inadequate reporting of adverse event data collected.

1) Inadequate collection of potentially important safety information

In order for the Agency to adequately assess the safety of Sabril®, and characterize the adverse events associated with its use, we must be able to review data from a sufficiently large cohort of patients followed forward in time prospectively. This cohort must be exposed to sufficiently high doses for an appropriate duration, all adverse event data must be collected contemporaneously with the conduct of the studies, and complete, or essentially complete, case ascertainment must be assured. Specifically, the status of all patients (i.e., whether or not they discontinued treatment) must be known at the time their contribution to the safety data base ends. For example, a given patient may contribute 6 months of exposure to the data base because he or she had received six months of treatment at the time of the cut-off date for data collection. In such a case, we can know with confidence the reason for such a patient not having contributed to the data base any data beyond 6 months (despite the fact that he or she might actually have continued on treatment). On the other hand, there must also be assurance that it was not an adverse event that led to discontinuation.

Your application contains data from 3 cohorts; 1)Domestic- we consider this cohort to consist of all patients who were treated with GVG in the United States (N=537), 2)CRF- this cohort consists of all patients who received GVG outside the US, and for whom data was recorded into the NDA database either directly from CRFs or from ICSs (N=1233), 3)ARF- this cohort consists of foreign patients for whom data was entered into the NDA database from secondary sources (N=1550).

We believe that the data from the Domestic cohort is complete and that there are prospective follow-up and disposition data on essentially all 537 patients. In contrast, we consider the ARF database as unreliable because the data in it have not been prospectively recorded and cannot, therefore, be considered to provide complete follow-up and disposition data on this cohort. It is the CRF data base that is critical to providing an adequate safety data base but whose status is

in question. It may be that these data can be made complete and reliable; at present, however, we cannot conclude they are.

For example, although you were very recently (April 14, 1995) able to provide a brief tabular summary of the nominal causes for discontinuations in the CRF database, the lack of primary case records makes it impossible for us to conduct an independent audit of this report. In light of the deficiencies identified in our review of your application, this presents a serious problem. Moreover, if the case reports forms are unavailable, we are perplexed as to the primary source of information used to construct the summary tabulations provided in your April 14th submission, especially in view of your repeated earlier assertions that the information provided was not available.

We are not disputing your belief that CRFs were appropriately designed to collect information on deaths and adverse events, nor your view that they would have captured these events, if they were used as intended. This, however, is irrelevant to the matter of how reliably information recorded on CRFs was transferred to ICSs, summary reports, and tables. This can only be evaluated objectively if we have access to the CRFs.

In sum, the reports provided in the application concerning the CRF database cannot be evaluated for accuracy and reliability because we do not have access to the CRFs.

In addition, you have acknowledged that information about hospitalizations (for any reason) was not systematically collected on the European CRFs. As you know, we regard hospitalizations due to adverse events as a signal of the severity of the event. Without an accurate accounting of the number of hospitalizations, we cannot adequately characterize the severity of any adverse events that may have resulted in hospitalization that might not have been recorded.

2) **Inadequate reporting of adverse event data collected**

As noted above, a detailed review of the CRFs you have submitted reveals many examples of inadequate reporting of data collected on the CRFs.

For example, in the study report for Study 006, a study performed in the US and designed specifically to monitor patients for evidence of ocular toxicity, you describe 12 patients with abnormalities and concluded that VGB had no important ocular toxicity. Review of all 45 CRFs, however, revealed 36 patients with abnormalities that may or may not have been related to treatment. Other examples of inadequate reporting include your assertion that no significant cardiovascular adverse events occurred. This statement cannot be independently confirmed because you have submitted none of the EKG data collected.

A problem that recurs in the application is the lack of complete, detailed, comprehensive reports of specific safety issues. For example, although you have collected a considerable amount of evoked response data, you have not provided a comprehensive summary report of the findings. Similarly, you have not commented upon potentially important findings seen in some of the

autopsy examinations, nor have you submitted an analysis and report of the cases of hepatic failure, even in the face of our explicit request to do so.

A particularly troublesome omission has been the absence of a single locatable report of the serious adverse events that have occurred in association with the use of VGB. Although reports of some serious events have been included in various sections of the application, we have been unable to find a single report that describes and discusses these events in a comprehensive manner. We acknowledge that there is a section titled Serious Adverse Events in the application, but this is, in reality, a list of hospitalizations (As discussed earlier in this letter, records of hospitalizations were not systematically kept, so that this categorization cannot be relied upon to include all serious adverse events that might have occurred).

Finally, once you have reliable data on all deaths that have occurred in association with treatment with Sabril®, it will be important for you to present data on Sudden Unexplained Deaths (SUDs) in the form of SUDs/per patient-years of exposure. In this way, we will be able to compare the incidence of these events with similar estimates for recently approved anti-epilepsy drugs.

In summary, the series of deficiencies described above have made it impossible for us to independently confirm or refute your conclusions that VGB is safe for the conditions of use proposed in your draft labeling. Although it is probable that data from the Domestic database may be re-analyzed and reported adequately, it appears that repairing the deficiencies in the CRF database may be more problematic, not only because you currently do not have access to them, but also because some important information may not have been collected. In the absence of reliable data from this cohort, even if the Domestic database can be repaired, the NDA would not contain data from a sufficiently large cohort to permit the conclusion that Sabril® is safe under the conditions of use.

We encourage you to pursue approval of this application; it appears probable that Sabril® will prove to be effective therapy of partial seizures. We also recommend that you consider submitting a Treatment protocol to your IND. The Treatment protocol would provide a mechanism for making the drug available to patients who could benefit from it, while serving the critical function of allowing you to accrue the patient experience necessary to establish the safety of Sabril®. The Division of Neuropharmacological Drug Products will be happy to discuss this option with you.

In addition, we have the following comments and requests for information that should be addressed:

BIOPHARMACEUTICS

1) While you have provided the results of a population based analysis of the interactions between Sabril® and other commonly administered AEDs, we suggest that you perform more formal interaction studies to examine the effects of Sabril® on plasma levels

of these drugs, as well as studies to examine the effects of these other drugs on Sabril® plasma levels.

2) We request that you study the effect of pH changes in urine and its influence on the urinary excretion of vigabatrin.

3) Please adopt the following dissolution methodology and specification for vigabatrin 500 mg film-coated tablet:

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

ENVIRONMENTAL ASSESSMENT

Please refer to an Agency letter dated January 31, 1995, providing for deficiencies in your environmental assessment. We requested that the exact address for the site of disposal of drug substance and drug product be included in the Freedom of Information (FOI) releasable environmental assessment document. The exact addresses for the backup locations for disposal at Dow Chemical in Plaquemine, Louisiana, and Freeport, Texas, are not given.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

Should you have any questions concerning this NDA, please contact Ms. Robin M. Pitts, Consumer Safety Officer, at (301) 594-2777.

Sincerely yours,

Robert Temple 4/28/95

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
NDA Orig.
HFD-120/DIV File
HFA-100
HFC-130/Allen\
HFD-5/THassall
HFD-80
HFD-100/RTemple
HFD-120/PLeber
/RKatz/CMcCormick
/Fitzgerald/BRosloff
/Blum/Guzewska
/RPitts
HFD 426/Baweja/Tammara
HFD 713/Nevius/Taneja
draft:March 20, 1995
draft2:April 10, 1995
draft/ with revision/leber/4/13/95
draft/with spellcheck/pitts/4/13/95
M:/dos/wpfiles/sabril/gvgna6.ltr
Not Approvable