

ATTACHMENT 5

PROTOCOL VIOLATIONS INVOLVING SEIZURE COUNTS EITHER INACCURATE OR CHANGED

STUDY C025

Patient ID	Period	Date	Comments
069-002			Pt had 12 different episodes of "clusters" that pt's mother could not count. Each episode was marked with "Z". On 11/25/92 (1 1/2 yrs later) the entry was corrected and "4" was entered for each cluster, even though mother was able to count up to as many as 11 sz. on a given day without difficulty.
013002		3/22/91	On 3/22/91 Pt recorded "2" as # of sz. On 11/30/92 this entry was changed to 18.
069003*		10/3/91 - 10/16/91	"W" recorded for sz count Comment: "no sz calendars available - therefore data are missing."
	S2V2	9/19 - 10/2/92	Comment "pt did not maintain constant doses of AED's - reason unknown"
		7/25 - 8/21/91	"Previous coordinator marked through seizures in workbook there is no documentation of sz. calendar. Therefore, data is entered as missing."
	S2V1	10/17 - 10/30	No sz record available
		10/31 - 11/13	Sz record not available.
		11/14 - 11/25	Sz record not available.

*(CANDA has 1c baseline 4.7, 1c final 14 where did these #'s come from?)
PT d/c due to ? # of sz.
Hospitalized in

Continued

Patient ID	Period	Date	Comments
069-002		3/4/91	"Z" recorded on 6/25/92 this was changed to "4"
073003		8/13/91 - 9/16/93	7 sz recorded IB; on this changed to 11
011107			
070010		11/16/91, 12/2/91, 12/3/91, 2/18/92	No sz recorded for 11/6/91, 12/2/91 or 12/3/91... Pt unable to find diary page for 12/4/91 to 12/28/91 but status that her sz pattern was similar to those submitted. No seizures reported for 2/18/92 Not (Pt given "0" for number of sz.)
011107		6/23/91	Sz recorded as 1; changed to 2 on 9/16/93
011107		7/2/91	No record - "0" added on 9/16/93
011107		8/31/91	3 sz recorded; changed to 1 on 9/16/93
011107		10/26/91	No entry on 9/16/93 an entry was added including Z sz
071007	slv1	5/10/91 - 6/5/91	Pt was to bring sz calendar in but never did. Due to flurry of sz and more severe sz on [redacted] Pt was admitted to hospital for 24 hr monitor.
073-903		12/16 -12/31	"W" given for # of sz. Comment: "Sz calendar was not received for December 16-31, 1991.
011-106		12/5 - 12/27	Pt did not provide diary form 12/5 to 12/27, no data available (end taper)
092-009		6/26/91	Pt had "Z" recorded for # of sz on 6/26/91. On 12/12/92 this was ? to 30, Comment "6/29/91 - pt describes 1AZ seizures as a cluster form 4pm to 7:30pm.
011102		7/2/91	Pt recorded 7 IB sz changed to 5 on 9/16/93.
011102		7/3/91	Pt recorded 8 IB sz, changed to 7 on 9/16/93.
010111	visit slv1		"Pt reports that mother has been working many hours and she may have had more {seizures}, but was unaware of them.
011-104	visit slv1s2	5/7/91	Patient recorded 1 sz (1B2C) and on 9/16/93 the number of sz was changed to 3

b(6)

011-104	visit S1V1S2	7/19/91	Sz type recorded as 3 IC and on 9/16/93 it was changed to IB2C.
011107	6/15/91	S1V1S2	No sz recorded for this day on 9/16/93 3IA sz, 1 IB IB sz, and 1 IC sz were recorded.
073008	12/31/91	S3V1S4	Pt recorded IC one sz on 9/16/93 this was changed to O.
071002		S2V1S1	"Pt verbally gave data. No hard copy diary available.
071002	8/17/91	S3V1S3	Pt recorded one IC sz. Changed to IB1C later on 9/16/93.
072002	6/5/91 - 6/17/91	S2V1S1	"Pt is unaware of his seizures and he was alone most of the time since last visit therefore we have no sz record for this visit.
071-011	2/18/92 - 2/29/92	S3V1S3	Pt lost seizure calendar for 2/18/92 thru 2/29/92.
071-012	11/92	S1V1S2	No sz calendar returned by pt.
097025		S1V1S1	Pt lives in a group home and seizure counts may not be accurate since seizures occur at night and he sleeps in a room by himself.
071004	4/2/91	S1V1S2	0 seizures recorded by pt. On 9/16/93 changed to one (1) IB1C seizures.
071004	5/1/91	S1V1S1	0 seizures recorded by pt but on 9/16/93 changed to 1B2C, one (1) seizures.
071004		S3V1S2	1B2C "W" recorded each day. Comment: Pt in status epilepticus from 8/16 to 8/23/91. Pt hospitalized from 8/17 to 8/24/91. (Aside: Therefore the seizures assoc. with status were not counted?)
071004	8/24 - 9/2/91	S3V1S3	"W" recorded in lieu of seizure counts. Comment: Diary not provided by pt.
074901	8/18/91	S1V1S1	Pt recorded "Z" later (11/25/92) changed to 12.
074901	8/19/91	S1V1S1	Pt recorded "Z" later (11/25/92) changed to 12.
074901	8/20/91	S1V1S1	Pt recorded "Z" later (11/25/92) changed to 12.
074901	9/13/91	S1V1S2	Pt recorded "Z" for number of seizures, later (11/25/92) changed to 12. Comment: pt able to count as many as 30 seizures/day)

074901	9/29/91	S1V1S2	Pt recorded "Z" for number of seizures, later, 11/25/92, changed to 12. Comment: pt had clusters of seizures which lasted all day.
012109	9/12/91	S2V2S1	Pt states having flurry on 9/12/91 at 12 am for many hours. According to [redacted] pt not sure if that was actually a sz or not. Was in vague confused state all night. Pt did not have one definite CPS on 9/12/91.
012901		S1V1S3	Pt recorded seizures as "Z" later (11/25/92) changed to 6
011118	1/30/92	S1V1S1	Pt had a prolonged period without seizures which does occasionally happen to him, prior to his cluster. Had approx. 4 CPS and 21 SPS (will bring in calendars to us - forgot to bring them today). SPS unsure - had visual hallucination. (Aside - no calendars appear to have been brought in since no seizure counts correspond to these numbers for IA & IB sz types during this period).
093007	5/13/92	S3V4	Pt had 4 sz during RAVL (REX auditory) test. Gave alternative version... only 3 sz were recorded on 1/30/92.
011120		S1V1S3	Took a total of 3m Ativan for seizure flurry with good response. [ASIDE 2 SPS and 2 CPS recorded; similar to previous days. No cluster of sz recorded].
012106	9/19/91	S3V1S1	Pt states may be forgetting to record some seizures.
012-001	9/15/91	S3V1S1	Pt recorded "Z" number of seizures; changed on 1/30/92 to 4.
	6/13/91	S1V1S3	"
	7/2/91	S2V1S1	Pt recorded "Z" for number of seizures, changed to 10 on 11/25/92. "AURAS throughout the day - this was a flurry.
	7/3/91	S2V1S1	Pt recorded "Z" for number of seizures, changed to "10" on 11/25/92.
	7/15/91	S2V1S1	Pt recorded "Z" for number of seizures, changed to "10" on 11/25/92.
	7/17/91	S2V1S2	Pt recorded "Z" IA4 seizures. No number assigned. Pt recorded "Z" IA4 seizures. No number assigned.

	7/18/91	S2Vis2	Pt recorded "Z" 1A4 seizures. No number assigned.
	8/5/91	S2Vis3	Pt recorded "Z" 1A4 seizures. Changed to 10 on 11/25/92
	9/4/91	S3Vis3	Pt recorded "Z" 1A4 seizures. Changed to 10 on 11/25/92.
012108	10/23/91	S2Vis1	Pt complains of HA after seizure cluster. No clusters recorded - only 2 sz.
013003	5/2/91	S1Vis2	The number of corrections made in the daily seizure calendar up to 5/2 are due to the fact that the patient's descriptions were initially misread. The current record accurately reflects seizures types and counts.
	S1Vis1	12/8/91	"Z" recorded for SPS, later (11/30/92) changed to "18".
006111	S3Vis3	4/30/92	"Z" recorded for SPS later (11/30/92) to "18".
010102	S1Vis3	5/13/91	Pt hospitalized for severe 2 sz and received valium 5 mg IV. ? 1 generalized sz. recorded that day.
069002	S1Vis3	3/4/91	Pt recorded "Z" for seizures (PCS with 2° generalization) on this day. Changed to "4" on 11/25/92.
011111	S1Vis1	7/19 to 9/12	"4" (PCS with 2° generalization) recorded for each day.
			"1" IC sz. (?)
		9/13 to 10/10/91	"11" (1B2C) recorded for each day or 1 "(IC) occas. " Mom says averages "10-12" staring spells a day."
		10/11 - 10/24	13 alternating with 14 (1B2C) every other day. Comment: "Mother estimates 12-15 staring spells/day."
		10/25 to 11/7	"7" 1B2C recorded on each day.
	S2Vis3	11/8 to 11/21/91	"5" alternating with "6" (1B2C) recorded on each day.
	S3Vis1	11/22 to 12/?	"3" alternating with "4" seizures recorded for each day.
	S3Vis3	12/20 to 1/16	"6" alt with "8" 1B2C seizures daily.
005101	S3Vis3	3/13/91	No sz recorded by pt. on 9/13/93 changed to 1 1B2B type sz.

006-104	3/20/91	S1Vis1	Pt did not record sz type only number one (1). Comment: Will have pt and mother keep better track of types of sz as well as number. Missing data is due to poor record keeping by pts mother.
	5/16/91 - 5/21/91	S1Vis3	"W" recorded for sz type and number. Pt in hospital - seizure record not kept.
	5/22/91		"W" was recorded for 1A type seizures. Changed to "20" on 9/16/93
	5/24/91	S2Vis1	Pt recorded "w" for PCS? later changed to 15 on 9/16/93. Comment: "unknown number of seizures for 5/24. Pt had one spell after another from 5/24 - 6:00am.
006105	8/19/91	S3Vis4	pt recorded one (1) PCS with 2° generalization seizure on this day. Changed to "7" on 9/16/93.
006106	5/9/91	S1Vis2	Comment: Missing data = a lot Pt had so many hard sz that she couldn't keep track of them. "W" recorded for PCS that day (what number was assigned.)
006-108	8/15/91	S1Vis1	Comment: Pt was home alone having complex partials and has no recollection. Estimated by amount of damage done to the house." 5 seizures recorded and called IB2A.
	10/26/91	S2Vis11	Comment: "several brief sz followed by disorientation, followed by more sz." Initially, number of sz not recorded. Changed on 1/25/92 to 1B2A.

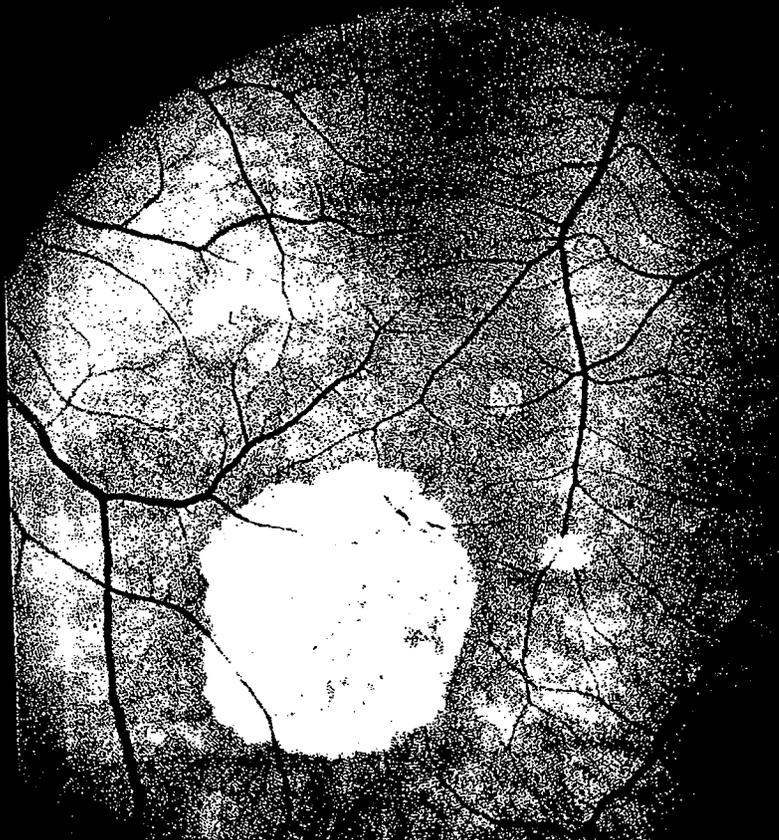
Attachment 5

Pt. 5-015
Left Eye 7/27/89

2001 270 112 1102

Appendix II

Appendix III



Pt. 5-015
Left Eye 7/27/89



Appendix II

Appendix III

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

DATE: April 13, 1995

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

SUBJECT: Disapproval of NDA 20-427, Sabril

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

This memorandum conveys my formal endorsement of the review team's recommendation that Marion Merrell Dow's NDA 20-427 for Sabril be disapproved because it fails to provide sufficient evidence to support a conclusion that Sabril will be safe for use under the conditions of use recommended in its proposed labeling.

My endorsement of a not approvable action is made with a clear understanding that results of two adequate and well controlled clinical investigations provide compelling evidence of Sabril's efficacy as an adjunctive treatment for the management of partial seizures that generalize and knowledge that Sabril is currently marketed as a treatment for epilepsy in 40 or so countries, among them virtually every major western democracy.

I am mindful, accordingly, that some may be perplexed by our recommendation. What could possibly explain the difference between FDA's views and those of other regulatory agencies? I cannot, of course, speak to arguments and evidence I have not reviewed, but I suspect the answer may lie in what is accepted as bona fide evidence.

Taken on face, the Sabril NDA provides safety related reports and summaries purporting to represent experience gained with more than 3000 Sabril treated patients. These reports and summaries give no indication that Sabril is causing and/or is associated with any intolerable level of serious side effects or risks; to the contrary, the reports, on face, reasonably allow a conclusion that Sabril is safe for use.

Unfortunately, these reports cannot be relied upon as either an accurate or complete depiction of actual clinical experience. We know this only because of Dr. McCormick's careful and painstaking comparison among line listings for individual patients (or other secondary data reports), group data summaries, and primary case report forms (i.e., those that were available¹). Dr. McCormick detected an unacceptably high incidence of errors, inconsistencies and misrepresentations. Although her audit did not identify any serious new risks, it was sufficient to convince her, and other members of the review team, that the sponsor's procedures for data collection, tabulation, transfer and recording were unreliable. Accordingly, both Dr. Katz and I concluded that it would be imprudent, even reckless, to rely on reports of 'safe passage' for any patient for whom a primary clinical report could not be provided.

Given this restriction, the evidence for Sabril's safety is meager from a quantitative prospective, arising from perhaps 500 or so patients. Indeed, this difference in perspective about the amount and quality of evidence available is all that is needed to explain the differences between our views and those of other national drug regulatory agencies.

It bears emphasis, nonetheless, that our averse conclusions about the safety of Sabril turns not on clinical findings that show it to be unsafe, but on the failure of the firm to provide reliable and verifiable reports from a sufficiently large number of patients either to 1) set reasonable upper limits on risks not seen, or 2) to provide accurate estimates of the incidence of serious risks (e.g., sudden deaths), that have been associated with the use of the drug.

In considering the need to collect sufficient clinical experience to reduce the upper limit on the incidence of risks not seen, it is important to recall that the sponsor has failed, despite the lapse of more than a decade, to obtain enough samples of human brain white matter to assess meaningfully the risk of Sabril causing intramyelinic edema (IME) in humans. Development of the drug was delayed for years because of this concern, one that cannot easily be dismissed because it was found in 4 different animal species. Accordingly, division staff consider it especially critical that only adequately monitored patients be included in the set deemed to represent Sabril exposures.

¹ As Dr. Katz explains in his 3/31/95 memorandum, the firm was unable to provide copies of primary case report forms for a majority of non-domestic patients included in the safety data base.

On the other hand, it is critical to acknowledge that there is an important distinction to be drawn between lack of evidence to show safety and affirmative evidence to show that a drug is unsafe. This distinction is critical to our recommendation that the sponsor be encouraged to submit a treatment IND (vide infra). It is only because we believe the case for the drug's safety can eventually be made that we encourage this option. If we thought there was positive evidence of danger, this option would be problematic from an ethical perspective.

As to a treatment IND, it seems one way to deal, at least in part, with a difficult situation that is hardly the fault of the patients with epilepsy who desire access to this effective drug. A treatment IND will make this drug available to patients who are in need of it, and, will provide the sponsor, spontaneously, with a source from which prospectively ascertained safety experience can be gained. Of course, the firm may elect not to open a treatment protocol, but that is a matter beyond our control.

Recommendation:

Issue the attached not approvable action letter.

A handwritten signature in black ink, appearing to be 'Paul Leber', written over a horizontal dashed line.

Paul Leber, M.D.
April 13, 1995

cc: NDA 20-427

HFD-100

Temple

HFD-120

Katz

McCormick

Feeney

Fitzgerald

Rosloff

Blum

Guzewska

Pitts

HFD-710

 Nevius

 Taneja

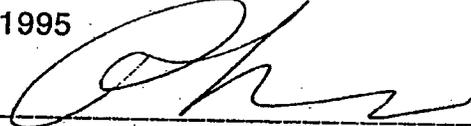
HFD-426

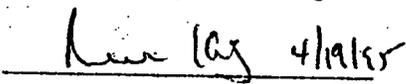
 Baweja

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MEMORANDUM

DATE: April 19, 1995

FROM: Director  4/19/95
Division of Neuropharmacological Drug Products/HFD-120

Deputy Director  4/19/95
Division of Neuropharmacological Drug Products/HFD-120

TO: Director
Office of Drug Evaluation I

SUBJECT: Additional Submission to NDA 20-427

In the course of several phone conversations between Marion Merrell Dow and members of the Division, the sponsor was made aware of our concerns regarding deficiencies in the recording and reporting of important safety information in NDA 20-427, Sabril for the treatment of seizures. One important question concerned the absence of complete accounting of all dropouts (both total number and causes for termination) in the so-called CRF database.

In a fax sent on 4/14/95, the sponsor now contends that they have a complete accounting of the total number of dropouts (as well as the causes for these terminations) for, essentially, this entire cohort. Dr. McCormick has reviewed this submission, and her review is attached.

She concludes, and we agree, that this submission does not adequately address all the concerns we raised in our earlier reviews, and that are described in the proposed Not Approvable letter we have previously forwarded to you. In essence, the line listings submitted by the sponsor cannot adequately address our concerns regarding the accuracy and reliability with which the information has been transcribed from primary sources, nor can it address concerns about the lack of collection of other important safety information. Indeed, we are not sure exactly which documents the sponsor inspected to generate the data in the current submission (they state that they reviewed the individual study databases,

without an explanation as to exactly what these are).

CONCLUSIONS AND RECOMMENDATIONS

While the submission of 4/14/95 adds information that we had requested (the number and cause for essentially all dropouts in the CRF database), it does not address other questions about the reliability of data recording and reporting, nor does it address questions about important information that may not have been recorded. For these reasons, we continue to recommend that the Agency issue a Not Approvable letter.

cc:

NDA 20-427

HFD-120

HFD-120/Katz/Leber/McCormick/Pitts

rk 4/19/95

MEMORANDUM

DATE: March 31, 1995

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

TO: File, NDA 20-427, Sabril

SUBJECT: Supervisory Review of NDA 20-427, Sabril for Adjunctive Treatment of Patients with Refractory Partial Seizures

BACKGROUND

NDA 20-427, for the Use of Sabril as adjunctive treatment for patients with refractory partial seizures, was submitted by Marion Merrel Dow on April 29, 1994. The complete NDA was reviewed by Dr. Cynthia McCormick, Medical Officer, and the definitive effectiveness trials were also reviewed by Dr. Baldeo Taneja of the Division of Biometrics. In this memo I will briefly review the relevant effectiveness trials, as well as describe in some detail what I believe to be flaws in the collection and reporting of the safety data of sufficient severity to preclude approval of the NDA at this time.

Initially, though, it seems important to provide a summary of the regulatory history of the development of this product.

REGULATORY HISTORY

The IND for Sabril was submitted on February 15, 1980. Chemically known as gamma vinyl Gamma amino butyric acid (Gamma vinyl GABA, or GVG), it is an irreversible inhibitor of GABA-transaminase, the enzyme responsible for the metabolism of GABA, the most important inhibitory neurotransmitter in the CNS. As a consequence of this pharmacological property, and the resulting elevation of CNS GABA levels, it appeared promising as a treatment for any number of conditions characterized by

neuronal hyperactivity, including, for example, Huntington's Disease, tardive dyskinesia, and epilepsy. The initial submission, however, documented the occurrence of intra-myelinic edema in a 3 month rat study, at the highest dose, and in the cerebellum only. The IND was permitted to proceed, but the sponsor was urged to further evaluate the lesion.

Several protocols had been submitted and were proceeding as of February, 1983, when we were informed by the sponsor that the intra-myelinic edema, previously seen in one species at the high dose, was now seen in 3 species (rat, mouse, and dog) at doses overlapping with the clinical dose, and in many other areas of the brain in addition to the cerebellum. After the Division's review of the studies, the sponsor was informed on April 7, 1983, that no new patients were to be enrolled in any on-going trials, but that patients currently enrolled and judged to have been receiving benefit (approximately 50 with refractory epilepsy at the time) could continue to receive drug. All new trials were placed on Hold, and the issue was discussed at a meeting of the PCNS Advisory Committee on May 18, 1984.

At this meeting, the Committee recommended that adequate and well-controlled trials should be permitted, in an effort to establish the utility of the treatment as rapidly as possible. Further, they recommended that additional animal work to further characterize the lesion, and, importantly, to validate a method to monitor the onset, progress, and potential reversibility of the lesion be conducted simultaneously with the clinical trials.

Subsequent to this meeting, the sponsor submitted protocols for definitive effectiveness trials, but these submissions essentially coincided with the completion of a 1 year monkey toxicity study. Because this study demonstrated the occurrence of the same lesion in the high dose monkey group, as well as evidence of irreversible neuronal injury, the issue was presented again to the PCNS Advisory Committee at a meeting held on October 18, 1985.

At this meeting, the Committee recommended that no new patients be

permitted to receive GVG until an adequate non-invasive method of monitoring for the lesion be developed and validated in an animal model. In particular, serial evoked potential and MRI monitoring in dogs, linked temporally to histologic verification of lesion onset and regression, was recommended to be performed.

A third meeting of the PCNS Advisory Committee was held on November 20, 1989, at which the results of evoked potential monitoring in the dog were presented, as were additional human data that was continuing to accrue in European trials. The Committee was convinced, based on the dog data, that evoked potential monitoring could be relied upon to detect the onset, and follow the course, of the lesion, should it occur, in humans, and that, coupled with the additional human data, adequately designed clinical trials could be permitted to proceed. As a result, the IND was taken off hold, and subsequent clinical trials employed evoked response monitoring. There have been no additional problems identified, and trials have continued without interruption.

EFFECTIVENESS

The sponsor has submitted the results of 2 controlled trials in patients with refractory partial epilepsy conducted in the United States. In addition, they have presented 13 small, often uncontrolled trials performed in Europe that presumably support the conclusion that Sabril is effective in this population. Because of the size and design of these trials, they have not been reviewed in detail by either Drs. McCormick or Taneja. I, too, will not discuss them any further, since they contribute no useful information beyond that contained in the 2 domestic trials.

STUDY 024

This was a multi-center, double blind, placebo controlled, parallel group, add-on trial comparing the effects of GVG 3 gms/day to placebo, in patients with refractory complex partial epilepsy being treated with one or two available AEDs. The study consisted of 3 Segments; Segment I was a prospective 12 week evaluation period, the last 8 weeks of which were considered the baseline period, and after which randomization occurred; Segment II represented a 4 week titration period in which patients were to be titrated from 1.0 g/day to 3.0 g/day, in weekly increments of 0.5 g/day; Segment III, which was a 12 week maintenance, the last 8 weeks of which were considered the maintenance phase. Seizure counts were collected in patient diaries. The primary outcome measure was designated to be the frequency of all complex partial plus all partial onset generalized seizures. Simple partial seizures that did **not** generalize were not included. Other, secondary measures, included 50% Reduction in the 2 seizure types, individual frequencies of simple partial, complex partial, and partial seizures that generalized, frequency of seizure free days, and various global evaluations.

RESULTS

Fifteen (15) centers entered a total of 203 patients into Segment I. Of this 203, 183 were randomized to treatment (90 placebo, 93 GVG). One GVG patient withdrew prior to receiving treatment.

PRIMARY OUTCOME MEASURE

Of the 182 patients receiving treatment, 170 completed the entire trial. Of the 12 who discontinued, 8 GVG and 2 placebo patients discontinued due to adverse events. The following table describes the baseline and final median data for the combined seizure types of interest for the Intent-to-Treat data set:

MEDIAN MONTHLY SEIZURE FREQUENCY

	<u>N</u>	<u>Baseline</u>	<u>Final</u>
Placebo	90	8.3	7.5
GVG	92	8.3	5.3

Various analyses of rank-transformed and untransformed frequency yielded p-values of between 0.001 and 0.0002 for the drug-placebo comparison.

SECONDARY OUTCOME MEASURES

The following Table describes the proportion of patients achieving a 50% or greater reduction in frequency of the combined seizure types (Therapeutic Success):

PROPORTION OF PATIENTS ACHIEVING THERAPEUTIC SUCCESS

	<u>N</u>	<u>% With 50% Reduction (N)</u>
Placebo	90	19% (17)
GVG	92	43% (40)

The p-value associated with this difference is <0.001.

(Results presented for the following Secondary Measures are those of the sponsor, and have not been independently confirmed by Dr. Taneja).

The following Table describes the effect of GVG on the Frequency of Complex Partial Seizures Alone (patients were included in this intent-to-treat cohort who had this seizure type at baseline) :

MEDIAN MONTHLY SEIZURE FREQUENCY (COMPLEX PARTIAL SZS)

	<u>N</u>	<u>Baseline</u>	<u>Endstudy</u>
Placebo	89	8.0	7.0
GVG	84	8.5	5.0

The drug-placebo difference was highly significant, with $p < 0.0006$.

While there was a numerical difference in the Median Monthly Frequency of Partial Seizures with Secondary Generalization (Decrease of 1.5 on GVG vs 0 on Placebo), this difference did not reach statistical significance. There were insufficient patients with Simple Partial Seizures Alone to perform an analysis.

The following Table describes the changes seen in the number of Seizure-Free Days per Month:

MEAN MONTHLY FREQUENCY OF SEIZURE-FREE DAYS

	<u>N</u>	<u>Baseline</u>	<u>Endstudy</u>
Placebo	90	18.4	19.1
GVG	92	18.6	20.8

This difference was significant, with $p = 0.0024$.

STUDY 025

This was a multi-center, randomized, double-blind, add-on, placebo controlled, parallel group, fixed dose ranging trial comparing the effects of 1, 3, and 6 gms of GVG and placebo. It was similar to Study 024 in most aspects, including patient population, general outline, and outcome measures. Segment II in this study, however, represented a 6 week titration in which patients were randomized to receive placebo, 1 gm GVG throughout, 3 gms GVG (reached by Week 3), or 6 gms GVG (reached by Week 5).

RESULTS

A total of 203 patients entered Segment I. A total of 174 patients were randomized to drug in Segment II (45 Placebo, 45 1 gm, 43, 3 gm, and 41, 6 gm), and a total of 149 patients (42 Placebo, 40, 1 gm, 36, 3 gm, and 31, 6 gm) completed the trial. There was a dose dependent increase in the number of dropouts due to ADRs.

The primary analysis was performed on the Intent-to-treat population. The following Table displays the results on the primary outcome measure, which represents the combination of complex partial seizures and all partial seizures that secondarily generalized:

MEDIAN MONTHLY FREQUENCY OF SEIZURES

	<u>N</u>	<u>Baseline</u>	<u>Endstudy</u>
PLACEBO	45	9.0	8.8
1 GM	45	8.5	7.7
3GM	43	8.0	3.7
6 GM	41	9.0	4.5

The results of a linear trend test across doses were highly statistically significant, with $p=0.0001$. While 1 gm was not statistically significantly different from placebo, both 3 and 6 gms were, with $p=0.0001$ for each comparison. The difference between the effects of 3 and 6 gms were not significant, with $p=0.81$.

SECONDARY MEASURES

The following Table displays the results by dose for the variable Therapeutic Success (again, defined as the proportion of patients with a 50% or greater decrease in frequency compared to baseline):

PROPORTION OF PATIENTS WITH THERAPEUTIC SUCCESS

<u>PLACEBO (N)</u>	<u>1 GM (N)</u>	<u>3 GM (N)</u>	<u>6 GM (N)</u>
7% (3/45)	24% (11/45)	51% (22/43)	54% (22/41)

Again, a linear trend test was highly significant, with $p<0.0001$. All comparisons between individual doses and placebo were significant ($p=0.02$, <0.0001 , and <0.001 for 1, 3, and 6 Gm respectively), and no difference was detected between 3 and 6 Gm ($p=0.97$).

(The following analyses of other secondary outcome measures have not been independently confirmed by the Division of Biometrics).

The following Table presents the results of analyses of the effect of GVG on Complex Partial Seizures:

MEDIAN MONTHLY FREQUENCY OF COMPLEX-PARTIAL SEIZURES

	<u>N</u>	<u>Baseline</u>	<u>Endstudy</u>
Placebo	44	8.8	8.3
1 GM	45	7.5	7.0
3 GM	43	7.0	3.5
6 GM	39	8.5	3.5

According to the sponsor's analysis, a linear trend test was highly significant ($p < 0.0001$). Individual comparisons of 3 and 6 Gm with placebo were both significant ($p = 0.001$, and 0.0001 , respectively).

Analyses of the effect of GVG on the treatment of simple partial seizures only in the subset of patients who had simple partial seizures at baseline yielded no statistically significant comparisons (Total $N = 73$). Similarly, analyses of all partial seizures that secondarily generalized did not detect significant differences (total $N = 53$).

According to the sponsor, there also was a highly significant dose trend ($p = 0.0001$) for the variable Seizure-Free Days, although the actual results are unavailable to me at this time.

The sponsor has proposed that the drug be indicated for complex partial seizures with and without generalization. Since the data were not presented for this particular seizure type specifically (all partial seizures that generalized was the categorization presented by the sponsor), we asked the firm to analyze this specific seizure type. They responded that they could not perform this analysis, since the data were collected as all partial seizures, not broken down into simple and complex partial seizures. Presumably, this primary data could be retrieved from the patient diaries, but this was not done. For this reason, we cannot perform this analysis for either study 024 or 025.

Analyses of both controlled trials demonstrates that levels of concomitant AEDs are not systematically increased (indeed, they may be decreased, particularly levels of phenytoin) in patients on GVG compared to patients treated with placebo. For this reason, effects on seizure frequency are not considered to be due to pharmacokinetic interactions with other AEDs.

In each study, the protocol stated that certain patients would be excluded from the primary analysis. Specifically, patients who experienced a 2-fold or greater increase in seizures while on treatment, or who developed status epilepticus would be excluded. This was not done. We asked the

sponsor to perform this analysis, and in addition to exclude data from patients who required treatment with additional AEDs (in the spirit of the philosophy of the protocol, which was to exclude patients with seizure worsening), as well as patients for whom seizure counts could not be recorded for a given episode (flurry, cluster), and for whom the sponsor assigned a seizure count. For purposes of this re-analysis, patients were considered to have withdrawn at the time of their event, and their subsequent data was not utilized. In addition, they were considered failures for the analysis of Therapeutic Success.

In this re-analysis, data from 8 patients in Study 024 and data from 35 patients in Study 025 were excluded. There were no substantive changes in any of the analyses of the primary outcome measure or Therapeutic Success.

SAFETY

Although the NDA ostensibly contains reports of a sufficient number of patients (upwards of 3000) on which to base an adequate decision about the safety of the product, a detailed review has revealed that there are deficiencies in two critical areas: 1) Primary documentation of exposure and adverse event occurrence, and 2) accurate transcription and reporting of adverse event data from primary sources. In the following section, I will detail what I believe to be serious inadequacies in the safety section as submitted. These inadequacies, in my view, make it impossible to assess the safety of GVG according to the usual standards for an NDA for a new chemical entity. Accordingly, I have not reviewed any specific safety concerns raised by the data, incidences of ADRs, etc. (although Dr. McCormick, in her review, has made a heroic effort to do so).

ISSUES RELATED TO EXPOSURE AND INADEQUATE DOCUMENTATION OF ADVERSE EVENTS

A total of approximately 3320 patients exposed to vigabatrin in a non-post marketing setting are reported on in the NDA. This represents domestic and European experience. A total of 443 patients with epilepsy and 94 patients with other diagnoses have received vigabatrin in the US, for a total of 537 domestic patients contributing data to the safety data base.

The remaining 2783 patients have been divided into 2 separate cohorts by the sponsor. These are the CRF cohort and the ARF cohort.

The CRF (Case Report Form) cohort consists of 1233 patients who received vigabatrin in various controlled and open studies in Europe. According to the sponsor (based on a telephone conversation of 3/14/95) essentially all patients in this cohort had adverse reaction data recorded contemporaneously on Case Report Forms. For 594/1233 (48%) of these patients, data from the CRFs was directly keyed into the sponsor's NDA database by MMD's European affiliate, and this data is the data presented in the NDA. For the remaining 639/1233 (52%), data from the CRFs was first transcribed onto a shorter form, called the Individual Case Study (ICS) Form, from which the data were then keyed into the NDA database. For this cohort, the data from the ICS represents the data presented in the NDA. According to the sponsor, the ICS, a relatively short form, was primarily designed to abstract Adverse Event data from the CRF, and was filled out for an individual patient when the sponsor felt that the original CRF did not contain sufficient data. In order to adequately fill out the ICS, information on the CRF was supplemented with adverse event data from original patient records, study reports, summaries, manuscripts, etc. In this same telephone conversation, the sponsor acknowledged that they did not have the original CRFs for any of this cohort of 1233, and that some percentage of them presumably might be available, but could offer no estimate of how many could be retrievable.

According to the sponsor, after the ICSs were created from the CRFs, they

(the ICSs) were shown to the investigator for his/her concurrence and signature. Also according to the sponsor, these ICSs could have been completed up to several years after the patient's participation in the study.

According to the sponsor, the CRFs from the European studies (both those from which data were directly entered into the NDA database and those transcribed onto the ICSs) were designed primarily to record Adverse Events, but important information ordinarily included in current CRFs was not necessarily captured. This was also presumably true for the data in the ICSs, despite the fact that these were supplemented with additional patient data. For example, by the sponsor's admission, whether or not patients were hospitalized as a result of an adverse event (or for any other reason) was not systematically or reliably recorded on the European CRFs.

The second data base, the ARF (Abbreviated Report Form) database, consists of data from the remaining 1550 patients. While the sponsor asserts that some proportion of these patients also had contemporaneous CRFs filled out, the data in the NDA database for this cohort was collected from sources **other than** the CRFs. That is, the data included in the NDA for this cohort was collected from study reports, published articles, and other secondary sources, not from primary data collected at the time of the patients' exposure to drug. As with the CRF database, original data, when it exists, is not available to the sponsor, and certainly not to us.

With regard to the ARF database, due to the nature of the collection and reporting of events, and the unavailability of primary data sources, we have no assurance that all events of interest have been reliably captured and reported, nor does the sponsor. For these reasons, we cannot accept data from this database as contributing to the safety data base.

Given the unreliability of the ARF database, any attempt to assess the toxicity profile of GVG must focus on data from the remaining 2 cohorts, the US domestic experience, and the CRF database. If data from both cohorts can be considered reliable, this would yield a combined safety

database of 1770, ordinarily a number of exposures quite sufficient on which to assess the safety of the drug. However, if the US cohort of 537 is the only cohort in the NDA for which reliable safety data is available, we would not be able to adequately assess the safety profile of the drug.

With regard to the US experience in 537 patients, we have confidence that all relevant safety information has been recorded and is available for our review. However, we have serious reservations about the presentation of this data, on which more later.

Whether or not the NDA can even be considered Approvable, then, depends on the assessment of the reliability of the data contained in the CRF cohort.

It has been extraordinarily challenging to figure out how the data in this cohort was collected, recorded, and presented. Our current view is based both on the submission itself, as well as multiple telephone conversations with the sponsor. On many occasions, the sponsor has acknowledged the shortcomings in this database, and has not been able to give completely satisfying answers to a number of questions.

Problems in the database are first encountered when examining dose and duration of exposure data. While the sponsor has presented tables of dose information, duration of exposure information, and dose and duration of exposure information combined, they have done so for the entire database of 3320. In these presentations, they have acknowledged that they do not have combined dose and duration data for approximately half of this cohort, **but we do not know to which patients the known dose and duration data apply.** Consequently, it is impossible to tell which, and what proportion, of the 1233 patients in the CRF database have reliable dose and duration of exposure data, so that we cannot say with certainty with what dose, and for how long, this cohort was treated.

Another serious deficiency in the database relates to the number of dropouts reported. The sponsor has presented the number of patients who left treatment as a result of death or adverse events. However, they

acknowledge that there may have been additional dropouts for whom they have not accounted (a number which they acknowledge may be large or small). That is, the sponsor does not know (and hence cannot, of course, report), the reasons why individual patients stopped contributing exposure data when they did. (For example, an individual patient's contribution to the NDA may have been 6 months of exposure because they had been on drug for 6 months at the time of the NDA cut-off date, or because the protocol in which they were enrolled ended at 6 months. However, the sponsor acknowledges that they do not know why some [unknown number of] patients stopped their contribution to the data base when they did.)

The sponsor is "confident" that they have reported all dropouts due to adverse events (and deaths), because they assert that the CRFs from which they abstracted the data were designed primarily to record adverse events and actions related to adverse events, so that if a patient discontinued treatment secondary to an adverse event, this action would have been recorded. However, they agree that, since they cannot be certain of how many patients actually may have discontinued treatment at the time they contributed data to the NDA or why, they cannot reliably conclude that none of these additional patients did not leave as a result of adverse events (or death). One reason to suspect that all relevant ADR related information was not collected, for example, is that, as noted earlier, information about hospitalizations, (for any reason), was not systematically collected on many of the CRFs.

Documentation about the number of deaths and in which cohort deaths occurred has also been a difficult problem. Dr. McCormick has, for example, identified reports in the Neuropathology section of the application of patients who died for whom no corresponding information is contained in the section on deaths. Multiple telephone conversations intended to get the sponsor to collate all deaths and identify in which cohort they occurred have still not, as of this writing, been entirely successful.

There are additional shortcomings in the safety data base as reported. For example, Serious Adverse Events have not been collected in one section of

the NDA. Although there is a Section of the NDA called Serious Events, inspection of that section reveals that this is, in fact, a list of hospitalizations. Since we have already seen that hospitalizations were not systematically collected for patients in the CRF database, this list is unreliable. Dr. McCormick has made every effort to accumulate and report those adverse events located throughout the NDA which appear to be serious; as of this date, because of the inadequacy of the submission, she cannot be confident that she has identified all such events.

ISSUES RELATED TO INADEQUATE DESCRIPTION OF COLLECTED ADVERSE EVENTS

In addition to those problems related to questionable primary data acquisition and documentation of exposure, there are many problems relating to the inadequate presentation of data that we know has been collected, including serious flaws in the reporting of data from the US database.

For example, the sponsor warrants that no significant cardiovascular adverse events were seen, but did not present **any** of the routine EKG data that was collected.

Because of the concerns raised about the potential for GVG to cause intramyelinic edema (IME) in animals, considerable attention was to be paid to evaluating any brain tissue that was obtained. As discussed by Dr. McCormick, tissue was derived from 2 sources; brain biopsy and autopsy. Since biopsy material was limited to areas of brain that were not necessarily expected to be involved with the neuropathology (based on the animal studies), attention was largely focused on the autopsy material. Beside the fact that very few of the 17 autopsy specimens had examinations of the areas of interest (e.g., only 2/17-12%- of autopsied brains had an examination of the fornix, an area with extensive IME involvement in animals), of more concern here is that the sponsor made no attempt to report or discuss findings that were seen in some patients that were at least consistent with the animal data. For example, Dr.

McCormick notes 4 patients in whom findings consistent with the animal lesions (axonal ballooning, spheroids in the cerebellum) were seen, but the sponsor made no comment of the findings (Dr. McCormick discovered the findings upon reading the primary pathology reports). It is also important to point out that there was no description of the methodology employed (e.g., how controls were chosen, maintenance of blinding), as well as any protocol for obtaining material and performing the pathology examinations.

Another critical example of the sponsor's inadequate reporting of potentially important drug related findings involves Study 97-006. This study was performed in the US and was undertaken specifically to examine any ocular effects of GVG, since studies in albino rats demonstrated retinal pathology, and because of theoretical concerns about the effects of GABA on pathways involved in visual function. The study involved 45 patients who underwent extensive ophthalmologic testing every 6 months. The sponsor reported that the results demonstrated that GVG was not associated with any ocular pathology, although they did list 12 patients with abnormalities. Dr. McCormick undertook a review of the CRFs of these patients, and uncovered multiple changes in a total of 36 patients (the description of the changes in the CRFs caused Dr. McCormick to request the primary ophthalmologic records-data from which was used to create the descriptions in the CRFs-and review of which revealed additional findings). Some findings included vessel narrowing (12 reports), retinal drusen (15 reports), retinal pigment epithelial loss and/or changes, and cataracts and other lenticular changes (7 reports). Much of this pathology was neither discussed, described, nor reported by the sponsor, other than in the CRFs. An ophthalmology consultant obtained by the Division felt that there was compelling evidence suggestive of possible ocular toxicity requiring further study. A similar "trial" was performed in Europe, and was described also as demonstrating the absence of any effects of GVG on the eye or visual system. However, no primary records are available to us that would allow us to independently confirm or refute the sponsor's conclusions.

Further, in the course of review, Dr. McCormick became aware of several

cases of liver failure (some had been reported to the IND, but not the NDA). The firm was requested to submit a tabulation of the cases and discuss and analyze the findings in their safety update. They submitted a tabulation, but no analysis or discussion. Dr. McCormick has described 12 cases of hepatic failure, with 7 deaths. Half of the cases of hepatic failure occurred in children below the age of 10.

As noted earlier, as a result of the concerns raised by the animal findings, evoked potential monitoring was incorporated into Studies 024 and 025, as well as into several other trials. In Studies 024 and 024, patients were monitored with Visual Evoked Responses (VER) at baseline and at 4 months of treatment. Dr. John Feeney has reviewed the sponsor's report of the electrophysiologic monitoring, as well as the individual tracings for Study 25 (no other actual tracings were submitted). His detailed inspection of the data for Study 25 reveals deficiencies strikingly similar to those found in the rest of the NDA. For example, data for latencies of wave forms (the primary outcome of interest) are presented for certain patients that review of the primary tracings cannot confirm. Also, in certain cases, the individual investigator performing the studies concluded that the tracings were inadequate and that the data generated should not be utilized, yet latencies for these patients are reported without comment by the sponsor. As with the larger safety data base, close inspection again reveals the disturbing disparities between the primary data and the sponsor's summary and reports of that data. While no consistent important findings are reported to have emerged in the entire evoked response experience (total N is difficult to calculate, but may be in the range of several hundred patients worldwide), we have the same concerns about the reliability and accuracy of the sponsor's reports, although, in fact, there is **no** comprehensive report of the total evoked response experience, an example of another generic flaw in the application.

Another important example of inadequate reporting is the sponsor's report of Study 025, the second controlled trial described in the first part of this memo.

In this trial a number of protocol violations not disclosed by the sponsor were discovered only upon review of the CRFs. For example, while 34 patients with violations relating to use of inappropriate concomitant anti-epileptic medication were reported, a total of 42 were discovered on review of the CRFs. The sponsor alleged that none of the additional 8 patients received sufficient doses of the additional medication to effect the outcome, but review of the CRFs revealed that investigators had prescribed these drugs specifically for the purpose of achieving increased seizure control, and in some cases documented (what they believed to be) a response. Other problems with reporting include the fact that the number of seizures during a seizure flurry were sometimes assigned by a company monitor, sometimes years after the trial had been performed. While this practice was described by the sponsor, according to Dr. McCormick, review of the CRFs demonstrated that the number of seizures assigned by the sponsor did not make sense in the context of the other seizure data for a given patient. The sponsor never made mention of these discrepancies, which Dr. McCormick describes as having occurred frequently. For example, in one case, the original seizure count during several flurries was listed as being uncountable (the code used was the letter "Z") for each flurry. The number of seizures assigned by the sponsor 1 1/2 years later to each flurry was "4", despite the fact that the CRF reveals that at other times in the study, the mother of the patient was quite capable of counting up to 11 seizures/day.

An additional difficulty related to the fact that seizure counts were sometimes not recorded during hospitalizations, a fact that was not highlighted by the sponsor, and, once again, only emerged after review of the individual case records. While deficiencies in the reporting of this trial do not impinge upon the assessment of the safety of the compound, they clearly are consistent with the serious reporting deficiencies in the other parts of the application.

COMMENTS

Review of the controlled trials reveals that GVG is effective as adjunctive treatment for adult patients with partial seizures. Data has not been submitted to answer the question of whether the drug can effectively treat complex partial seizures that generalize (an indication the sponsor proposes). There is little, if any, evidence to suggest that doses greater than 3 grams/day offer any benefit beyond that seen with 3 gms/day.

Review of the safety data base reveals, however, that much of the data from the cohorts described has not been adequately recorded and/or reported. In the first instance, we have no confidence that adverse event data has been adequately collected in the ARF database, since it has been derived retrospectively from manuscripts, articles, summaries (in other words, secondary sources).

While the CRF database appears on the surface to be adequate, closer inspection reveals it, too, to be seriously flawed. The primary concerns are that we do not know the dose and duration of treatment for this cohort, and we do not reliably know how many deaths and dropouts there actually were in this cohort (nor, of course, do we know the reasons for any additional deaths and/or dropouts not reported). Further, other important information (e.g., hospitalizations), was not systematically recorded. In addition, the organization of the NDA has made a complete review difficult, if not impossible. As an example, as noted earlier, Serious Adverse Events were not described or analyzed in one section, making it extremely difficult to gather and review this important information.

In addition, we have found many examples of inadequate reporting of information that has been collected. Serious deficiencies in the reporting of all adverse events seen in Study 006 (the ophthalmology study), as well as similar serious omissions in the reporting of protocol violators in efficacy study 025 make all the data in the NDA as reported by the sponsor suspect with regard to its completeness and accuracy.

The question of the accuracy of the sponsor's reports takes on particular importance in light of the fact that **almost no primary data sources are now available to the sponsor**. Given our experience with finding additional important information in CRFs (in Studies 006 and 025, for example,) not reported by the sponsor, I think it is critical that we have the ability to retrieve and review (should we find it necessary) the CRFs for all patients included in the safety data base before we can conclude that the data are as the sponsor claims they are.

Given the deficiencies in the data in the CRF database, it would seem that the only cohort for which we currently have reliable data is the US cohort (although, as stated, even this cohort is inadequately reported). It is my view that a cohort of 537 patients is not sufficiently large on which to base an assessment of the safety of a new chemical entity. This is particularly true in this case, where there is concern about the occurrence of potentially serious neurotoxicity. I should hasten to add that, at the moment, I am not aware of any toxicity identified that would preclude approval of this compound. However, I believe that we have not adequately characterized the toxic potential of the drug, and certainly, we cannot rule out the occurrence of any serious adverse events (that could theoretically preclude approval) that may occur at small, but potentially important, rates.

As of January, 1994, GVG was approved in 31 countries, including the UK, France, Spain, Germany, and Canada. The sponsor states that at the time of submission of the NDA 200,000 patient years of exposure had accrued. While the sponsor alleges that this experience supports the safe use of GVG, it should be noted for the record that post-marketing data of this sort cannot substitute for detailed data obtained in a sufficiently large cohort of patients treated with an appropriate dose for a clinically meaningful duration, and followed prospectively with essentially complete follow-up.

RECOMMENDATIONS

Although the sponsor has submitted substantial evidence of effectiveness, they have not provided sufficient safety information on which to adequately assess the safety of the drug, and, therefore, I recommend that a Not Approvable letter should be issued.

In order to make the application Approvable, they must submit data on a sufficiently large cohort of patients followed prospectively for sufficient duration and for whom essentially complete and accurate adverse event information has been collected and appropriately reported. This particularly applies to all deaths and discontinuations, and the reasons for all of these events, but it certainly also applies to the collection and reporting of all serious and other adverse events, as well as all laboratory data. Further, of course, accurate and complete information about the doses given and the duration of treatment for each patient included in such a cohort must be available and reported. Whether the current body of information available to the sponsor can be rehabilitated to conform to this standard is very questionable.

Should it become necessary for the sponsor to enroll new patients in order to accrue a sufficient number of adequately evaluated patients, a reasonable mechanism that might be employed would be a Treatment protocol. It appears that all of the criteria for granting a Treatment protocol would be met in this case (the criterion that there be no other alternative therapy available could be met by restricting the use of GVG to those patients shown to be inadequately controlled on available AEDs), and I believe that our willingness to entertain this as an option should be included in any Not Approvable letter that issues.



Russell Katz, M.D.

cc:

NDA 20-427

HFD-120

HFD-120/Katz/Leber/McCormick/Pitts

rk 3/31/95

Review and Evaluation of Clinical Data
NDA 20,427

Sponsor: Marion Merrell Dow Inc.
Drug: Sabril (vigabatrin) Tablets
Proposed Indication: Partial seizures
Material Submitted: Evoked Potential Assessment (3 volumes);
EP Tracings from Study 25 (12 volumes)
Correspondence Date: Unknown
Date Received: January, 1995

Introduction: In the 1980s, investigators recognized that vigabatrin caused intramyelinic edema (IME) in animals. This finding had a predilection for the optic tracts, thalamus, hypothalamus, fornix, reticular formation, and cerebellum. IME was seen in rats and dogs. Only equivocal findings existed in monkeys, perhaps because of the lower plasma levels obtained in this species. In the rat and dog, even the lowest doses of vigabatrin had the potential to produce this lesion if the duration of exposure was extended. For purposes of characterization, the sponsor found that 300mg/kg/day in the dog for several months served as a useful model. In this dog model, the pathologic lesion occurred after several weeks and the occurrence of the lesion coincided with prominent changes seen in visual evoked potentials (VEPs), somatosensory evoked potentials (SSEPs), and magnetic resonance images of the brain (MRI).

The premise behind the EP monitoring in humans is that, if IME occurs in humans in tracts involved in EP generation, prolonged EPs will be present. If the IME occurred in humans, but in areas of the nervous system not involved in the generation of EPs, the premise was that MRI would demonstrate the lesion.

In dog studies of 300mg/kg/day, EP latencies increase by 15-30% in the presence of the IME. This is in contrast to minor "physiologic" increases in latencies that might be expected with centrally acting medications. To this effect, only one published report in humans demonstrated a change in EP latencies after vigabatrin:

Kalviainen et al¹ randomized 34 pts to receive carbamazepine or vigabatrin. SSEPs were performed at baseline and after a 3-month maintenance phase. In both groups, a statistically significant change in SSEP latencies was demonstrated. However, the magnitude of the effect was small, 4% with carbamazepine and 2% with vigabatrin. The authors concluded that the increase seen was unlikely due to IME because the increase was much more pronounced in dogs showing IME. In the same study, there was no significant prolongation of VEP latencies.

Overview of Studies: Studies 24 and 25 were the large, controlled trials performed in the U.S. EP data was collected in both of these at baseline and again after 4 months of treatment. The sponsor performed an analysis based on percent change from baseline latency. Additionally, pts with a 15% change in latency were identified.

Study 21 is a Canadian study which is still in progress.

Eleven other human studies which incorporated EP data are summarized. Nine of these have resulted in publications between 1985-1993.

Protocol 25: This protocol allowed for randomization to placebo, 1 gm/day, 3 gms/day, or 6 gms/day. Approximately 144 patients from 12 centers entered the study. Dose was escalated over 6 weeks with a 12 week maintenance phase.

The sponsor provided the actual tracings for all patients in Study 25. Altogether 32 patients exposed to the high-dose, 6 gm/day dosage had VEP data. All the VEP tracings for this high-dose group were reviewed by myself resulting in the following observations:

1. Occasionally the actual tracings are not submitted and only the interpretation is provided. This is a rare problem.
2. When tracings were reviewed, it was clear that different centers and even different physicians within centers approached the collection of

¹Kalviainen, Aikia, Partanen, et al. J.Child Neurol. 1991; 6(Suppl): 2S60-2S69.

evoked potential data with different degrees of care. There are cases where latencies are reported, but review of the provided tracings could neither confirm nor deny the reported values. Sometimes the waveforms varied from trial to trial for a given patient (i.e. were not reproducible), yet a latency is arbitrarily reported from one of the tracings.

3. Not infrequently, the physician recognized that reproducible tracings had not been obtained and suggested that the study be repeated; yet, arbitrary latency values from these studies appear in the sponsor's database. To quote one investigator, [REDACTED] (patient 093-002), "The quality of these recordings is inadequate, and I do not feel that these studies should therefore be used for following the patient's progress." Nevertheless, those values appear in the database.

b(4)

Note that the sponsor does not openly present or discuss this flaw in the data at any point in the documents reviewed here. Without individually seeking out the actual reports from each patient, this fact would not have been brought forward.

4. Where care was taken to obtain reproducible waveforms, no clear trend was observed for prolongation of VEP latencies at this dose and for this duration of treatment.

5. One case deserves special comment because reproducible waveforms are nicely displayed both before and after treatment and a clear prolongation occurred on treatment in the VEP latencies after stimulation of each eye. Patient 013-006 was studied at the [REDACTED]. The prolongations are not great (11%,5%), but they are reproducible and were commented upon by [REDACTED] who interpreted the test. For this case, careful review of the MRI data would be important (I have been told that preliminary review of this patient's MRI revealed no unusual findings). Likewise, the clinical course of the patient should be researched. If the patient continued on vigabatrin for long-term treatment, follow-up results of VEPs would be valuable.

b(4)

The sponsor reports that there were no significant mean changes from baseline for either VEPs or SSEPs. Only 28 patients had a 15% increase in latency of VEP, SSEP, and/or BAEP: 12 placebo, 7 low-dose, 3 intermediate-dose, and 6 high-dose. The sponsor states that "No prolongation was associated with symptoms." The tracings for the 6

outliers in the high-dose group were studied as part of my review. 3 of the 6 outliers in the high-dose group occurred in SSEP latencies. For the first 2 of the 3 (both from center 011), I would disagree about the designated absolute latencies and/or the reproducibility of the tracings. The third SSEP outlier is reported in error by the sponsor: the values entered in the database are taken from tracings that were mislabeled; corrected tracings are provided and do not appear to show a prolongation. The remaining 3 outliers occurred in BAEPs. Because BAEPs have not, to my knowledge, been shown to detect IME in animal models, I have less concern for these abnormalities; in fact, the prolongations may only be due to improper latency determination.

Protocol 24: In this study, patients received either placebo or 3 gms/day of vigabatrin. VEPs and SSEPs were collected. The results are presented in the same manner as in Study 25. Percent change from baseline is computed and, additionally, patients with a 15% change from baseline or greater are identified.

The sponsor's analysis showed that no statistically significant differences were found between vigabatrin and placebo for any of the evoked potential variables.

15 patients had a 15% increase in latency on either the VEP or the SSEP: 9 placebo and 6 vigabatrin. According to the sponsor, "No prolongation was associated with symptoms." The tracings from this study were not submitted; I would presume that the same problems arose in the conduct of this study as were seen in Study 25.

Protocol 020/026: This is a continuation study of protocols 24 and 25 mentioned above. 280 pts across 2 studies had EPs performed. The duration of study 20/26 appears to be one year based on the table of studies in Volume 1 of 3.

57/280 pts had a 15% prolongation of at least one EP latency by end of study. 37/57 developed the prolongation during the study. 20/57 had a prolongation previously and continued with the prolongation. "No prolongation was associated with symptoms although one pt (013-004) discontinued the study because of prolonged VEP latencies."

Review of the actual latencies for pts with 15% prolongations reveals a large group of pts where minimal concern might be generated because absolute latencies are relatively normal despite within study prolongations of 15%. Nevertheless, the absolute latency data combined with relative changes in latency elevates the level of concern for several of the patients. No clinical summaries for these pts exist and no follow-up is given. Dose is not given.

Of note is that 41 pts who entered this study with a 15% prolongation actually improved during the study and no longer had the 15% prolongation by study end.

Mean change from baseline for all EP modalities was insignificant.

There is no published report for this study. As far as I am aware, the sponsor has not commented on the significance of these results in the submission. The sponsor should attempt to explain the significance of 57/280 pts having prolonged latencies in the setting of vigabatrin.

Protocol 097-005: No details of study design are provided. It appears that some pts were exposed for up to 4 months. No publications are included. Only VEP data is listed. Line listings for about 74 pts are presented. Clearly not all of these pts had baseline VEPs performed. The sponsor concludes that "no trend toward prolonged latencies over time was observed in any patient." Pt 005-006 did discontinue due to abnormal EPs, but "subsequent testing showed patient fatigue responsible for the variability in test results." How this conclusion was reached is not explained.

Protocol 097-006: 64 pt listings are provided. Not all pts were studied with all modalities of EPs. Duration of exposure extended out several years for some pts. VEP latencies showed some transient prolongations > 15% but no worrisome trends. Two pts had SSEP latencies which increased during study and remained prolonged at end of study (011-009 and 012-002). Dosage is not available for any patient.

Protocol 246: The data consists only of a published report from 1985. Treatment duration for the 20 pts was only 3 months at a dose of 3gm/day. Only VEPs and ABRs were performed. SSEPs were not performed. Actual latencies are not reported. A brief statement by the authors states that no changes were found.

Protocol 263: Data is summarized for 17 pts who received vigabatrin and placebo in a crossover study. No significant changes occurred on vigabatrin. Of note is that VEP latencies are longer on average even at baseline; I suspect this is due to technique, but details are not provided. Treatment duration was only 7 weeks.

Protocol 363/307: This was a long-term extension of study 263 and another single-blind study. 16 pts were treated for 6-35 months at doses of 1-3gms/day. No trends for prolongation of latencies were seen. Again, the baseline VEP latencies were excessive, perhaps due to technique.

Protocol 097-WOLD: 51 pts were treated in this long-term extension study for up to 2 years. For some patients, baseline measures were available; for others, comparison could only be made to the first EP performed while on drug. On average, no significant change in VEP or SSEP latencies were seen; however, there are clearly some isolated cases where the EP latencies increased by 10-20% during treatment compared to baseline or first recording (see figs. 3b and 4b). The dose range is not clearly stated.

Protocol 097-329: 25 pts were treated for up to 10 months. On average, no statistically significant differences in EP latencies were observed on vigabatrin, although at least one patient had a 15% change in latency.

Protocol 320: 17 pts were treated for up to 3 months. Data is only presented as published literature reports. No significant changes reported.

Protocol 335: 34 pts were randomized to carbamazepine or vigabatrin. VEPs did not change. The SSEPs were minimally prolonged in both groups (4% and 2%).

Protocol 907-W-Aus-01: Data provided consists only of a published abstract. 15 pts were treated for up to 8 weeks only. No changes in VEPs or SSEPs were noted.

Protocol 21: No details of study design are provided; in particular, the length of treatment is not stated. But it appears that about 50 pts were randomized to placebo and 50 pts were randomized to vigabatrin. No significant changes in mean latencies were noted for either SSEPs or VEPs. Only 4 pts in the vigabatrin group had latencies increase by 15% or greater. An equal number of placebo pts had 15% increases.

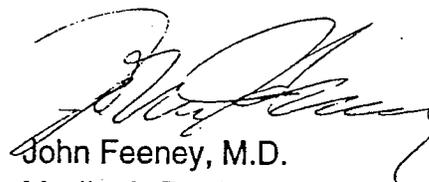
Summary: My overall impression after review of the indexed volumes is that this was a monitoring program marked by neither forethought nor afterthought. The sponsor did not seem to anticipate the amount of effort needed to acquire quality evoked potentials. Clearly, even when center electrophysiologists requested repeat studies because of poor quality or poor reproducibility, the sponsor did not push to see that this was accomplished. Likewise, the sponsor did not seem to devote much time to the analysis of the results. Numerical values were placed into a statistics program with minimal attention to the waveforms themselves. To this effect, the sponsor reports extreme latency prolongations which are easily shown to be false positives, simply by reviewing the actual tracings.

Beyond the actual quality of the data, the limitation of the EP data reviewed here is the relatively short duration of exposure i.e. 4 months for most. Recall that while the lesion of IME was obvious at higher doses in the dog after only a few weeks, lower doses given for longer periods of time produced the lesion also. Perhaps a better cohort of study would be patients treated for 4-5 years. Some 15% latency prolongations occurred in this relatively small group but little else is known for those patients.

In the extension study, 20/26, mentioned above, a fair percentage of patients developed latency prolongations after 1 year, but, as far as I am aware, the sponsor has not addressed this finding or its significance.

The sponsor's conclusion that "No studies of evoked potentials in humans have produced conclusive evidence of IME" is correct. However, the sponsor has not addressed the significance of latency prolongations where they have occurred. I have mentioned a rare case that merits further research. In the review of study 25, I have made recommendations to obtain a narrative account of patient 013-006 with regard to clinical state and MRI findings, as well as longterm follow-up if any.

If future studies of this sort are planned, I believe the quality of the data would be improved by requiring each center electrophysiologist to become more actively involved, reading both the baseline and follow-up tracings and reporting the latency changes with an understanding of the purpose of the study and a realization of the findings in animal studies.



John Feeney, M.D.
Medical Reviewer
February 21, 1995

cc: HFD-120

NDA 20,427

HFD-120/Leber/Katz/Feeney/McCormick/Pitts

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

COMPLETED

SEP 28 1994

Receive date: 7/29/94

Review completed: 8/25/94

Drug name: Sabril
Generic name: Vigabatrin
GVG in European Study

Sponsor: Marion Merrell Dow, Inc.
Kansas City, Missouri 64137

Pharmacologic Category: Specific irreversible inhibitor of gamma-aminobutyric acid transaminase enzyme.

Proposed Indication(s): Anti-epileptic drug

Dosage Form(s): tablet

Route(s) of Administration: oral

Review Type: Consult from HFD-120

Submitted:

1. Request for consultation and summary of eye findings in NDA 20-427.
2. Non-clinical ophthalmological data
3. Case report forms of vision related adverse events
4. Human ophthalmological data
5. Protocol U.S. Study 97-006
6. European Study 97-WOLD and 97-WDRISE

Resume: Evaluation of possible ocular toxicity was initiated by the sponsor based on:

1. The theoretical possibility that increasing GABA concentrations would be capable of disturbing the normal inhibitory pathways present in the visual system given the normally high concentration of GABA in the retina.
2. Animal safety studies which revealed neuropathological changes in the white matter of the central nervous system of small animals consisting of localized areas of micro-vacuolation due to splitting of the neurolemma sheath. The distribution of these changes varied by species but the visual tract appeared to be involved in both dogs and rodents. Further, in the albino Sprague Dawley rats dose dependent retinal toxicity has been reported with histopathologic findings of foci of diffuse disorganization of the outer nuclear layer. These retinal findings, however, were not reproducible in pigmented rats, dogs or monkeys.

SEP 27 1994

Summary

Sponsor's Summary of Eye Findings

A table furnished by the sponsor of controlled US studies (Protocols 71754-3-C-024 and 71754-3-C-025) in which patients were randomized to either placebo or 1,3, or 6g/day vigabatrin is reproduced below. In discussion with Dr. McCormick, it was noted that the study duration was less than a year.

Table 2: Incidence of Placebo vs. Vigabatrin-treated Patients Who Reported One or More Occurrences of a Vision-Related Adverse Event During US Controlled Epilepsy Clinical Studies

Adverse Event Preferred Term	TREATMENT-RELATED				ALL EVENTS			
	Placebo N=135		Vigabatrin N=222		Placebo N=135		Vigabatrin N=222	
	N	%	N	%	N	%	N	%
Patients with one or more Vision-Related AEs	15	11.1	42	18.9	21	15.6	60	27.0
Blepharospasm	0	0.0	1	0.5	0	0.0	1	0.5
Conjunctivitis	1	0.7	2	0.9	4	3.0	4	1.8
Diplopia	6	4.4	12	5.4	7	5.2	19	8.6
Dry Eyes	0	0.0	1	0.5	0	0.0	2	0.9
Eye Abnormality	1	0.7	2	0.9	2	1.5	5	2.3
Eye Pain	0	0.0	5	2.3	0	0.0	8	3.6
Lacrimation Abnormal	0	0.0	0	0.0	0	0.0	1	0.5
Myopia	0	0.0	0	0.0	0	0.0	2	0.9
Photophobia	0	0.0	0	0.0	0	0.0	1	0.5
Strabismus	0	0.0	1	0.5	0	0.0	1	0.5
Vision Abnormal	8	5.9	25	11.3	12	8.9	30	13.5
Visual Field Defect	0	0.0	1	0.5	0	0.0	1	0.5

Note: A patient may have had more than one vision-related adverse event. Therefore, the sum of the patients experiencing an adverse event may exceed the total number of patients.

Reviewer's Comments: *This short term data is suggestive of increased visual symptomatology.*

Protocol U.S. Study 97-006

This is reported to be an uncontrolled long-term open-label multi-center study of 66 patients. The mean age in the group was 36 years old. Of these 65 patients, 28 had eye exams pre-vigabatrin. The mean duration of vigabatrin exposure in Protocol 097-006 was 4.2 \pm 3.6 years, with a median of 3.2 years (the actual total duration of vigabatrin exposure was additional 14 to 16 weeks due to prior exposure in a preceding study). The overall duration of this study was >eight (8) years. However, only 35% of the patients completed the study for an average of 8.5 years. Ocular adverse events were not a cause for discontinuation.

A protocol amendment was added 12/12/83 to include ophthalmological exams (fundoscopy and slit lamp) every six months.

Exclusion criteria for this protocol were the presence of any of the following:

-clinically important hepatic, renal, or cardiopulmonary disease, or any other medical, neurologic, or psychiatric condition that would compromise the patient's safety or the

-the use of valproic acid or clonazepam. These two medications were excluded because of their theoretical GABAergic mechanisms of action which might have confounded interpretation of results.

The ocular adverse events reported in the Full Integrated Clinical Study Report by the sponsor cited treatment-related adverse events consisting of "eye abnormality, retinal pigmentation, photophobia, and retinal disorder." This reviewer's reading of the ophthalmic case reports in the consult submission reveals a somewhat different distribution of ocular adverse events:

Ages	Cataract	Macular	Retinal Pigment Epithelial Changes	A/V crossing changes or arteriolar narrowing	Visual Field Abnormal	Optic Nerve
20 to 39 (39 patients)	5	2	1	6	2	2
40 to 55 (4 pts)		1	1			
56 + (4 pts)	4	1		1		

There were fifty-seven (57) case summaries submitted with 12 reported as not having had an eye exam. One had no age reported. This reviewer was unable to determine from the information submitted what the duration of treatment was in each subject.

Retinal detachments were reported in 3 patients; nystagmus in 3; neurologic field defects in 2. The refractive error of the subjects was not reported.

Visual evoked potentials were also looked at as part of the neurological evaluation. It is reported that there were transient increases in some patients during the course of the study compared to the first evaluation, but no persistent prolongation was ever noted and in no instance was associated with symptoms.

Reviewer's Comment:

There is a very high incidence of ocular findings in this study group. Whether or not the group of patients with hard to control partial complex seizures requiring adjunctive medication has a high incidence of eye findings from the beginning cannot be determined from the data submitted given the lack of baseline exams. Worrisome is the apparent increase in cataract findings in the 20 to 39 age group and the suggestion of progression during the study. There is nothing in the case study data submitted to indicate metabolic and /or genetic conditions which would manifest a tendency to early onset of cataracts.

Also, given that the exclusion criteria disqualified from participation patients with significant cardiovascular disease, the frequency with which A/V crossing changes/ arteriolar narrowing findings were noted in the younger age grouping is disturbing. A concern is that the vigabatrin may be impacting on microvascular neural-autoregulation. It would be helpful to determine if there was any impact on blood pressure readings or

concern is that the vigabatrin may be impacting on microvascular neural-autoregulation. It would be helpful to determine if there was any impact on blood pressure readings or kidney function in the long term patients.

European Study 97-WOLD and 97-WDRISE THE LONG TERM OPHTHALMOLOGICAL FOLLOW-UP OF PATIENTS TREATED WITH VIGABATRIN FOR DRUG RESISTANT EPILEPSY IN PHASE III.

The European study population consisted of 406 patients recruited from 39 different study centers in eleven (11) different European countries. The largest population of patients was recruited from Germany (136) followed by France (67), Finland (54) and Switzerland (35). The patients ranged in age from one (1) to seventy (70) years of age, with a mean reported of 30.2 years. The median total observation period for these patients was 18.3 months. All patients were on multiple medications for epilepsy with the most common concomitant one being carbamazine. The mean exposure time to the drug was 22.9 months, with a SD of 16.0 months.

The protocol required the investigator to carry out or have carried out by an ophthalmological colleague, a full examination of the eyes. The eye exams were to be performed at baseline, then repeated after 16 weeks, 24 weeks, 32 weeks, 40 weeks 48 weeks and every 3 months.

The most common of these findings on initial exam were:

Myopia	11
Limited visual fields or hemianopsia	10
Strabismus	7
Amblyopia	4
Nystagmus	2
Optic Atrophy	2
Exotropia	2
Cataract	2

The following were reported in a single patient: localized retinal pallor, eye prosthesis, red and itchy eyes, presbyopia and exophthalmus.

Abnormalities listed as a change after the start of Vigabatrin were reported in nine (9) patients with a total of ten abnormal ophthalmological reports.

Patient	Visit #	Pre GVG rating	Change Noted	Post GVG Rating
001.006	3	Normal	Small hemorrhage in papillomacular area	Normal
004.001	7	Abnormal	Conjunctivitis	Normal
017.001	11	Normal	Infectious Conjunctivitis	Normal
021.002	3	Normal	Non-pathologic MPG	Normal
025.008	5	Normal	Genetic abnormality	Normal
025.020	3	Normal	Pain in eyes with soft visual focus	Normal
033.011	1	Normal	Visual disturbances	Normal
033.021	1 2	Abnormal Abnormal	1)Pale papilla 2)Visual disturbance	Normal
033.025	4	Normal	Slight macular edema	Normal

Reviewer's Comments:

Given the numbers involved in the European study (405) versus the US (57), the differences in the observation of ophthalmic changes are striking. In a much larger sample, there are no reports of cataracts and only one instance reported of microvascular changes. The basis for such a difference in findings may be due to different standards of reporting and also in what is deemed sufficiently clinically significant to be reported. It is also difficult to understand how a genetic abnormality could be negative both at the beginning and the end of the trial.

There were seven patients in the European study who withdrew from the study due to adverse ophthalmological events. The document states that " in most cases these events were not reported on the ophthalmological examination form as this particular exam was performed at specified times during the study by an ophthalmologist on behalf of the clinical investigator". Thus, only one patient in the above table was among the group of patients discontinuing the drug cited below:

Patient #	Pre GVG Rating	Adverse Event	Severity of Adverse Event
001.006	Normal	Small hemorrhage in papillomacular area	Moderate, later mild
001.042	Normal	Light irritation of eyes and blurring of vision	Mild to moderate
007.007	Normal	Blurred vision	Moderate
017.006	Normal	Jerking eye movements and feelings of eye twitching (not observed)	Moderate
033.005	Normal	Diplopia and vertigo	Mild
041.017	Normal	Diplopia	Mild
045.009	Normal	Vision abnormal (flickering of eyes)	Mild

Reviewer's Comments: *The failure to include these patients in the previous table calls into question other ophthalmic ADR which may have occurred between visits.*

Questions Submitted in the Neurology Consult Request and Ophthalmology Recommendations

1. Are the reports presented herein sufficient to make a determination regarding this drug's ocular toxicity or lack thereof? How would you describe it?

The data submitted is not sufficient to make a causal determination regarding ocular toxicity due to the lack of clinical controls in the study and poor reporting. Though eye exams were amended to be part of the long-term monitoring, the absence of baseline examinations limit determination of causation. Of concern, however in the long-term U.S. study are the subjects where there appeared to be an onset and suggestion of progression of cataracts and microvascular abnormalities of retinal vessels in a relatively young population (ages 20 to 39) on vigabatrin.

2. If not, what further information would be needed from the sponsor at this time?

It would be helpful to better characterize the subjects with early onset cataract and retinal microvascular disease as regards their metabolic /cardiovascular status. The exclusion criteria indicated that subjects would not be included who had significant cardiovascular disease but did not specify if mild degrees would be allowed. Where there any subjects with metabolic problems

involving glucose or calcium metabolism?

3. How might the sponsor better characterize this drug (in terms of further human exposure) with regard to its oculotoxic potential, so that adequate labeling might be developed:

Given the suggestive evidence in the non-clinical as well as clinical data, baseline ocular exams should be required prior to administration of this medication and routine follow-up ocular evaluations to include slit lamp and dilated funduscopy every 6 months in a controlled clinical trial.

4. How should this be evaluated in children who will likely be a target population for this drug? Note that pediatric trials are about to begin.

Again, in a controlled clinical trial, baseline ocular examinations should be performed and follow-up evaluations performed every 3 months, given the potential increased susceptibility in the pediatric population.

Recommendations:

Though no common pathophysiological pattern was found, there is compelling suggestive evidence of possible oculotoxicity which requires additional study.



Jonca Bull, M.D.
Medical Officer, Ophthalmology

cc: HFD-120
HFD-540/Consult File
HFD-540/SMO/Chambers WAC 9/15/94
HFD-540/DDIV/Wilkin

fw 9/21/94