CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-427

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	7/20/09
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22006 (000): Infantile Spasms 20427 (000): Complex Partial Seizures
Applicant	Ovation
Date of Submission	12/28/07
PDUFA Goal Date	6/16/08
Proprietary Name / **Established (USAN) names**	Sabril Vigabatrin
Dosage forms / Strength	Packet for Oral Solution: 500 mg Tablet: 500 mg
Proposed Indication(s)	1. Infantile Spasms 2. Complex Partial Seizures
Recommended:	1. Infantile Spasms: Approval 2. Complex Partial Seizures: Complete Response

1. Introduction/Background

Vigabtrin IND was initially submitted in 1980 for development as adjunctive treatment of partial seizures. A clinical hold was placed on the IND in 1983 because a result of animal studies that indicated that Sabril resulted in vacuoles in the myelin lamella (intramyelinic edema or IME). The IND was subsequently taken off of hold in 1989 when the Sponsor demonstrated that this white matter lesion could be monitored with the use of MRI and evoked potentials.

An NDA (# 20427) was submitted in 1994 requesting approval of Sabril in the adjunctive treatment of seizures of partial origin. A "Not Approvable" letter was issued on 4/28/95 in response to this submission. This decision was principally a result of the structure and content of the submission including: 1) inadequate collection of potentially important information and 2) inadequate reporting of adverse event data collection. As part of that action this division noted that while efficacy for *partial* seizures had not been definitively demonstrated, there may be evidence for efficacy in *complex partial* seizures (CPS). Because of problems with the database, this conclusion was considered tentative and the Sponsor was asked to address concerns and perform their own evaluation of CPSs. Moreover, because of the potential of IME, it was noted that when approved vigabatrin would have to be indicated as a second line treatment.

The Sponsor responded to the 1994 not approvable letter with a submission in 5/29/97. In a approvable letter, which issued on 11/26/97, the division concluded that there was adequate data to justify labeling for CPS. It was also concluded that, if approved, vigabatrin would have to be considered as a second line of treatment because of the IME. Additional safety analysis in cognitve/neuropsychiatric adverse events, demographic subgroup analysis was requested and other safety analyses were requested.

The Sponsor responded to the 1997 approvable letter with a submission on 4/24/98. The division determined that IME as well as other issues previously raised do not serve as a barrier to approval. However, new postmarketing reports indicted visual field deficits are observed in a large number of patients. This new finding resulted in a not approvable letter, which issued on 10/27/98. Additional informtion and analysis of this phenomenon was requested. The Sponsor's response to the not approvable letter constitutes the present NDA 20427 submission.

Included in this review document is a review for a new and additional indication which the Sponsor is requesting. Thus, the Sponsor is requesting approval for the treatment of infantile Spasms (IS). This constitutes NDA 22006. The studies that makes up this latter NDA are principally derived from published reports.

In order to obtain additional input from the Neurologic community the division convened an Advisory Committee on 1/7/09 and 1/8/09 with experts in adult and pediatric epilepsy as well as ophthalmology.

2. CMC/Device

Not apply.

3. Nonclinical Pharmacology/Toxicology

In addition to prior nonclinical studies, which had previously been reviewed, the Sponsor has submitted studies in young animals to support approval for Infantile Spasms. A simple light microscopic examination was performed on the tissue of animals exposed to vigabatrin. Dr Fisher, the pharm/tox reviewer, noted that, in general (but, see below), toxicity was of similar nature except that young rats appeared to have a greater sensitivity, then adults, to systemic, retinal and neuronal effects of vigabatrin.

The one important difference identified was that lesions were identified in a number of gray matter locations in neonatal/juvenile rats. Sites involved included central midbrain (tegmentum), substantia nigra, dorsal subiculum, medulla oblongata, hippocampal CA1 region, thalamus, deep cerebellar nuclei, and basal forebrain. These were different from those observed in adult animals, which appeared to be predominately white matter type lesions that are believed to represent IME. These lesions occur at exposures expected in patients treated for infantile spasm. The lesions in animals, at times, appeared to be associated with spasms and weakness with long term exposure.

In his review, Dr Fisher recommends not approving this application for infantile spasms because of the potential for neurotoxicity in this young population. Based upon the seriousness of IS and previous experience with human exposure, this reviewer, as well as the Advisory Committee, has reached a different conclusion, (see below).

In an attempt to better define the nature of these, potentially new, intracranial lesions an additional neurohistopathological study was performed using both using both light microscopy and ultrastructural examination. The Sponsor contends that this additional study confirms the fact that these lesions represent IME. An FDA expert neuropathologist opinion was requested. Dr. Larry Schmued, (Division of Neurotoxicology, National Center for Toxicological, FDA) provided this review. In examining the histopathological slides Dr Schmued concluded that the study did not conclusively demonstrate that lesions were limited to white matter structure and may not represent IME. This conclusion was based upon the fact the aforementioned study demonstrated that the lesions appear to occur in regions of the brain primarily populated by cell bodies, dendrites and axons and not myelinated fibers. While he concluded that lesions may represent cell death, he noted that a number of factors in this study preclude a definitive demonstration of this. Thus the study was not optimally designed to demonstrate cell death. These include: 1) the study may not have used the most optimal type stains (to examine apoptosis, 2) developmental period of exposure was not ideal (studies were performed during a natural period of apoptosis), 3) examination should not have been limited to brainstem regions but have looked at forebrain areas rich in cell bodies and believed to be involved in

seizure generation, 4) survival period following exposure was too long to ideally pick up an apoptotic effect.

These data were presented to the advisory committee. The advisory committee concluded that this should not prevent approval of Sabril for IS.

Considering the fact that there are no approved treatments available for IS, this reviewer agrees with approval, but feels additional studies are required to clarify the potential for neurotoxicity. The reader is also referred to the clinical safety section on MRI abnormalities.

Recently published nonclinical data suggests that taurine depletion may be casually related to visual toxicity of Sabril. Thus taurine supplementation may ameliorate retinal toxicity in albino rat. For this reason a PMR will be requested to confirm this association. If adequate conformation is achieved additional clinical studies will be requested.

4. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology issues are being dealt with in post marketing requirement/commitments and labeling.

5. Clinical Microbiology

Does not apply.

6. Clinical/Statistical- Efficacy

Two indications are being requested by the Sponsor, adjunctive treatment in complex partial seizures (CPS) and monotherapeutic treatment for patients with infantile spasms (IS). These two indications will be separately described in the two sections below. Clinical trials for CPS were previously reviewed by this division and, in an approvable letter, thought to be adequate for the demonstration of efficacy. Because of this the description of evidence for efficacy will be brief. A more through description of this data can be found in prior reviews by this division.

Partial Complex Seizures

Two pivotal, multi-center, double-blind, placebo-controlled parallel-arm trials were submitted for proof of efficacy as adjunctive treatment in partial seizures, study 24 and study 25. Both studies were of relatively typical design with an 8 week baseline followed by a 16 to 18 week experimental phase. Study 024 examined 184 evaluable patients in two, approximately evenly divided, arms (placebo and 3 grams/day). Study 025 examined a total of 174 evaluable patients approximately evenly divided amongst 4 arms (placebo, 1gram/day, 3 grams/day and 6 grams/day). All dosing was divided twice daily. The primary endpoint was the reduction in mean monthly seizure frequency of *all* partial seizures from baseline. Median frequency at baseline and during the experimental period (final) is presented from both studies of *all* partial seizures along with the statistical analyses in the two tables below.

Median Baseline and experimental Period Monthly Seizure Frequency in Study 024

	N	Baseline	Final	P-value
Vigabatrin	92	8.3	5.3	
Placebo	90	8.3	7.5	.001-.0002

Median Baseline and experimental Period Monthly Seizure Frequency in Study 025

	N	Baseline	Final	P-value
Vigabatrin 1 gm	45	8.5	7.7	NS
Vigabatrin 3 gm	43	8.0	3.7	.0001
Vigabatrin 6 gm	41	9.0	4.5	.0001
Placebo	45	9.0	8.8	

A Not-Approvable letter was issued in March, 1995 principally for reasons of safety (see below). Efficacy issues were, however, noted. At that time it was determined that Study 025 supported efficacy. But, a number of deficiencies were identified in Study 024 including the misclassification of patients with major protocol violations and inadequate ITT analysis. A reanalysis that was made possible by additional information provided by the Sponsor, described in an approvable action taken on November of 1997, demonstrated a statistically significant effect on partial seizures. An analysis of subtype seizures including simple partial, complex partial and partial secondarily generalized (type 1A, 1B and 1C, respectively), however, failed to provide adequate supportive data for an effect on 1A and 1C seizures. For this reason the recommendation was made for labeling only for Complex Partial Seizures (CPS, or type 1B). An Approvable action was however taken because of safety issues at that time (see below). But, it was specifically noted that the drug could only be approved as a second line of treatment in CPS seizures because of safety issues related to intramyelinic edema (see safety). Additional safety analysis was requested (see below).

Final analysis that targeted only CPS (not including CPS secondarily generalized) are presented in the tables below

Median Baseline and experimental Period Monthly CPS Frequency in Study 024

	N	Baseline	Endstudy
Placebo	89	9.0	7.0
3 gm/day SABRIL	84	8.5	5.5

*P<0.05 compared to placebo

Median Baseline and experimental Period Monthly CPS Frequency in Study 025

	N	Baseline	Endstudy
Placebo	44	8.8	8.2
1 gm/day SABRIL	45	7.5	7.7
3 gm/day SABRIL	41	7.0	3.5*
6 gm/day SABRIL	41	8.5	3.5*

*P<0.05 compared to placebo

According to the Sponsor enrolled patients were required to have:

> "...a documented history of CPS or partial seizures with secondary generalization and, during the last 8 weeks of baseline, to have had at least six CPS or partial seizures with secondary generalization and not to have a seizure-free interval exceeding 28 days. Patients were required to be on an adequate and stable dose of at least 1 but no more than 2 AEDs at baseline and have a history of failure of an adequate trial of CBZ or phenytoin"

These requirements are not that different from other anticonvulsants studied and approved today. Moreover, at the time of study patients had limited therapeutic choices and in these studies were only required to have failed one of two anticonvulsants (carbamazepine or phenytoin), both of which possess very similar mechanisms of action. Since this study, there are many newer anticonvulsants with very different mechanisms of actions. Unless proven otherwise, this reviewer believes that an alternative anticonvulsant, other then vigabatrin, could be found as effective in the treatment of similar refractory patients.

For these reasons an argument can be made that, while efficacy has been proven for the treatment of CPS in adults, this drugs safety profile should preclude its approval for this indication and that a comparitive study may be in order. Such a study would attempt to demonstrate superiority over available choices. Thus, there are numerous alternative anticonvulsants (>10) approved for partial epilepsy.

A counter argument can be made that such studies are difficult and would not necessarily identify the possibility of unique therapeutic benefit in individual cases. Moreover, the restrictions on use will be so onerous that only patients who failed all other regimens will be started on vigabatrin. It is probably for these reasons that the advisory committee voted to approve vigabatrin for CPS.

While this reviewer would favor a comparative trial before approval, I understand that this is a "close call." If approved, a consideration for a phase 4 commitment for such a comparitive study should be considered.

If approved the "Indications and Usage" section should have a statement that clearly notes that the drug is intended for refractory patients and a consideration of risk/benefit must be carefully evaluated. I agree with the wording that has been fashioned at this time which is as follows:

> SABRIL® is indicated as adjunctive therapy for adult patients with refractory complex partial seizures (CPS) who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)]. SABRIL is not indicated as a first line agent for complex partial seizures.

In the absence of a comparitive study there should be clear informtion in the label that informs the prescriber that there is no definitive evidence that demonstrates superiority of vigabatrin to other potential therapeutic agents in the treatment of refractory seizures so as to reinforce the idea that this is a last line of pharmacotherapy. This can be added to the "Indication and Usage" or "Clinical Studies" sections. Such a statement might say:

> "These studies were not capable by design of demonstrating direct superiority of Sabril over any other anticonvulsant added to a regimen to which the patient had not adequately responded. Further, in these studies patients had previously been treated with a limited range of anticonvulsants."

CDTL Conclusions

This division previously concluded that there was sufficient evidence to conclude a therapeutic benefit of vigabatrin in the treatment of CPS, but there was inadequate evidence for a therapeutic benefit in other forms of partial seizures. The effect appears first at 3 grams/day. No additional effect is observed at higher doses of 6 grams/day. Because of significant safety issues, I do not recommend approval unless proof can be presented that demonstrates a significant therapeutic advantage over available agents. There is presently no such evidence. In view of the Advisory Committee's for recommendation for approval, I would suggest that studies be preformed to confirm the superiority of this agent and/or the label clearly notes the absence of data on superiority.

Infantile Spasms

The Sponsor has submitted 3 studies as proof of efficacy in IS. The studies were atypical in that they were not performed by a single commercial Sponsor, but by different individual investigators. All studies were published in refereed journals. Studies were also not of typical designs, which are generally required by this division for the demonstration of efficacy in epilepsy. As expected for such studies, the FDA served a limited role in the planning,

monitoring and performance of these trials. This will be further discussed, by study, below. Dr Philip Sheridan, Medical Officer, reviewed these studies.

Study 1A

Study 1A was a multi-center, randomized, parallel, "single-blinded," monotherapy, low/high dose study. Patients were either naive to treatment or may have been considered to have failed prior treatment. They were permitted to be on other non-IS anticonvulsant drugs as long as the dose was stable. The primary endpoint consisted of the proportion of patients achieving a complete cessation of spasms for 7 consecutive days, based upon seizure diaries that were confirmed through video/EEG monitoring. The patient's family was not blinded to the drug that they received, but were considered blinded as they were unaware as to whether they were receiving the high or low dose. The investigator was not blinded although the video-EEG reader was blinded. The study did not follow a single predefined design as is the standard for such trials. It went through several alterations in design. These are summarized as follows:

- The study originated as a compassionate use program.
- The agency, requested that the study be redesigned as a high/low dose comparison that called for a minimum of 44 patients.
- The sample size was subsequently increased to a maximum of 150 subjects and later to 250 subjects through a series of amendments.

The primary endpoint was the complete freedom from spasms based upon a 7 day clinical observation period (by parents/guardian) and confirmed through the blinded video/EEG performed within 3 days of the seven day period of cessation. As opposed to some other forms of epilepsy, as noted by Dr. Sheridan, the endpoint of complete cessation from seizures with EEG confirmation is generally considered an adequate measure. He also notes that a more appropriate way to measure this would be by daily clinical and EEG examination, although he notes that would be impractical.

Table 1 presents the results of the study in the form of a time line (reading from the left to right columns with more recent events on the right). Amendments and other significant events are noted. The shaded columns represent FDA post-hoc analyses (all performed *post-hoc* at the time of review). The final primary endpoint analysis (Pearson's Chi Square) performed by the Sponsor revealed a statistically significant effect . Because the Sponsor performed previous "interim" analyses using a Fisher's Exact test, the statistician performed this same analysis on the final data. The results were of borderline significance. After 142 patients completed the trial patients were analyzed and results were reported in the literature. (4/2/02), conformed by statistics, was statistically significant.

Time line and primary endpoint results for Study 1A.

Date	9/27/1996 (Cut-off Date)	1/1997	5/31/1997 (Cut-off date)	2/28/1999 (Cut-off date)	2/28/1999 (Cut-off date)	10/2000	4/2/2002 (Cut-off date)	4/2/2002 (Cut off date)
Description	FDA post-hoc analysis	Amend-ment 4	First analysis	Second analysis	Second analysis Revised (FDA post-hoc)	Amend-ment 5	Final analysis	Final Analysis (FDA post-hoc)
Comments	First 44 Infants (original minimal number to be recruited)	Increase to 150 Infants		This analysis used in Feb 2000 report & *Neurology* article	This FDA analysis uses same primary outcome as the final analysis	Increase to 250 Infants	Based upon the SAP of 10/2004; no correction for interim analyses	Using Fisher's Exact; no correction for interim analyses
N randomized			89	179	179		227	227
N analyzed	44		62	142	142		221	221
Responders Low Dose	0% (0/22)		15% (5/33)	11% (8/75)	5% (4/75)		7% (8/114)	7% (8/114)
Responders High Dose	14% (3/22)		28% (8/29)	36% (24/67)	15% (10/67)		16% (17/107)	16% (17/107)
P-value	.23 Fisher's Exact		.35 Fisher's Exact	<.001 Mntl Hszl Chi Sqr	.09 Fisher's Exact		.0375 Pearson Chi Sqr	.0544 Fisher's Exact

Both Dr Sheridan (Medical Reviewer) and Dr. Luan (Statistics Reviewer) have identified a number of limitations of the study analysis and its conclusions. These are described as follows:

- Although the patients' parents/guardians were blinded to dose, they were not to the actual dose. There, however, was a potential that discussions with other participating families may lead to unblinding of group
- There were 2 interim analyses with little information as to how this influenced the decision to continue the study with regard to requested increase in "n" size and the type of analysis selected. This would lead to a misrepresentation of the alpha error.
- Aventis (previous sponsor) did not develop a unifying SAP for Study 1A, and as a result there were different analyses at different times. Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Reports.
- The final Statistical Analysis Plan was not signed-off until October 2004; last patient completed in April 2002.
- Dr Luan's examination of the number of responders in the published results revealed many more responders on the 2/28/99 cut off then at the final analysis (sees Table 1) of 4/2/02. On Dr Luan's investigation of this the Sponsor noted that the wrong responder definition was applied on the earlier analysis.

These issues are partly mitigated by the following factors:

- The problem in blinding is mitigated by the blinding of the video/EEG reader as discussed in Dr Sheridan's review.
- Although there were two amendments to increase the n size there was a general understanding at the time that this was appropriate, as the study was designed for compassionate use application. Moreover, while second request for an "n" size increase (in October 2000) came after the second interim analyses, that analyses was thought to be positive, at least based upon the final published report (see Table 1). Although it is noteworthy that a post hoc analysis by the division, using the Fisher's Exact Test, which was used as the first Sponsor's analysis, was not statistically significant.

The primary endpoint called for a 3 day window for the performance of a confirmatory video/EEG. Some patients were not able to have such an EEG in the time frame and were therefore not identified as responders. A sensitivity analysis was performed allowing a confirmatory video/EEG beyond the three day period. When this was performed the treatment difference between placebo and control increased: i.e. with a 9 day limit responder rate in the low dose was 11% and in the high dose was 26%.

Secondary endpoints included percent change in spasm free patients (without video/EEG confirmation). Time to spasm free response and physician global analysis (physician was unblended). All such analyses were statistically positive. This supports the primary endpoint, but are not completely free of the problems described for the primary endpoint.

Open label follow-up was performed on patients for at least a year. Dosage adjustments (up or down) were permitted during this time in dosage, but only by a circumscribed amount. For patients who met the liberal window criteria for the video/EEG, up to 12% of patients in the high dose and 46% of patients in the low dose group experienced a relapse. Most of those who relapsed became spasm free after a vigabatrin adjustment. The results are reassuring, but it must be remembered these results are completely un-blinded. These data are also difficult to evaluate because of the absence of a placebo control. As pointed out by Dr. Sheridan, it is the natural history for infantile spasms to resolve over time, making the absence of placebo controls in long term studies even more confounding. Moreover, the data are further confounded by the allowance of other anticonvulsant treatments . In conclusion the long term data are, perhaps, supportive of the controlled phase of the study, but are inadequate to allow a conclusion for long term efficacy.

In conclusion, the study does not meet normal standards for the FDA for reasons described above (e.g. lack of a predefined protocol, interim evaluations without a fire wall, absence of a pre-defined statistical plan, questions regarding the completeness of the blinding). Nonetheless, the primary endpoint analysis would suggest a positive effect.

Study W019

WO19 was a small (n=40) multicenter, randomized, double-blind, placebo-controlled (1:1), parallel group, in-patient study that examined efficacy of vigabatrin as monotherapy in newly diagnosed IS patients. The study consisted of a 2 to 3 day baseline period followed by a 5 day treatment period. The study was designed using a flexible treatment paradigm so that treatment was increased over the experimental period from 50 to 150 mg/kg untill an adequate response was observed. The primary efficacy endpoint in this study was the percent change from baseline on day 5 of treatment in daily average spasm frequency as measured over a 2-hour Video/EEG epoch. Although a slightly greater reduction in the percent change in seizure frequency was observed (54.4% in drug and 41.5% in placebo), this was not found to be statistically significant (p=0.562). This endpoint was generally considered inadequate by Dr. Sheridan as it provided a very small sampling of seizures and therefore was likely to result in a large variance. I agree with his conclusion. This combined with the small size of the study was unlikely to provide adequate power to identify a treatment effect. One of the secondary endpoints included a 24 hour clinical observation window. When this is examined a large and statistically significant (p=0.030) difference is observed with a 68.9% percent reduction in the vigabatrin group and a 17.0% in the placebo group. This analysis is based upon clinical observations and lacks the rigor of electrophysioplogic monitoring which, as noted above, is considered standard for such studies. Moreover, Dr. Sheridan notes that the actual endpoint measure of percent change is not standard for such studies; complete session of seizures is a more common endpoint. The Sponsor, however, performed an additional secondary analysis which may be more consistent. Thus, 45% of the vigabatrin-treated subjects and 15% of placebo-treated subjects achieved only one or less spasm per day on the last day of the study, based upon clinical observations. This difference was statistically significant (p=0.036). The Investigator's Overall Assessment also indicated a statistically significant improvement (p=0.001). Thus, while the primary endpoint of this study was negative, the endpoint was poorly selected and secondary endpoints, which were also not optimal, suggested an effect.

Dr. Liu, the statistician had no specific statistical issues. Her evaluation of the primary endpoint and the secondary endpoint of seizure freedom over 24 hours confirmed the Sponsor's analysis.

In conclusion while this study has a generally better design then study 1A in that in is a true blinded placebo-controlled study, without any statistical issues, the sample size and endpoint may have not been appropriately selected. Secondary endpoints do however suggest a therapeutic response.

Study FR03

While presented as a pivotal trial StudyFR03 would not normally meet the criteria as a pivotal trial. The study, however, may be considered supportive. It was not blinded and there was no prior statistical plan. This study was a multicenter, open-label, randomized, cross-over study (n=23) that compared vigabatrin (150 mg/kg/day) to hydrocortisone (15 mg/kg/day) as first-line monotherapy treatment in patients with IS due to tuberous sclerosis. Approximately half of patients started out on vigabatrin with the other patients starting out on hydrocortisone.

Subjects were evaluated every 2 weeks during the study. After 1 month (4 weeks) of therapy, subjects who had an incomplete response to the first treatment or had signs of intolerance crossed over to the other treatment, whereas subjects who responded (total disappearance of spasms) were not crossed over. Response to treatment was based upon clinical observation, not EEG. The primary efficacy endpoint in this study was the proportion of infants with a total disappearance of IS. There was no formal statistical plan. A total resolution of seizures was observed in all 11 subjects started on vigabatrin, while only 4 of 12 achieved cessation who stated on hydrocortisone. Of those who crossed over all achieved complete cessation of seizures on vigabatrin. These differences were statistically significant. While unblinded these data support the conclusion for efficacy.

Uncontrolled studies

Two additional uncontrolled open-label studies were submitted as supportive. These consisted of one prospective 3 month study in 43 patients and one retrospective analysis of 192 patients. These studies demonstrated that 47% to 68% of patients became spasm free following the initiation of Vigabatrin.

Long Term Follow-up

The controlled studies were of shorter duration then are generally required for approval for an epilepsy indication. The only long term follow-up consisted open label experience (up to about 2 years). These data suggested a relapse rate of 20% to 23%. This is consistent with a relatively long term effect, but without a controlled study it is impossible to be definitive about such a conclusion. It should also be noted that infantile spasms exist in a very well circumscribed period of time (1 month to about 2 years of age) making any definitive conclusions from uncontrolled data even more difficult.

CDTL Infantile Spasms Efficacy Conclusions

While not of a design normally expected by agency standards, these studies strongly support vigabatrin's efficacy in IS. The persistence of effect and the need for continued therapy, however, have not been well studied. Because of the less than optimal study design and safety issues (see below) the question of efficacy was presented to an Advisory Committee. They concluded that there was enough evidence to conclude efficacy. I agree with this decision, and feel that additional studies should be performed to examine the persistence of effect and determine the correct time for drug withdrawal. The Advisory Committee expressed a similar conclusion.

7. Safety

Previous reviews examined general safety issues for vigabatrin in the treatment of CPS. These will only be briefly described. The present submission included new safety data in children (most of whom were being treated for infantile spasms), an analysis of MRI data in prospective trials and the literature as it relates to IME and gray matter changes in non-clinical studies, and an examination of visual toxicity in children and adults.

Safety Data for Children with Infantile Spasms

The review of Safety in children was performed by Dr. Gerry Boehm, safety reviewer, and Dr. Sally Yasuda, Safety Team Leader. This safety database included data from 3 controlled IS studies and 1 uncontrolled IS study (n=325), as well as safety data from subjects < 3 years old from non-IS studies (n=21). It also includes data from a retrospective study of 250 IS patients. One-hundred and seventy two patients were exposed for at least 6 months and 120 for more then 1 year. The dose ranges of these exposures were representative of therapeutic doses. While these numbers do not fulfill general ICH guidelines, as noted by Dr. Yasuda, the full developmental program, including patients with CPS, more then makes up for this. There was however little long term (no greater then 14 days) placebo-controlled data for comparison, which is generally considered the highest quality data, which allows for a clearer determination of causality.

Three deaths, from a total of 325 patients were identified. The deaths were due to sudden death, pneumonia, pulmonary hemorrhage (thought to be secondary to pulmonary angiomatosis), and cardiac arrest. Sudden death and pneumonia are not completely unexpected in this population of generally rather sick children. Drs Boehm and Yasuda did not suspect that this represented causality. I agree.

Dr Boehm identified that 23% of patients experienced one or more serious adverse events (SAEs). The most common SAEs were pneumonia (3.2%), status epilepticus (3.2%), pyrexia (1.7%), convulsion (1.5%), bronchospasm (1.2%), viral infection (1.2%), and gastroesophageal reflux disease (1.2%). Pneumonia, viral infections and convulsions, as serious adverse events, would not be unexpected background adverse events in this population. Of interest, there were a number of cases of status epilepticus. It is important to note that these data constitute events occurring during open label evaluations and there is not extensive placebo control experience for comparison. For these reasons an absolute signal for such events cannot be concluded. There was a slight preponderance of status epilepticus in CPS studies in drug versus placebo groups, which lend some support for causality of this event. This reviewer feels that although it is difficult to discern this as a true signal. This informtion is being included in the adverse events section of the label, which this reviewer agrees with. Dr Boehm examined 37 post-marketing SAE reports and, except for MRI abnormal (n=6) and visual field defect (n=6), a signal was not identified. These latter SAEs are discussed below. Importantly, Dr Boehm found no reports of hepatic failure, aplastic anemia, anemia, or Stevens Johnson syndrome.

Sixty-two percent of the subjects in the safety population for IS discontinued a trial prematurely. The most common single reason for discontinuation was "other" (22%). This category predominately included non-adverse related events such as becoming seizure free (n=64), changed to Sabril obtained from Canada (n=4), study closure (n=5), medication no longer available (n=2). Other common reasons for discontinuation were lack of efficacy (19%), administrative reasons (10%), protocol violation (4%), and adverse event (3%). Twenty-two of 346 subjects in the safety database (6.4%) discontinued from a trial due to adverse events. As Dr Yasuda points out there was particular pattern, "cluster," which could be identified that would constitute a signal. This reviewer agrees. The interpretation of this data is hampered by the small database size and the brief duration of the placebo-controlled period.

CDTL Conclusions on New Children Safety Data

No definitive additional adverse events, outside those observed in other reviews by the agency or described in other sections of this review (see IME and visual changes) were identified. Although some important serious events should be included in the labeling on adverse events the quality of the data makes a determination of causality difficult.

Intramyelinic Edema and MRI abnormalities

The potential for intramyelinic edema (IME) in patients was originally raised as an issue as a result of animal studies in multiple species, except monkeys (see pharm/tox). These IME lesions in animals appeared reversible upon drug discontinuation, although residual astrocytosis and mineralization was apparent in some cases. These phenomena correlated with MRI changes (bright T2 signals) as well as evoked potential prolongation in animals. In a submission, for which the division had taken a "Not Approvable" action in 1997, the Sponsor argued that autopsy results in 11 patients of surgically collected temporal lobe specimens indicated the absence of IME. The division, however, felt that the autopsy results were limited in number and the neurosurgical specimens were limited to temporal lobe sampling, an area that generally free of IME in animal studies. Of note, the Supervisory review by Dr. Katz at that time noted that this safety profile of the drug would lead to "no bar to ultimate approval." A number of issues were requested in the approvable actions in 1997, which were not directly related to IME. However, based on the issue of IME and the conclusions of the unpredictability of its detection, the Sponsor was notified in the 1997 action letter that vigabatrin could not be considered a first line agent. Additional analysis for IME in patients included evaluation of the clinical trial CPS database (427 adults and 200 children) for evoked potential and MRI reports. These analyses were unable to provide evidence that IME occurs in this population of patients. Because of new findings of increased T2 signal lesions in deep nuclear regions identified in infants (see below), the Sponsor performed a reanalysis of MRI data provided in prior studies with additional attention to gray matter areas. The previous examined images were examined by blinded neuroradiologists for increased signals on T2 or FLAIR imaging that was not explainable by a preexisting pathological process (e.g. ischemia). These data are contained in this submission and are reviewed by the Dr Phil Sheridan, the

Medical Reviewer. No statistically significant difference was observed in either the prevalence or incidence of such lesions. For example the incidence between groups was 10.8% and 8.0% for patients exposed to drug versus placebo, respectively, which proved not to be statistically significant (p=0.437). Dr Sheridan also notes that when analyzed by age group, the differences between treatment groups are small, vary in direction and are not statistically significant. Dr Sheridan concludes that the "weighing of benefit to risk ratio should however include the consideration that there are multiple alternative therapies approved for complex partial seizures." I believe that these data do not rule out the possibility that such a pathological process does not occur, but only that it is not detectable behind the background of similar findings (i.e. increased MRI signal) that occur in the same population. The data and "potential risk" should be noted in the labeling, and the agent should never be used as a first line agent. This reviewer believes that the value of the use of MRI in monitoring such lesions is highly limited because of the high background frequency of such lesions.

As noted above new grey matter lesions were identified in infants following the 1997 approvable. These were reported in the literature reports as an increase T2 signal in a small number of infants in the deep gray matter. Such lesions may be different to those described above, as generally deep nuclear lesions would not be expected with IME type lesions. Nonclinical studies have also demonstrated a potentially similar lesion in animals (see below). As per Dr. Sheridan's review, a clinical panel assembled in 2007 by one of the authors determined that the MRI lesions could not definitely be attributed to vigabatrin and such lesions were unlikely to have sequella. A retrospective study examining such lesions was, however, recommended. Because of this the Sponsor has performed a retrospective review of patients with infantile from 5 institutions. Twenty-three of 204 patients exhibited the potential lesion. About half of patients were noted to have resolution of these lesions either with continued treatment or upon discontinuation. No information is available on the remainder. An additional study (OV-1019) provided by the Sponsor included a blinded retrospective examination of MRIs of 205 patients with infantile spasms from 10 North American institutions who were being treated with vigabatrin or another medication. This study clearly demonstrated an increase in MRI lesions in vigabatrin-exposed (36%) versus non-vigabatrin exposed patients (5.9%). This difference was statistically significant and suggested causality. The effect also appeared to be dose dependent. Also noteworthy, that while clinical studies generally reported no associated clinical symptoms, there was a single Finnish report that described 3 children with abnormal movements coincident with the development of lesions which resolved with drug discontinuation. With this informtion the EMEA concluded that the benefits outweighed the risk. Such effects are however labeled in Europe.

Dr Sheridan concludes that the lesions seen in infants lesions likely represent IME seen in animals, although there is some disagreement with this conclusion. Pharm/Tox believes these lesions may be more similar to the gray matter lesions observed in juvenile animal and for which there is not enough evidence to conclude whether this represents IME or could potentially represent neurotoxicity. Dr Sheridan also believes that, because of the limited data, it is difficult to be certain if there are any clinical sequela to such lesions But, he believes that these lesions still represent a safety concern and must be considered in weighing the benefit/risk ratios. The lesion should be clearly described in the label. In the whole this

should not prevent approval of this drug when considering the benefit-to-risk ratio, because of the seriousness of infantile spasms. The question is whether MRI monitoring should be recommended, and if recommended what actions should be taken if such a lesion is observed. The problem confronted in this case is that such imaging adds another risk factor because of the need for sedation and in many cases there are no observable clinical sequela and reverse without drug discontinued. It can be argued in this case that the information should be provided and the decision be left to the clinician whether to discontinue or continue treatment or perform imaging studies. Dr Sheridan feels that a phase 4 requirement may be necessary to better describe any clinical sequel to such lesion if the drug is approved. I agree with this. The issue of benefit risk, regarding these findings was addressed by the Advisory Committee, who felt that this should not prevent approval. The committee was also uncertain if animal findings were related to the deep gray matter lesions observed in infants.

CDTL Conclusion on MRI Changes

The clinical significance of animal finding and IME is still uncertain. There is no direct evidence from MRI examination that such lesions occur in adolescent and adult patients exposed to vigabatrin. Thus, no increased rates of white matter lesions were apparent when comparing drug to placebo exposed patients. Whether this is a reflection of the fact that such lesions do not occur in this population or is a result of the limited sensitivity behind a small to moderate background of similar type lesions (white matter ischemia, "UBOs" etc) is unknown. No obvious clinical sequela to such lesions has been definitively identified despite its long term use in Europe. This reviewer does not feel that this adverse event should prevent approval, but this informtion should be maintained in the Warnings section and this phenomena needs to calculated into benefit/risk considerations for the use of this drug. As is apparent from MRI studies, the value of monitoring this lesion through MRI is highly questionable.

I believe that there is evidence that the grey matter lesions observed in infants is related to vigabatrin treatment. The clinical significance of these lesions, however, is still unclear. In some studies they appear to resolve with continued use in others they resolve with drug discontinuation. We don't presently know if they are related to the lesions observed young animal studies and what the animal lesions represent (IME or apoptosis). Nor do we know what the clinical seqeula for lesions are. One isolated report does not "abnormal movement." But, at the present time there is little data to corroborate this. This alone, however should not prevent approval for IS, considering the need for a medication effective in the treatment of IS. It is unlikely that risk/benefit would call for routine monitoring for these lesions, considering the need to sedate infants for such examinations and the risk of sedation. Physicians should be clearly made knowledgeable about this lesion. It should be included as a boxed warnings and the Sponsor should be required to collect additional data on MRI and potential associated clinical changes as part of the registry. Decisions on monitoring should be left individually to the physician. The Sponsor will be asked to clarify the grey matter lesions observed in the juvenile animal studies. A finding of apoptosis in such studies may require serious consideration of additional clinical data or monitoring.

Visual Toxicity

Following the 1997 approvable letter, DNP became aware of numerous reports of visual field abnormalities associated with the use of vigabatrin. Because of this the division issued a "Not Approvable" action in 1998 asking for additional data, including additional studies in which patients are adequately monitored for this finding. The division was particularly interested in the incidence, topography (central Vs peripheral), severity, latency, reversibility, risk factors and the ability to monitor premonitory features of this toxicity. The Sponsor has now responded in this application to the divisions concern. Data included an analysis of patients with CPS and IS from four general sources: 1) reporting from efficacy and open label extension trials for COS and IS, 2) published case reports and 3) Periodic safety Update Reports, 4) phase 4 studies designed to examine visual function. Dr Farkas, an ophthalmologist and Medical Reviewer in DNP, performed the primary review of these data. Dr Wiley Chambers, a supervisory Medical Officer in DAIOP, supervised this review.

In his review of the original efficacy/safety trial database Dr Farkas notes few visual changes attributable to the reported visual defects of interest. The division believed that long term follow-up of children in the original IS studies would be most informative. The Sponsor was only able to obtain follow-up information on 55 of 279 patients enrolled. Although, field defects were noted in 24 of these patients, they were not believed to be vigabatrin related. Dr Farkas concluded that these data were uninformative because of the lack of power and the difficulty in indentifying all but severe visual field loss. Phase 4 studies, specifically looking for this particular pathology is, therefore, crucial.

A number of studies were performed and are summarized below. Dr Farkas notes that the studies were plagued by numerious shortcoming including low enrollment, non-random patient selection, high drop out rate, poor quality assurance and post-hoc analysis.

A number of studies were reviewed by Dr. Farkas relevant to the treatment of patients with CPS. The salient aspects of relevant studies are described below:

- *Study 4020:* This was an open-label, multicenter study pooled cohort (patients treated and remaining on vigabatrin, patients treated and discontinued from vigabatrin, patients never treated with vigabatrin). Patients on vigabatrin who were enrolled into this study were prescreened for visual deficits thought secondary to vigabatrin. Dr Farkas notes that the non-random selection of patients may have introduced serious bias into the study. Thus, it may have excluded patients with visual deficits that were simply not thought to be characteristic of vigabatrin, such as central deficits. Moreover, patients selected may have been biased to lesser visual defects, as these would be patients to continue on vigabatrin. Recording of deficits were through perimetry, but the perimetry methodology did not appear performed carefully or standardized. Indeed many patients without exposure were identified as having visual field deficits. The study did confirm the appearance of bilateral concentric visual field deficits in patients exposed

to vigabatrin. The Sponsor estimated that the risk was25% in adults and 15% in children. Because of the technical problems with this study Dr. Farkas concludes that these incidences can only be considered a lower limit. The Sponsor noted that the earliest onset of the visual field deficit was 12 to 16 months. Dr Farkas questions the accuracy of this number because of the study design and considers such a number to be an upper limit.

- *"Pooled Cohort Study":* This study examined visual fields of 67 patients who participated in a variety of vigabatrin studies. The prevalence of field deficits for patients exposed to vigabatrin was 36% for patients with more than 3 years of treatment with 1/3 of these patients having "profound" defects. No deficits were observed in patients not exposed to vigabatrin. While the mean severity was followed overtime, Dr Farkas does not believe that these data can be used to follow the natural course of severity in individual patients. Thus, the rate of and pattern of progression in individual patients remains unknown. The data suggested that cumulative dose, and not necessarily time of exposure, may be a factor in the development of the visual field deficits. From these data, Dr Farkas concluded that the visual deficit may occur within weeks or months of exposure. Study
- *Study R003:* This was a small prospective study examining 25 patients with perimetry and ERGs performed every 3 months. Patients remained in study for a mean of 500 days (range 2 to 988 days). Dr Farkas notes that, although small, this study was valuable in that it was prospective study and therefore less biased. Important conclusions from this study included: 1) the detection of deficits after only 63 days, 2) Visual field deficits occurring in about 1/3 of patients, 3) perimetry appeared insensitive to the detection of mild visual field defects, 4) ERG was even less sensitive then perimetry.
- *Studies 4021 and 4103:* These were small studies. Dr Farkas notes that little additional information can be concluded from these studies.
- *Boston Children's Hospital Study:* This was a retrospective study examining ERGs that supported a positive correlation between exposure and severity of retinal damage.

Dr Farkas also reviewed a number studies pertinent to vigabatrin use in the Infantile Spasm population. These are summarized as follows:

- *Toronto Study:* This study included an examination of 246 IS patients in both a retrospective and prospective fashion. ERGs were conducted every 3 to 6 months. About half had ERGs at baseline. Visual field by confrontation was also performed. The Sponsor concluded that 25% of patients exhibited a sustained visual field abnormality. Because if the limitation in methodology (e.g. insensitivity of ERG and study design issues) Dr Farkas concludes that this can only be considered a lowest value for the potential incidence of the range of abnormality. While the Sponsor wanted to conclude that this study can be used to draw conclusions of the time of onset of visual deficits, failure to progress once vigabatrin was discontinued and the absence of central acuity change, Dr. Farkas convincingly argues that the limitations of the

study do not allow any such conclusions. A major problem in this study is the specificity and sensitivity of the ERG.

- *Westall Group Publication:* Dr Farkas notes that evidence in this paper may indicate that the central retina may be potentially affected as the toxicity progresses. Also concluded from this publication, based upon individual cases, is the insensitivity of ERGs in detecting visual toxicity (as compared to fields), the potential for precipitous decline in visual function even after many years of exposure and the potential for progression after stopping vigabatrin. These conclusions, however, were based upon individual cases and are subject to the inadequacy of the ERG as a tool.
- *Study 0201:* This was a 1 year open-label follow-up study of 210 children on vigabatrin derived from patients in prior studies. Dr Farkas notes that the study supports the association between vigabatrin exposure and retinal damage, but the study cannot be used to obtain more detailed information on the nature of this pathology in this population of patients.

Dr Farkas also examined 519 post-marketing visual deficits, but concluded because of insufficient informtion, little can be gleaned from such reports. Dr Farkas does note 3 isolated reports that may suggest central (macular) involvement.

Some important conclusions made by Dr Farkas include the following:

- *Visual acuity:* While visual acuity (central retinal vision) largely does not appear to be affected some isolated observation suggest the possibility that this may rarely occur.
- *Reversibility:* The data suggests that the lesion is not reversible.
- Latency: There is little clear data as to when the earliest visual deficit may be observed, although cases have demonstrated potential visual loss as early as 2 months.
- *Progression with continued Use:* Progression of visual deficit does occur with continued use. However, the number of patients who experience continued deterioration and the rate of deterioration are not well understood.
- *Progression with Disconnection:* The data suggests that once vigabatrin is discontinued, progression of visual loss ceases. Dr Farkas believes that this conclusion must be tempered with the understanding that damage may wrongly be attributed to age related pathologies.
- *Exposure:* There is a correlation between visual damage and daily/cumulative dose and time of exposure. The data that suggests this, however, may not be particularly clear so as to allow one to conclude what cumulative dose might be considered completely safe.
- *Monitoring of Visual Loss:* Neither Visual Field nor ERGs are perfect ways to monitor visual Damage. Because the rate at which damage progresses may be variable an absolute schedule cannot be devised. Once damage occurs it will be irreversible. The ERGs are a particularly poor way of monitoring, because of their lack of sensitivity and specificity.

CDTL Conclusions on Visual Toxicity

This reviewer concurs with Dr Farkas' conclusion. The visual deficit although mild in some cases can be severe in a substantial total number of patients exposed. For this reason I do not recommend approval in CPS, were there may be other, equally beneficial treatments, without further efficacy studies (see above). Approval in IS is another matter, considering the seriousness of the disorder and the need for a treatment. Approval in any case would require a REMS (described below) and additional studies to better characterize the nature of the lesion.

8. Advisory Committee Meeting

In a desire to obtain additional input from the Neurologic community the division convened an Advisory Committee on 1/7/09 and 1/8/09 with experts in adult and pediatric epilepsy and ophthalmology. The principal issues discussed were as follows: 1) Benefit/Risk of the use of Sabril in the treatment of CPS in adults, in specific regard to visual toxicity 2) The adequacy of the unconventional IS trials in support of an indication for IS in infants, 3) The Benefit/Risk for the use of Sabril in the treatment of IS with regard to visual toxicity and potential central neurotoxicity. Efficacy in CPS was not an issue at these meetings as a concurrence on efficacy was decided in previous reviews by the agency.

The following paraphrases the final minutes regarding the decisions made by the committee on 1/7/09 in reference to the treatment of adults with CPS:

- The majority of the committee agreed that continued treatment results in clinically meaningful loss of vision in some patients (No formal vote taken.)
- The majority of members believed that data to show that the visual defect can be detected before it is clinically meaningful (14 yes, 7 No, 3 Abstain).
- The Committee agreed that the sponsor has not adequately shown that discontinuation of treatment halts the progression of the visual loss. (No formal vote taken.)
- The committee agreed that the sponsor has not adequately shown that vigabatrin does not cause central visual loss. (No formal vote taken.)
- The Committee unanimously agreed that there were conditions (patient population and conditions) under which approval of Sabril for CPS can be made (24 yes, 0 No, 0 Abstain).
- The committee did not agree with the sponsor's definition of "refractory" being failure of only 2 other anticonvulsant drugs. Panel members agreed that it is difficult to determine the appropriate patient population for this drug. Additionally, it was noted that Sabril (vigabatrin) has not been shown to be more effective than other anticonvulsant drugs; additionally, there is no data showing how effective this drug is in refractory patients. However, the committee agreed that no additional effectiveness (comparative) data in the refractory population were

needed prior to approval of Sabril (vigabatrin). The committee concluded that it is difficult to define "refractory" since individual epileptologists may define this differently. The committee agreed that Sabril (vigabatrin) should be reserved for patients with complex partial seizures who are refractory to good trials of several anticonvulsants. (No formal vote taken.)

- The committee agreed that Sabril (vigabatrin) should be made available only under restricted conditions and continued access to the drug should be linked to results of ophthalmologic monitoring. (No formal vote taken.)

- The committee agreed that there should be a requirement for periodic ophthalmologic monitoring and that the sponsor's plan for monitoring is not adequate. The committee recommended the following ophthalmologic monitoring be performed: at baseline (may need several visual field perimetry tests to determine baseline), at 3 months, every 4-6 months thereafter, and for a period (undefined) after discontinuation of Sabril (vigabatrin). (No formal vote was taken.)

- The majority of the committee agreed that no additional data related to the visual loss should be obtained prior to approval of Sabril, but the committee noted that studies of visual loss should be conducted as a post-marketing requirement. (No formal vote taken.)

- The committee agreed that there is no data to address the issue of intramyelinic edema seen in animals and its clinical consequences in adults. They believed that no additional clinical requirements were needed, regarding this findings, before approval. (No formal vote was taken.)

- The committee unanimously voted that Sabril (vigabatrin) be approved for the treatment of refractory complex partial seizures in adults. (24 yes, 0 No, 0 Abstain)

The following paraphrases the final minutes regarding the decisions made by the committee on 1/8/09 in reference to the treatment of children with IS:

- The committee unanimously voted that the sponsor provided sufficient evidence that vigabatrin is efficacious in the treatment of infantile spasms? (25 yes, 0 No, 0 Abstain)

- The committee agreed that the studies indicate that Sabril is efficacious in the cessation of spasms and there is substantial evidence that it can ameliorate the EEG. (No formal vote taken.)

- The majority of the committee did not feel that the studies indicate that Sabril prevents other seizure types later in life. (No formal vote taken.)

- The committee agreed that the sponsor should be required to adequately study (post-approval) whether chronic treatment with vigabatrin provides an additional benefit beyond a brief treatment course. Some committee members proposed that the sponsor should conduct a randomized withdrawal study at some point post-approval. There was discussion regarding the design of a withdrawal study but the committee did not arrive at a consensus regarding the design of such a study. The Biostatisticians commented that data from a patient registry will not be adequate to study this question. (No formal vote taken.)

- The Ophthalmologists on the committee agreed that there is no method to practically and reliably predict or detect the lesion with the tests currently available. Additionally, it was agreed upon that ophthalmologic testing can not detect the visual defects any better than observations by the Pediatric Neurologists evaluating the patient. It was commented that visual defects can occur and can be severe and irreversible; thus, families need to be informed but also cautioned that visual testing may not prevent the occurrence of visual defects.(No formal vote was taken.)

- The committee agreed that Sabril should not be approved for use in any specific subset of patients, but rather be approved for all patients with infantile spasms. Patients who may have pre-existing visual conditions should be cautioned about the adverse effects but Sabril should not be contraindicated in any patient population. The committee also agreed that additional efficacy studies are not needed in any subset of patients. (No formal vote taken.)

- The committee agreed that Sabril (vigabatrin) should only be available under REMS and should be made available only under restricted conditions. The committee recommended that the REMS for the refractory complex partial seizure indication should be different than the REMS for the infantile spasms indication. (No formal vote taken.)

- Regarding the intramyelinic edema identified in animals, the committee noted that the intramyelinic edema seen in animals does not seem to correlate with MRI changes. The committee agreed that no data is available to answer this question. (No formal vote taken.)

- The committee separately considered the issue of neuropil vacuolation observed in young animals and agreed that that no data is available to determine if the phenomena are related to MRI findings in children and of clinical concern. (No formal vote taken.)

- The committee did not recommend that additional safety data should be obtained prior to approval of Sabril. (No formal vote taken.)

- The committee unanimously voted to approve Sabril for the indication of IS (23 yes, 0 No, 0 Abstain, 2 absent).

9. Pediatrics

Complex Partial Seizures

In prior reviews this division has ruled that the present data is adequate to approve adjunctive treatment in adults and not in children.

The division has decided to waive the pediatric study requirement for ages birth to 10 years for a number of reasons:

- Visual toxicity is difficult to monitor in children 10 years of age and less and other drugs are available to treat Complex Partial Seizures. Thus, the risks of Sabril use in this population are clearly outweighed by any benefit.
- Because Sabril is intended only for the adjunctive treatment of *intractable* complex partial seizures, neonatal and early infant patients would not have had complex partial seizures for a sufficient time to establish a diagnosis of intractability.
- Complex partial seizures are difficult to identify as an entity in the very young child.

Pharmacokinetic studies will also need to be performed. Considering risks these should be performed in patients taking medication for therapy as part of the requested efficacy trials.

The Division met with PERC on 2/25/09 who suggested that a single reason be given for waiver and that pharmacokinetic study be performed in patients who are talking Sabril for epilepsy.

This reviewer believes that the studies in older children (>10 years) should only be performed in patients who are truly "highly refractory" to treatment and should be designed in a fashion to allow a determination of superiority to other marketed anticonvulsant treatments not yet tried by the patient.

Infantile Spasms

There is no PREA requirement for IS as this is an orphan indication.

10. Other Relevant Regulatory Issues

CSS has concluded that vigabatrin possesses no abuse potential.

Three investigators for IS efficacy were inspected in study 1A. In total, according the inspector, 4 significant protocol violations were observed (2 for dosing and 2 for recruiting). The inspector, Dr. Sheryl Gunther, found no reason to question the general integrity of the study. Following the examination of these 4 cases, this reviewer does not believe they significantly altered the studies final conclusions nor do they put in question the integrity of the study.

11. Labeling

The reader is referred to the label.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Infantile Spasms: This reviewer recommends that Sabril be approved for IS. While the data does not meet the typical standards of the FDA, it is relatively strong. Such a drug would be important considering the fact that there are no drugs presently labeled for the treatment. While there is a definite risk, the benefits of treatment of this serious condition outweigh the risk when combined with an adequate REMS program (see below). The review team concurs with this decision as does the Advisory Committee who has voted unanimously to approve the drug for this indication.

Complex Partial Seizures: This reviewer cannot recommend approval of Sabril for CPS. I do not believe the benefit of seizure control is outweighed by serious irreversible damage to the vision. A case for approval could be made if this drugs is superior to the multiple other drugs approved for this indication, but the Sponsor has not provided a convincing argument for this. Before approval this reviewer would recommend that a study be performed to demonstrate the superiority of this drug to other available therapies. The study might consist of a randomized, double-blind crossover study in adults and children (>10 year of age) with refractory complex partial seizures. Sabril will be compared to a standard antiepileptic drug for treatment of refractory complex partial seizures. Selection of patients can consist of patients who have not received a trial of Sabril and any other marketed anticonvulsant. Two major phases of the cross over can be compared: i.e. the addition of Sabril vs addition of another anticonvulsant for which the patient is naive to. The trial will be designed to demonstrate superiority of Sabril over the alternative antiepileptic drug active control arm.

It should be noted that the Advisory Committee does not concur with this decision and voted unanimously to approve Sabril for this indication. They believe that the problem of benefit/risk can be dealt with a strict REMS program (see below).

Recommendation for Postmarketing Risk Management Activities

There is concurrence by the division and the advisory committee that REMS will be required. Some of the salient aspects of the REMS will be as follows:

- Visual function toxicity will be included as a Boxed Warning.
- MRI changes in infants will be included as a Warning.
- Because of visual toxicity all patients will be enrolled in a registry.
- Allowance of drug distribution through a specialty pharmacy.

- A requirement to monitor visual function in both adults and children.[1] This should include both visual field and refracted acuity. No drug will be administered without such monitoring. The exact type of testing may need to be adjusted to the circumstance and the ability of the patients. The Advisory Committee recommended 4 to 6 months. Because there is inadequate data describing the course and rate of visual loss the ophthalmic experts in the division are recommending visual monitoring every 3 months. Monitoring should also occur at least one time after drug discontinuation. This may not only allow the collection of informtion of any progression following termination but also document any serious final field loss for which the patient may need to aware of in order to understand functional limitations (e.g. driving).
- Required information collected in the pediatric population should include MRI, but as the data of the significance of these changes is unclear and MRI evaluation in infants possess some risk (use of sedation) periodic MRIs will not be recommended. The collection of data on potential neurologic events associated with MRI may also be useful.
- A MedGuide will be distributed that will describe visual changes, MRI findings and suicidality. The latter is considered as anticonvulsant class labeling.

Recommendation for other Postmarketing Study Requirements/Commitments

The following post-marketing requirements should be requested:

- There is concurrence amongst all members of the review team that the Sponsor will be asked to use registry data to conduct cohort analysis to evaluate dosing associated with development of visual lesions, timing and risk of the development of concentric field loss, the risk of visual acuity deficits, and potential for progression of the lesions if therapy is continued and once therapy has been discontinued. This study could only be carried out in adults where accurate visual monitoring is possible, but data would be pertinent to the infantile spasm indication.
- There is concurrence amongst the review division, and a recommendation by the Advisory Committee that a randomized, withdrawal study in infants treated with Sabril for Infantile Spasms be performed. The initial cohort of infants responding to Sabril would be randomized to withdraw therapy after a fixed extended period of exposure (e.g. 9 months) or to continue therapy. The incidence of relapse for the two arms will be compared. The duration of therapy for successive cohorts would be progressively shortened to determine the minimal duration of therapy required for sustained remission of spasms.

[1] There was some expression in the Advisory Committee that monitoring of children could be carried out by the treating Neurologist, but the division's ophthalmological experts (Drs Farkas and Chambers) believe that the examination should be performed by someone with expertise in ophthalmological evaluation.

- The pharmacokinetic reviewer is recommending an open label clinical study to assess the single and multiple dose (at steady state) pharmacokinetics in infants with infantile spasms that are 1-5 months of age at a clinically relevant dose.
- A study is being requested that studies the effect of taurine treatment on vigabatrin-induced retinal toxicity in pigmented animals. This may require exposure to high intensity light with concomitant mydriasis induction. If this is successful, the study should be conducted in both albino and pigmented animals. The final study protocol should be submitted to the Agency for comment prior to study initiation. If these data indicate replicate published data, additional clinical studies will be requested.

The following post-marketing commitments should be recommended:

- The pharmacokinetics reviewer recommends an *in vitro* study to evaluate the ability of Sabril to induce CYP1A2 and CYP3A4 using methods described in the FDA Guidance for Industry: Drug interaction studies: Study Design, Data Analysis and Implications for Dosing and Labeling.

As this reviewer suspects the division will be moving toward an approval in CPS, the above described superiority study should be requested as a PMC.

This reviewer would also recommend expedited reports be provided for all cases of potential neuropathy. The Sponsor should make every effort to document a diagnosis of neuropathy with special testing, including nerve conduction studies and electromyogram, and obtain follow-up. An analysis of post-marketing neuropathy cases should be included in all quarterly safety reports." Similar pharmacovigilance should be added reagrding MRI changes in patients with IS and any clinically associated changes.

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/s/

Norman Hershkowitz
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