CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-006

OFFICE DIRECTOR MEMO

Office Director's Memo to File

Date: August 21, 2009

From: Robert Temple, MD, Director, ODE-I

Subject: **Office Director's Decisional Memo**

NDA: 20-427: Complex partial seizures
22-006: Infantile Spasms

Drug Name: Sabril (vigabatrin), Oration Pharmaceuticals Oral solution (infantile spasm), and Tablet (complex partial seizures

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I. Introduction/Background

Vigabatrin (Sabril) is intended for two distinct uses (and with 2 NDAs), infantile spasm (IS), a disease of very young children with no approved treatment (ACTH is used and is thought to be effective but has no approved application), and complex partial seizures (CPS) in adults. The adult claim has a long history. It was first marketed in Europe in 1989 and there was an initial NDA submission (NDA 20-427) in 1994, with an NA letter for various deficiencies in April 1995. **The sponsor's May 1997 response to the NA letter led to an approvable letter in November 1997** for CPS, but with a caveat that the drug would be second line because of concerns related to **IME (intramyelinic edema, a finding in rodents). The sponsor's April 1998 response to the** approvable letter proposed last resort use in CPS because by that time the visual field defect problem had become recognized (almost 10 years after initial European marketing and 18 years after the initial 1980 IND), but the Agency sent another NA letter in Oct 1998 because the risk was considered insufficiently characterized. Finally, in 12/28/07, the most recent applicant response, now being considered, was submitted. The resubmission of the NDA for CPS was accompanied by a resubmission (following our April 5, 2007 refusal to file letter, of NDA 22-006 for IS.

The effectiveness of vigabatrin in CPS as adjunctive therapy is relatively straightforward; IS is more complicated as there is little prior experience with treatment for this use. Surrounding consideration of all uses is a significant concern about ophthalmic toxicity, most strikingly manifested as progressive loss of peripheral vision in a large fraction of patients, but with potentially significant loss of visual acuity as well.

This has led to a REMS that includes a Medguide, elements to assure safe use (limited distribution, registration of prescribers and patients, and steps to assure ophthalmic monitoring and monitoring for benefit so that it can be stopped if not useful), labeling with a boxed warning and a second line indication for refractory CPS (adjunctive therapy in patients who have responded inadequately to several alternative treatments). Apart from ophthalmic toxicity, a

further safety concern is the possibility of neurotoxicity, with the finding of a novel variant of a long-recognized animal toxicology finding of intramyelinic edema (IME) and, more recently, MRI changes seen in treated infants (about 20% vs about 4% in untreated patients). To date there have been no clear consequences of the MRI changes and the abnormality usually resolves with discontinuation and, in some case, even with continued use.

Dr. Katz's Division Director memo and Dr. Hershkowitz's CDTL review describe in detail the basis for their conclusions about the approvability of vigabatrin and enumerate the many reviewers involved in the evaluation of vigabatrin and indicate how clinical reviews by Drs. Sheriden (IS), Boehm, Farkas (ophthalmic data), and Yasuda were all critical in the evaluation of risk and benefit. I will try not to repeat the thoughtful discussions already in place but will comment on several critical issues. I note that there have been two internal disagreements, both discussed at length by Dr. Katz. Dr. Ed Fisher, primary pharm-tox reviewer, recommended against approval for IS because of the somewhat uncharacteristic (involving gray matter in addition to the usually involved white matter) intramyelinic edema (IME) seen in juvenile rats. Dr. Lois Freed, supervisory pharmacologist, believed approval was nonetheless appropriate. Dr. Hershkowitz, CDTL, supported approval for IS but not for CPS, even for refractory patients, believing there was insufficient evidence to show effectiveness in truly refractory patients and therefore insufficient benefit to overcome concerns about ophthalmic effects. Dr. Katz did not agree. These issues will be discussed further below.

II. Effectiveness

A. Adults, PCS

Effectiveness was shown in 2 double-blind well-controlled studies of similar design, studies 24 and 25, very similar except for a longer (6 week vs 4 week) titration period in study 25. Study 24 evaluated a 3 g/day dose while study 25 examined 1, 3, and 6 g/day. The baseline observation periods and maintenance periods were each 12 weeks in both studies, (although only the last 8 weeks of baseline served as the comparator for the 12 week maintenance period) and the primary endpoint was median monthly seizure frequency. An additional endpoint of interest, however, was proportion of patients with at least 50% reduction. Results were favorable for both all seizures and for CPS seizures.

1. Study 24

Study 024 N = 183

All seizures – median monthly

	N	Baseline	Final	P-value
V	92	8.3	5.3	
placebo	90	8.3	7.5	0.001-0.0002

CPS only-median monthly

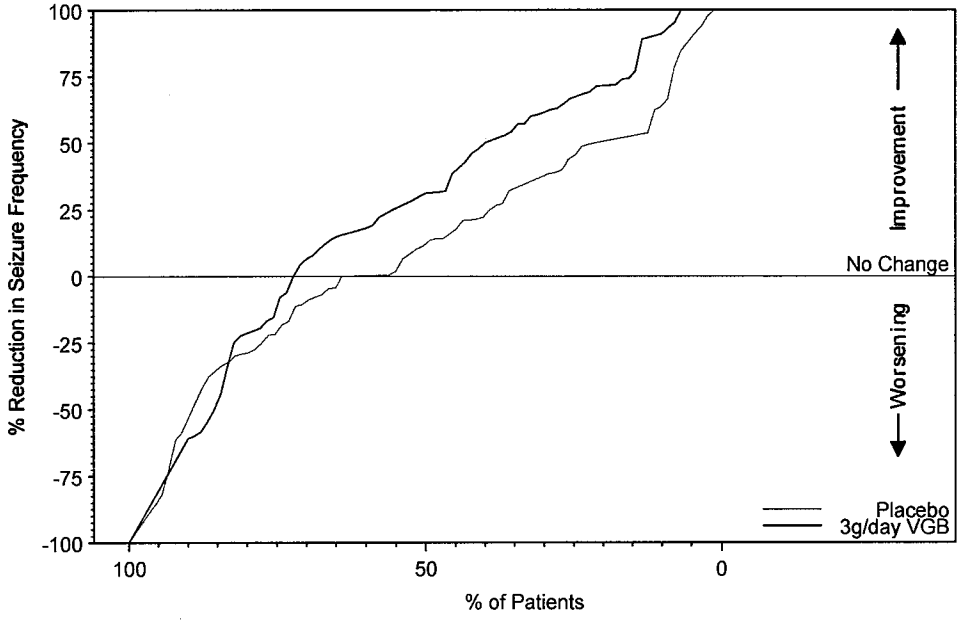
	N	Baseline	Final	P-value
V	84	8.5	5.0	
placebo	89	8.0	7.5	< 0.0006

Proportion with 50% reduction

	N	%	
V	92	43	
placebo	90	19	< 0.001

The last analysis seems of particular interest. Use of vigabatrin is reasonable only if there is a meaningful effect, and a 50% reduction in seizure rate (an effect seen in 43% of vigabatrin patients and 19% of placebo patients) seems to meet that test. A more complete description of response is shown in labeling, in a figure reproduced here.

Figure 2: Percent Reduction from Baseline in Seizure Frequency



2. Study 25

Study 025 N = 174

All seizures – median monthly

	N	Baseline	Final	P-value
V 1g	45	8.5	7.7	NS
V 3g	43	8.0	3.7	0.0001
V 6g	41	9.0	4.5	0.0001
placebo	45	9.0	8.8	----

CPS only – median monthly

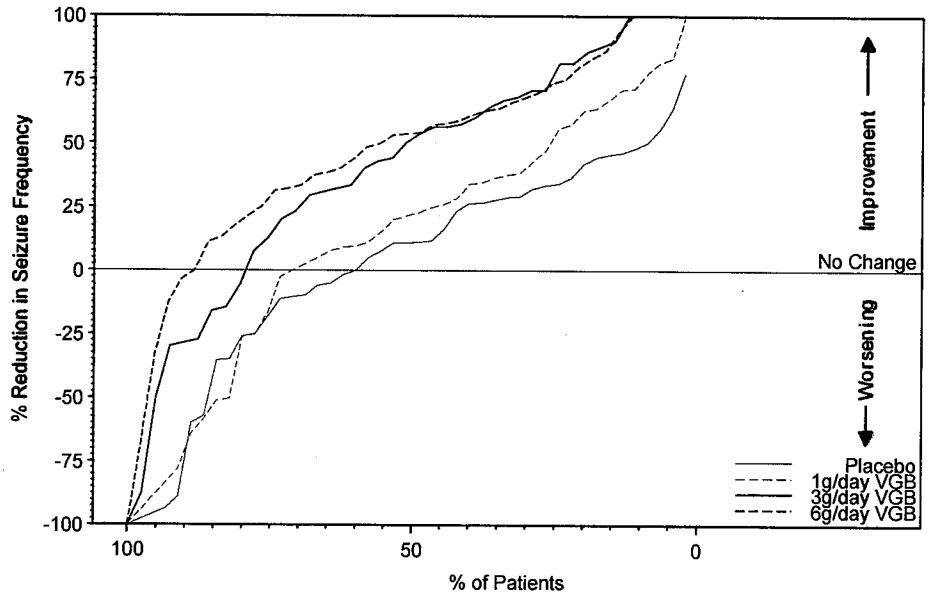
	N	Baseline	Final	p-value
V 1g	45	7.5	7.0	NS
V 3g	43	7.0	3.5	0.001
V 6g	39	8.5	3.5	0.0001
placebo	44	8.8	8.3	---------

Proportion with 50% reduction

	N	%	p-value
V 1g	45	24%	0.02
V 3g	43	51%	< 0.0001
V 6g	41	54%	< 0.0001
placebo	45	7%	--------

Again, many patients had a very substantial reduction in seizures. Labeling also shows cumulative response rates.

Figure 1: Percent Reduction from Baseline in Seizure Frequency



The 6 gm dose shows little, if any, increase in effect and has more adverse effects. Labeling is clear in not recommending it.

B. Infantile Spasm
There were 3 studies contributing to the evidence of effectiveness in IS; none wholly problem free.

Study 1A randomized patients to low (18-36 mg/kg/d) or high (100-148 mg/kg/d) doses of vigabatrin. Patients were titrated for the 1st 7 days, then left on treatment for 7 days. If the patient became spasm free within those 14 days, 7 days of a constant dose were given. If caregiver (who was blinded) considered the patient spasm free this was to be confirmed by a blindly interpreted video EEG within 3 days. The effectiveness measure was the number of patients who **were confirmed "spasm-free."**

One difficulty was that sample size "evolved," with patients accumulating from 44 all the way to 250, with no entirely specified plan, and FDA-determined statistical significance improved with increased study size. As Dr. Hershkowitz notes, however, the setting was one of a compassionate use goal and sample size was increased at a time the study was thought (in error, as it turned out, because response rate was incorrectly calculated) to be positive (indicating it was not improved to improve results). It should be noted also (Katz review, p 11), that the spasm-free rates (and the difference) were fairly similar for all proper analyses, 16% vs 7% ($p = 0.0375$) at the final analysis; the $p = 0.0375$ was based on a Pearson chi-squared **analysis, while a Fisher's Exact test gave =0.0544. As all reviewers note, the planned 3 day** window for EEG was often unattainable and was in retrospect unreasonable. When a window of > 3 days for the confirmatory EEG was allowed (to make verification possible in more patients),

the analysis was stronger still: with a 9 day limit for EEG confirmation, still in people considered spasm free for 7 days and up until the time of EEG, the responder rate was 26% on the high dose vs 11% on low dose (p = 0.0025). An open label follow-up (unblinded) showed a 12% relapse rate on the high dose vs 46% on low dose, an encouraging finding but, for reasons explained by Drs. Sheridan and Hershkowitz, not definitive in the unblinded, therapy-changing setting of the follow-up. Reviewers found the study untypical, in a number of ways, of studies we typically rely on, but nonetheless persuasive.

Study WO19 was a double-blind placebo-controlled monotherapy study in 40 patients. After a 2-3 day baseline to identify the optimal 2-hour period to conduct video/EEG monitoring, there was a 5 day treatment period (50-150 mg/kg as needed to gain an adequate response). The planned analysis of 2 hour periods showed a favorable trend but there were few spasms and considerable variability, so that a 24 hour value was also assessed (a planned secondary endpoint). Results (reduction in spasms from baseline) are shown in the following table:

	% reduction	
	2 hours	24 hours
Vigabatrin	54	69
Placebo	40.5	17
P value	0.56	0.03

Considering an endpoint similar to the study 1A endpoint, 35% of vigabatrin and 10% of placebo-treated patients became spasm free on day 5 of treatment; considering patients who attained ≤ 1 spasm per day, rates were 45% vs 15% (p = 0.036). Thus, although the planned primary endpoint (poorly planned, as it happens) did not support effectiveness, a wide range of more sensible secondary endpoints did so.

Study FRO3, in patients with IS and tuberous sclerosis (who appeared to respond particularly well in study 1A) was small (n=23) but provided further support. It compared vigabatrin 150 mg/kg/day with hydrocortisone (15 mg/kg/day) in previously untreated patients. Patients were randomized to each treatment for one month and crossed over if spasms did not completely disappear and were then treated for another month. The 11 patients randomized to vigabatrin all were spasm free and none crossed over. In contrast, 7 of 11 analyzed patients given hydrocortisone crossed over (i.e., 4/11 were spasm free). The 7 who crossed over all became spasm free. A p-value for the comparison was p=0.001; note, however, that the study was open label.

III. Safety

There are two principal safety concerns with vigabatrin: 1) visual field defects and some potential for damage to central visual acuity 2) concerns about neurological injury raised by animal data and by MRI data in pediatric patients.

A. Visual Field Defeats

These are discussed thoroughly in Dr. Farkas' review of 7/18/2009 and by Drs. Katz and Hershkowitz. As all reviews and commenters note, the data on visual field defects are imperfect, with almost all studies planned after the fact, leaving completeness of the assessment of the exposed population somewhat uncertain and the timing of injury, especially early in treatment,

not fully defined. In addition, the studies used a wide variety of measurements. Two of the studies, however, in my view provide a reasonable sense of what the risk is.

1. **The "pooled cohort" study**
   From among a group of 403 vigabatrin-exposed patients (and 112 unexposed) in 14 phase 2-4 studies in Finland, Japan, the US, UK, Spain, Germany, and Australia, 367 patients were followed and 335 had usable visual fields. The duration of exposure averaged about 3 years and each patient was examined once unless the result was considered unreliable. About 1/3 (31%) of all vigabatrin exposed patients had a visual field defect (VFD), as did about 36% of patients with > 3 years exposure. Severity ranged from a localized nasal defect of 30-40% to severe concentric constriction, with about 1/3 **of affected patients having defects considered "profound." No patients not exposed to** vigabatrin had a defect, probably because only relatively severe defects were called positive findings. Oddly, in an additional 112 patients added later, defects were found in only 6%; giving an overall rate for 454 of about 25%. The reason for this decrease in rate is unclear.

   VFD severity was not clearly related to duration or dose but a significant fraction of VFD's appeared promptly, within a few months, with peak incidence at one year; over time, however, prevalence continued to rise slowly to about 40% at 7-8 years. The rate in women was about half that in men.

2. Study 4020
   I will not describe this in detail, as entry criteria, follow up, and most aspects of the trial are harder to discern, but would note that it too found a rate of about 25% in adults after mean treatment of 4.2 years.

3. Study R003
   This was a prospective observational study in 25 Canadian subjects, observing patients **every 3 months with perimetry and electro-retinography. VFD's were seen in about 1/3 of** patients after < 2 years of treatment, with one VFD manifested at 63 days. It appeared **that defects were generally not detected until at least "moderate" in severity (i.e., to within** 20-25 degrees of fixation).

The problem with assessment of VFD in children is that young patients cannot take visual field tests and electro-retinograpy is not a reliable monitoring approach. The limitations of the pediatric data, especially ERG (electroretinography) are well-discussed by Drs. Katz and Farkas. ERG abnormalities were seen in at least 25% of children but there is a fair rate of such abnormalities **in children not given vigabatrin. Clearly, VFD's and** visual problems generally will be very difficult to monitor in children, especially early lesions.

In addition to the most prominent visual problem, VFD, there is also concern with possible effects on visual acuity. There have been cases of markedly reduced acuity, but as Dr. Farkas points out, these are hard to distinguish from other causes such as glaucoma or macular degeneration. **There is, as Dr. Farkas notes, "meaningful reassurance" from the fact that 2 decades of** marketing in some 350,000 exposed patients have yielded very few cases of severe visual deterioration after stopping the drug. Such loss of acuity, unlike PFD, would surely be noted

(although, again, it could be attributed to other causes). It thus appears that major decreases in central vision, if they occur, are relatively rare, although lesser decreases are not. This also suggests that monitoring at 3 month intervals, as will be called for in the REMS, should prevent serious loss of visual acuity as well as most cases of very severe VFD's. Monitoring in the required registry should assess this definitively. As VFDs can occur rapidly, however, monitoring will not prevent them. It is hoped that cessation of treatment in patients who develop VFD's will minimize the severity of VFD's although it is likely that some degree of progression can occur even after drug is stopped.

Dr. Farkas' conclusions, briefly, are for adults:

1. That visual acuity is only rarely seriously affected and can probably be avoided if patients are monitored for PFDs, but mild to moderate loss may occur (20/25-20/50), consistent with observable damage in the central retina.

2. That PFD lesions can occur rapidly (2 months in one case), but have a peak appearance rate at about one year, are not reversible and progress with continued use, although perhaps slowly in most cases, to eventually affect 30-50% of people.

3. That PFD generally seems not to progress in most patients after vigabatrin is stopped, although there are some late worsenings, and available data leave some uncertainty about the increase of the defect and the extent of progression after stopping the drug. There are clearly some patients who develop severe impairment, which can affect the ability to engage in common daily activities.

4. That monitoring will not prevent VFDs but may prevent severe loss; the variable rate of progression leaves some uncertainty in this. There appear to be some patients who do not perform perimetry well enough for the test to be useful.

B. Neurologic Injury
Like many GABA – increasing drugs, vigabatrin in adult animals causes IME, intramyelinic edema, but this, although a significant concern in the past, has not prevented development of the drugs. Vigabatrin, however, causes a somewhat different lesion in juvenile rats, with lesions in gray matter (IME ordinarily involves white matter) in addition to the lesions in white matter. This led Dr. Fisher to recommend non-approval. His supervisor, Dr. Freed, however, did not concur. Dr. Larry Schmued, an expert neuropathologist from the NCTR, concluded that the lesions may indeed have involved gray matter, where there are primarily cells, dendrites, and axons, not myelinated fibers, a difference from IME, and could represent cell death, although this was not certain.

Possibly (but by no means certainly) related to IME are recently described MRI lesions in pediatric patients. Review of previous MRI studies in adults, which had been considered not to show lesions, is described in Dr. Katz's and Dr. Hershkowitz's memos; these MRIs were carried out to evaluate the long-standing concern with the pre-clinical IME findings. The new blinded analysis of over 400 MRIs from previous studies found no significant difference in rate of abnormalities between patients treated with vigabatrin (10.8%) and those given placebo (8.0%). Examination of about 200 infant patients at 10 North American institutions, however, did show an

increase in MRI lesions (36%) vs non-vigabatrin exposed patients (5.9%), but no associated neurological symptoms have been reported. Reviewers generally, and the advisory committee, felt the MRI lesions needed to be noted in labeling but should not bar approval for IS, given the lack of other therapy and the absence of apparent neurological sequelae, albeit in a difficult-to-assess population.

C. Other Safety Concerns
Drs. Boehm and Yasuda describe the safety data in some 4000 patients, almost 3500 treated for at least 6 months, over 2700 for at least one year, and over 400 treated for over 5 years. About 1100 and 600 patients were exposed to 3-4 g/day (the recommended adult dose is 3 g/day) for at least 6 and 12 months, respectively. There is, of course, also a 2 decade experience in Europe. Vigabatrin causes somnolence, dizziness, diplopia, typical of many AEDs, as well as:

1. Small dose-related decreases in Hg and Hct (about 0.44% in Hct at 3 g)
2. Decreased transaminases, a finding of no known significance.
3. Weight gain, about 3-4 kg vs 1.5-2 kg on placebo in controlled seizure trials, with some 17% (vs 8.5% on placebo) gaining at least 7% of baseline weight.
4. Peripheral edema, dose-related (0.23/100 patient years at 5 g/day vs 0.06 on placebo), but without apparent CV, renal, hepatic, or pulmonary signs of symptoms.
5. Depression, which was not increased in studies, but labeling will bear the standard AED language.

IV. Risk/benefit considerations and Risk Management

A. Risk/Benefit
There is uniform agreement by all clinical reviewers, as well as the Peripheral and Central Nervous System Advisory Committee (PCNS), who met on Jan 7-8, voting 23-0 to recommend approval, that vigabatrin should be available for the treatment of IS, a condition with no approved **treatment, despite concern with the drug's visual effects, which even with monitoring, will not be** prevented. It will be approved, as the PCNS agreed, only under the REMS conditions that will be described below and there will be post-marketing requirements for several studies to evaluate needed duration of treatment. Drs. Katz and Hershkowitz have described the PCNS Committee discussion in more detail.

Although there is clearly concern about the MRI findings and juvenile rat toxicity, which is probably different from the IME commonly seen with other AEDs, Drs. Katz and Hershkowitz explain why they believe this should not interfere with approval and, as noted, Dr. Freed concurs. There is considerable exposure of the IS population, so far with no evidence of neurotoxicity, but in a population that is clearly difficult to evaluate for such toxicity, given the high rate of pre-existing disease. As part of the REMS, patients will be closely watched for neurological effects.

The PCNS A.C. (24-0) and Dr. Katz (his reasons are well described in the Division Director Overview memo) support approval of vigabatrin in CPS and I concur. Dr. Hershkowitz had two principal reservations: 1) the ophthalmic toxicity can be serious and cannot be wholly avoided, **even with careful monitoring. 2) we don't really know how refractory the patients were and** recently approved drugs were unavailable for these older studies.

There is no doubt the visual loss is important. The lack of more than a few reports of severe loss of acuity in trials and in considerable marketing experience is somewhat reassuring, but it is noteworthy that the loss of peripheral vision, which at least in some cases is surely obvious, was not appreciated for almost a decade after European marketing and was not detected in early trials, obvious as it may seem in retrospect. The distribution and monitoring system required under the REMS, however, will assure detection of such events and will almost certainly minimize the more serious ones.

I am very sympathetic to the second concern. I have long advocated more attempts to actually compare drugs for refractory disease to alternatives and, in particular, to do studies in "non-responders," where patients are randomized to the new drug and to the drug they previously failed, but there are several arguments against waiting for such data in this case. First, if the fraction of people who respond only to vigabatrin is fairly small, detection would be extraordinarily difficult even if there were in fact a population that benefited uniquely. Second, AED's differ considerably in mechanism, so that differential responsiveness is a priori more probable than it is within a class of pharmacologically similar drugs. Third, the REMS will make use of vigabatrin significantly more difficult than use of any other AED, and will assure informed prescribers and patients, so that there is every reason to believe only truly refractory patients will be given it. The REMS will also assure ophthalmologic monitoring. Fourth, the effect size is fairly large and includes many people with meaningful (50% or more) reductions in seizure rate, again a reason for optimism. Finally, labeling is very clear in urging that the drug be stopped if it does not provide "substantial clinical benefit."

Approval is contingent on the conduct of several post-marketing studies:

1. Refractory partial complex seizures
a. Deferred Controlled Trial in 10-16 year olds to evaluate its safety and effectiveness; use in younger children is considered unacceptably risky because visual toxicity is difficult to monitor, so that the PREA requirement is waived for this group.

b. Analysis of the REMS – required registry
Registry to follow development and progression of visual lesions, both of concentric field loss and visual acuity, both during and after therapy.

c. An animal study examining the protective effect of taurine on vigabatrin-induced retinal damage in rodents.

d. An in vitro study to examine the ability of vigabatrin to induce CYP 1A2 and CYP 3A4.

2. IS
a. A toxicology study in the juvenile rat examining the potential for vigabatrin to produce neuronal damage.
b. A juvenile animal toxicity study in a non-rodent species.
c. A clinical trial to assess the single and multiple dose (at steady state) pharmacokinetics of viagabatrin at clinically relevant doses in infants with IS who are 1-5 months of age.
d. There is, in addition, a post-marketing commitment to conduct a trial in IS to characterize the minimum duration of therapy needed for sustained suppression of spasms.

B. Risk Management
The REMS will have many elements beyond physician labeling. Labeling will, however, be very important.

1. Labeling
In both Highlights and the full PI, concern about vision loss and the need for monitoring is very prominent.

a. Refractory CPS
Labeling is very cautious because of the serious risk/benefit consideration that should go into every use of vigabatrin.

- Highlights have a boxed warning about progressive and permanent bilateral concentric visual field constriction in a high percentage of patients, noting relation of risk to dose and duration, emphasizing need for monitoring, and noting that no dose is known to be free of risk.
- Highlights note the restricted distribution.
- Highlights note drug is indicated only for patients who have responded inadequately to several alternatives.
- Full labeling has a very detailed Boxed Warning about vision loss, again emphasizing the nature of visual loss, need for vision testing, need to be sure there is a benefit before continuing beyond 3 months and the restricted distribution.

WARNING: VISION LOSS

- SABRIL causes permanent bilateral concentric visual field constriction in 30 percent or more of patients that ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability. In some cases, SABRIL also can damage the central retina and may decrease visual acuity.
- The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years
- The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss
- Vision testing at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy is required for adults on SABRIL. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy. Once detected, vision loss due to SABRIL is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.
- It is possible that vision loss can worsen despite discontinuation of SABRIL
- Because of the risk of vision loss, SABRIL should be withdrawn from patients who fail to show substantial clinical benefit within 3 months of initiation, or sooner if treatment failure becomes obvious. Patient response to and continued need for SABRIL should be periodically reassessed.

- Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient, can still adversely affect function.
- SABRIL should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from SABRIL has not been well-characterized, but is likely adverse.
- SABRIL should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks
- The lowest dose and shortest exposure to SABRIL should be used that is consistent with clinical objectives

Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program called SHARE, by calling 1-888-45-SHARE. Only prescribers and pharmacies registered with SHARE may prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE [*see* WARNINGS AND PRECAUTIONS, Distribution Program for SABRIL (5.2)].

- Labeling also has a detailed description of needed ophthalmic monitoring.
- Labeling describes the SHARE program, limiting prescribing and distribution to enrolled prescribers and pharmacies, including prescriber agreement to:
  - Enroll all patients in SHARE
  - Review the Medguide with every patient and educate patients on risks
  - Order and review visual testing at initiation and every 3 months
  - Remove patients from therapy if they do not experience meaningful reduction in seizures
  - Remove patients who do not comply with program requirements.
- Labeling notes the MRI abnormalities in some infants, and describes animal toxicity (intramyelinic edema and other abnormalities).
- Labeling notes, in Warning and Precautions, suicidality risk (all AEDs), anemia, somnolence, fatigue, peripheral neuropathy, weight gain, and edema.

b. IS

Labeling elements are similar to the adult CPS labeling, with essentially identical Highlights and a Vision Loss Box Warning modified only slightly to reflect the different population. Other critical parts are essentially the same.

WARNING: VISION LOSS

- SABRIL causes permanent vision loss in infants, children and adults. Because assessing vision loss is difficult in children, the frequency and extent of vision loss in infants and children is poorly characterized. For this reason, the data described below is primarily based on the adult experience.

- In adults, SABRIL causes permanent bilateral concentric visual field constriction in 30 percent or more of patients that ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability. In some cases, SABRIL also can damage the central retina and may decrease visual acuity.
- The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years
- The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss
- It is possible that vision loss can worsen despite discontinuing SABRIL
- Because of the risk of vision loss, SABRIL should be withdrawn from patients with infantile spasms who fail to show substantial clinical benefit within 2 to 4 weeks of initiation, or sooner if treatment failure becomes obvious. Patient response to and continued need for SABRIL should be periodically reassessed.
- In infants and children, vision loss may not be detected until it is severe. Nonetheless, vision should be assessed to the extent possible at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy. Once detected, vision loss due to SABRIL is not reversible. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy
- Symptoms of vision loss from SABRIL are unlikely to be recognized by the parent or caregiver before vision loss is severe. Vision loss of milder severity, although unrecognized by the caregiver, may still adversely affect function.
- SABRIL should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from SABRIL has not been well-characterized, but is likely adverse.
- SABRIL should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks
- The lowest dose and shortest exposure to SABRIL should be used that is consistent with clinical objectives
- The possibility that vision loss from SABRIL may be more common, more severe or have more severe functional consequences in infants and children than in adults cannot be excluded

Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program called SHARE, by calling 1-888-45-SHARE. Only prescribers and pharmacies registered with SHARE may prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE [see WARNINGS AND PRECAUTIONS, Distribution Program for SABRIL (5.2)].

2. REMS

a. Medguide will both 1) inform patients of vigabatrin's significant risks (visual impairment) so that these can be weighed against potential benefits and 2) help ensure steps (visual monitoring) are taken to minimize those risks and ensure that vigabatrin is discontinued in patients who do not respond.

b. Elements to assure safe use (ETASU) include making vigabatrin available only through a restricted distribution system (SHARE) intended to assure informed patients/caregivers, appropriate visual monitoring, and discontinuation of treatment in the absence of substantial clinical benefit. Only prescribers and pharmacies registered with the program will be able to prescribe and distribute vigabatrin and Sabril can be dispensed only to enrolled patients who meet all conditions of SHARE. All patients will be entered into a registry that will characterize prescribers and patients, and collect periodic ophthalmic assessment data and response rate data. There is a detailed REMS assessment plan.

To enroll, prescribers must understand the risks of vigabatrin and complete the SHARE Prescriber Enrollment and Agreement form indicating their agreement to:

- Enroll all patients in SHARE
- Review the SABRIL Medication Guide with every caregiver
- Educate caregiver(s) on the risks of SABRIL, including the risk of vision loss [see BOXED WARNING: VISION LOSS]
- Arrange for visual field and retinal exam by an expert examiner and review visual evaluation prior to initiation of SABRIL treatment and every 3 months during therapy
- Remove patients from SABRIL therapy if the patients do not experience a meaningful reduction in seizures
- Counsel caregiver(s) who fail to comply with the program requirements
- Remove patients from SABRIL therapy whose caregiver(s) fail to comply with the program requirements after appropriate counseling

Patients/caregivers will sign a Sabril agreement form indicating that they have read the Medguide, understand the intended use of vigabatrin and its risks and authorize treatment.

There is also a required communication plan that will be used during product launch and for 3 years. It is focused on vision loss, the IME annual findings and MRI signal.

The overall goals of the REMS are to

1. Reduce the risk of vision loss while delivering the benefits of vigabatrin
2. Ensure that all patients receive baseline ophthalmic evaluation within 2-4 weeks of initiation.
3. Discontinue vigabatrin if there is inadequate clinical responders.
4. Detect vision loss as early as possible.
5. Ensure regular vision monitoring to allow ongoing risk-benefit assessment.
6. To be sure parents or guardians are aware of the visual risks as well as risks of suicidality.

V. Conclusions

Vigabatrin represents an important new treatment for infantile spasms and an effective adjunctive treatment for CPS. Because of its ophthalmic toxicity it is subject to a REMS with a limited distribution arrangement, steps to assure appropriate communication with patients and caregivers and appropriate monitoring, a registry that will allow assessment of ophthalmic outcomes and physician behavior, and planned communications. Labeling and a Medguide identify problems and needed monitoring. The REMS assessment will assess REMS performance but there is good reason to expect the protections in place to allow use of a valuable agent in informed patients (or with informed caregivers) and to control risk.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
MF 20427	ORIG 1	(b) (4)	
NDA 22006	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

APRILE BLOUNT
08/21/2009

ROBERT TEMPLE
08/21/2009