

## CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
Application Number(s)	NDA 20427 S-011/S-012 (tablet) NDA 22006 S-012/S-013 (oral solution)

Priority or Standard	Priority
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Reviewer Name(s)	Philip H. Sheridan, M.D.
Review Completion Date	September 27, 2013

Established Name	Vigabatrin
(Proposed) Trade Name	Sabril
Therapeutic Class	Anticonvulsant
Applicant	Lundbeck Inc.

Formulation(s)	Tablet Sachet for Oral Solution
Dosing Regimen	BID
Indication(s)	Complex Partial Seizures Infantile Spasms
Intended Population(s)	Adult and Pediatric

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

Approval of pediatric indication (age 10 years and older) for refractory complex partial seizures.

Inclusion of results of the Canadian Pediatric Epilepsy Network (CPEN) study in sections 8.4 (Pediatric Use) and 14 (Clinical Studies) of labeling to guide duration of therapy for infantile spasms (IS).

Approval of CBE-0 to include “Stevens Johnson and Toxic Epidermal Necrolysis” under section 6.2 (Post Marketing Experience) in labeling

Merging and updating of the two labeling documents for Sabril tablets and Sabril oral solution into a single labeling document

### **1.2 Risk Benefit Assessment**

#### **Refractory Complex Seizures in Pediatric Patients Age 10 Years and Above**

Although several antiepileptic drugs (AEDs) have been approved for treatment of complex partial seizures (CPS) in children, these seizures are often refractory to available drugs with up to 30% of pediatric patients not achieving acceptable seizure control. The rate of mortality in individuals with epilepsy is 2 to 3 times that of the general population and most deaths are due to the underlying cause of epilepsy. Other sources of mortality are Sudden and Unexplained Death in Epilepsy (SUDEP) and suicide.

Vigabatrin has proved useful in controlling refractory complex partial seizures (rCPS) in adults.

Vigabatrin is also being used off-label to treat pediatric patients age 10 and above with rCPS. As of August 22, 2012, 33.2% (395/1189) of the patients enrolled in the Sabril registry have been from >10 to <17 years of age. Current labeling does not provide dosing information for these pediatric patients age 10 years and above.

The overall safety profile of vigabatrin has been described in previous submissions as well as in numerous scientific publications. The safety profile for pediatric patients age 10 years and older (summarized in section 7 of this review) are consistent with

postmarketing experience and are largely similar to that previously observed among adults in vigabatrin studies as described in the currently approved label,.

Vision data from prospective clinical studies, supplemented by the ongoing Sabril registry and recently published results from independent assessments of vision in vigabatrin-treated children, demonstrate similar profiles of vision changes in the pediatric and adult populations. Approval of the new indication for rCPS in pediatric patients will be restricted to patients age 10 years and older so that most of these pediatric patients will be old enough to cooperate with visual function assessments (including perimetry).

Current labeled warnings will be retained and will appropriately inform physicians and patients/guardians to evaluate closely the benefits and risks of vigabatrin treatment. Moreover, the current Sabril Risk Evaluation and Mitigation Strategy (REMS), which includes periodic vision testing, will continue to provide a mechanism to ensure ongoing vision monitoring of pediatric patients with rCPS (with annual summary reports of this monitoring to the Agency), and to facilitate risk-benefit discussions between patients/caregivers and physicians.

Vigabatrin would represent an efficacious and well-tolerated addition to the current treatment options for pediatric patients 10 years of age and older with rCPS who have not adequately responded to first-line drugs for CPS. Traditional and pharmacometric bridging-type analyses are used in this submission to confirm the vigabatrin dose-response in these older pediatric patients with rCPS and to demonstrate that the dose-response relationship is similar between adults and pediatric patients 10 years of age and older following a weight-based correction for exposure.

Vigabatrin is well tolerated at the doses studied as adjunctive therapy in pediatric patients 10 years of age and older with rCPS. The safety profile of vigabatrin documented in this program is generally similar to that reported among adults in vigabatrin studies and in postmarketing experience for vigabatrin. No new safety concerns have been identified.

Although the short-term and long-term safety data is derived from pooling safety data from a number of different pediatric studies as discussed in section 5.3 of this review, it appears adequate to establish that the safety profile for pediatric patients age 10 years and older is similar to that of adults age 17 years and older. Therefore, the benefit-to-risk ratio for vigabatrin therapy (using either the tablet or the oral solution) for pediatric patients age 10 years and older with rCPS who have not adequately responded to first-line drugs for CPS is acceptable.

## **Infantile Spasms**

The benefit to risk ratio for vigabatrin therapy of infantile spasm was already found acceptable at the time of the approval of the oral solution of vigabatrin for this indication on August 21, 2009. (The Sabril tablet will continue to be approved for rCPS but not for infantile spasms.)

The results of the Canadian Pediatric Epilepsy Network (CPEN) study regarding therapy infantile spasms imply that a total duration of 6 months therapy is sufficient to prevent recurrence of spasms. Currently approved labeling gives no indication of how long the duration of therapy for infantile spasm should be.

It is likely that the toxicity of vigabatrin (including visual toxicity) is proportional to the cumulative exposure (dose and duration of vigabatrin therapy). The addition of the CPEN study information to labeling sections 8.4 and 14 (suggesting that the duration of therapy be limited to 6 months) should improve the already acceptable risk to benefit ratio for vigabatrin treatment of infantile spasms using the oral solution.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

Continue existing REMS.

Following regulatory approval of Sabril on August 21, 2009, a Risk Evaluation and Mitigation Strategy (REMS) was initiated with the aim to reduce the risk of Sabril-induced vision loss while deriving benefit to the appropriate patient populations. The Sabril REMS elements include a Medication Guide, Communication Plan, and several Elements to Ensure Safe Use. Registry data are collected on both Sabril prescribers and patients via enrollment and treatment forms. Periodic vision testing is included and will be reported annually to the Agency.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

The following clinical postmarketing requirements (PMRs) from the August 21, 2009 approval letter are fulfilled by this submission:

- An adequately controlled trial in infants treated with Sabril for Infantile Spasms to further characterize the minimum duration of therapy required for sustained submission of spasms. The protocol for the trial should be discussed with the Agency prior to being submitted as a special protocol assessment (SPA).

- An open label clinical trial 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.

The following nonclinical PMR from the August 21, 2009 approval letter is fulfilled by this submission:

- A toxicology study in the juvenile rat examining the potential of vigabatrin exposure during development to produce neuronal damage. The study protocol should be submitted to the Division for comment prior to study initiation

The following nonclinical PMR from the August 21, 2009 approval letter is pending completion of the study.

- A juvenile animal toxicity study of vigabatrin in a non-rodent species. The study protocol should be submitted to the Division for comment prior to study initiation

No new PMRs are required at this time.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Sabril (vigabatrin) is an irreversible inhibitor of GABA transaminase, the enzyme responsible for the catabolism of the inhibitory neurotransmitter GABA, resulting in increased concentrations of GABA in the brain. As a GABA metabolic blocker, vigabatrin appears to provide a unique mechanism of action in comparison to other AEDs.

The tablet form and oral solution form are proposed for the treatment of refractory complex partial seizures (rCPS) in adults and in pediatric patients age 10 years and older. The tablet form is already approved for adults with rCPS.

The oral solution form is already approved for the treatment of infantile spasms. The tablet form is not approved for or proposed for the treatment of infantile spasms.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

**Table 1 Approved antiepileptic drugs in common clinical use for the treatment of partial epilepsy**

Carbamazepine
Clobazam
Gabapentin

Lacosamide
Lamotrigine
Levetiracetam
Oxcarbazepine
Phenobarbital <sup>1</sup>
Phenytoin
Potiga
Pregabalin
Primidone
Tiagabine
Topiramate
Valproic acid
Zonisamide

<sup>1</sup>Phenobarbital does not have FDA-approved labeling

**Table 2 Approved antiepileptic drugs for the treatment of infantile spasms**

ACTH Gel
Vigabatrin

### 2.3 Availability of Proposed Active Ingredient in the United States

Sabril is currently marketed in the United States.

### 2.4 Important Safety Issues With Consideration to Related Drugs

Vigabatrin has a unique mechanism of action. It binds irreversibly to the GABA transaminase and thus raises the level of the inhibitory neurotransmitter GABA in the central nervous system. There are other antiepileptic drugs which enhance GABAergic transmission. These include valproate, gabapentin, pregabalin, and tiagabine. The usual adverse effects associated with these other GABAergic antiepileptic drugs are typical of the whole class of antiepileptic drugs and include somnolence, sedation, and ataxia.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Two New Drug Applications (NDAs) for Sabril were approved on August 21, 2009.

NDA 20-427 was approved as adjunctive therapy for adult patients with rCPS who have inadequately responded to alternative treatments and for whom the potential benefits

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outweigh the potential risk of vision loss. Sabril is not indicated as a first line agent for complex partial seizures (CPS).

NDA 22-006 was approved for the use of Sabril as monotherapy for pediatric patients from 1 month to 2 years of age with IS for whom the potential benefits outweigh the potential risk of vision loss. Both NDAs were approved under a comprehensive Risk Evaluation and Mitigation Strategy (REMS) in light of the potential risk of visual loss associated with vigabatrin.

## 2.6 Other Relevant Background Information

A Type C Meeting was held on November 10, 2011 to discuss the sponsor's proposal to use available data from previously conducted studies in pediatric patients with rCPS to address the PREA study commitment and the associated long-term safety study listed in the Pediatric Written Request (PWR). The sponsor proposed to use pharmacometric-type bridging analyses to satisfy PREA to support an earlier implementation of appropriate pediatric labeling for Sabril. The sponsor also presented an overview of available safety data in the intended population. The results of the pharmacometric analyses were requested for review before the Agency would consider amending the PWR. Following the meeting, the pharmacometric analyses were submitted for review to Investigational New Drug 17,213 on March 15, 2012 as Serial No. 0748.

A second Type C Meeting was held on June 8, 2012 to further discuss amendment of the PWR. In this meeting, the sponsor described their plan to address each of the studies listed in the August 25, 2011 PWR. In addition to using available data (see section 5 of this review) to address the PREA requirement for an efficacy study in pediatric rCPS and associated long-term safety studies, the sponsor proposed to use published data (the CPEN study discussed in section 6.1.10 of this review) to define the minimum duration of use for patients with infantile spasms, and pharmacokinetic (PK) modeling to characterize clearance in infants to address the remaining 2 studies listed in the August 25, 2011 PWR. Overall, the Agency agreed with the sponsor's approach. The key discussion points and agreements during the meeting can be summarized as follows

The Agency did not agree with the sponsor's request

(b) (4)

(b) (4)

(b) (4)

However, the Agency agreed that the information should be submitted for review in the supplemental New Drug Application (sNDA) as part of the overall submission.

The Agency requested summary tables by category for available safety data for review following the meeting and the sponsor agreed.

The Agency agreed to include language in the amended PWR to acknowledge the nonrodent juvenile study as ongoing at the time of the BPCA deadline. The study report would need to be submitted upon completion. The sponsor agreed to this.

On July 24, 2012, the sponsor submitted a proposed amendment to the PWR (IND 17,213; Serial No. 0754). This proposed amendment adhered to agreements made at the two Type C meetings described above. As part of the submission, details regarding available perimetry data in children aged 3 to 17 exposed to Sabril were included, as requested by the Agency during the second Type C meeting. In a request for information from the Agency dated November 26, 2012, clinical trial general safety exposure information, vision safety information, and neurocognitive development data for patients stratified by age (< 10 years; 10 to 12 years; and 13 to 16 years) were requested. The sponsor responded accordingly on December 7, 2012 and provided exposure information for patients aged 3 to 16 from pediatric CPS controlled and open-label studies and the ongoing registry study, but included 1 patient from the clinical trial experience who was 17 years of age. Similarly, the exposure data from the Registry study included patients who were 17 years of age. In a follow-up request dated January 4, 2013, the Agency requested further clarity on the age ranges, and requested an age limit cut off of 16 and not 17 years.

The sponsor submitted a response on January 10, 2013, describing exposure information for pediatric patients aged 3 to 16 years that would be included for analyses of general safety, neurocognitive/development, and visual toxicity. This is summarized in section 7.2.1 of this review.

The PWR was revised and then reissued on April 18, 2013

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

The data and analyses are presented as previously agreed with the Agency. The limitations of the efficacy safety data derived from eight previously conducted pediatric studies are appropriately acknowledged.

#### **3.2 Compliance with Good Clinical Practices**

Adequate compliance with Good Clinical Practice.

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### 3.3 Financial Disclosures

The sponsor has documented that Studies 118, 192, 221, 201, and 294 were completed prior to February 2, 1999, the effective date of 21 CFR Part 54 requiring a Financial Disclosure Certification. In a updated Form FDA 3454 dated October 17, 2013, the sponsor further states that it has acted with due diligence to attempt to obtain financial disclosure information from the previous sponsor for vigabatrin (Sanofi-Aventis) for these five studies and for Studies 0098, 4020, and R003. However, this information is not available. This is documented in a letter from Sanofi-Aventis to the sponsor (formerly called Ovation Pharmaceuticals) dated December 7, 2005 which is included in this submission.

The only other study, (b) (4) is the (b) (4)  
(b) (4) was conducted in  
(b) (4) has signed and submitted Form 3455  
stating that he has no financial interests with the sponsor. (b) (4)

**Table 1. Financial Disclosure Information**

Study No.	Investigator Name	Sponsor	Affiliation	Disclosable Financial Information
(b) (6)				(b) (6)
				following financial agreements with Lundbeck:
				▪ \$148,850.00 payment (b) (6)



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**Reviewer Note:**

***This reviewer is satisfied that the sponsor has acted with due diligence to attempt to obtain financial disclosure information for those studies which predate the Financial Disclosure Certification requirement as discussed above.*** (b) (4)

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

No change from currently marketed product.

The scored 500 mg tablet (b) (4) is not currently “functionally” scored according to the technical standards for functional scoring. (to allow administration of a 250 mg dose by tablet). However the scoring allows for a sufficiently accurate dose (within about 5% error) to be clinically acceptable for the administration of a 250 mg dose (e.g., during dose escalation for pediatric patients age 10 years and above).

### **4.2 Clinical Microbiology**

No change from currently marketed product.

### **4.3 Preclinical Pharmacology/Toxicology**

Two PMR preclinical study reports were included in the pediatric written request. The third preclinical PMR is addressed in an interim report since the study is currently ongoing. These are enumerated in section 1.4 of this review.

Based on his review of the results presented in these PMR preclinical study reports, the nonclinical reviewer Dr. Edward Fisher has revised one paragraph in Section 5.4 Neurotoxicity in current labeling as follows:

Administration of vigabatrin to rats during the neonatal and juvenile periods of development produced vacuolar changes in the brain gray matter (areas including the thalamus, midbrain, deep cerebellar nuclei, substantia nigra, hippocampus, and forebrain) which are considered distinct from the IME observed in vigabatrin treated adult animals. Decreased myelination and evidence of oligodendrocyte injury were additional findings in the brains of vigabatrin-treated rats. An increase in apoptosis was seen in some brain regions following vigabatrin exposure during the early postnatal period. Long-term neurobehavioral abnormalities (convulsions, neuromotor impairment, learning deficits) were also observed following vigabatrin treatment of young rats. These effects in young animals occurred at doses lower than those producing neurotoxicity in adult animals and were associated with plasma vigabatrin levels substantially lower than those achieved clinically in infants and children [see Use in Specific Populations (8.1)].

#### 4.4 Clinical Pharmacology

##### 4.4.1 Mechanism of Action

No change from currently marketed product.

##### 4.4.2 Pharmacodynamics

As discussed below in section 6 of this review, traditional analysis and pharmacometric dose-response modeling of efficacy data from three controlled studies of vigabatrin as adjunctive therapy for pediatric patients with rCPS (Studies 118, 192, and 221) have supported proposed dosing for pediatric patients age 10 years and above who require vigabatrin as adjunctive therapy for refractory complex partial seizures.

##### 4.4.3 Pharmacokinetics

As discussed below in section 6 of this review, traditional analysis and pharmacometric dose-response modeling of efficacy data from three controlled studies of vigabatrin as adjunctive therapy for pediatric patients with rCPS (Studies 118, 192, and 221) have supported proposed dosing for pediatric patients age 10 years and above who require vigabatrin as adjunctive therapy for refractory complex partial seizures.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

**Table 3 Studies providing clinical efficacy and safety data**

<b>Study</b>	<b>Description</b>	<b>Data provided for this Submission</b>	<b>Pediatric Patient Enrollment</b>
118	Placebo Controlled Pediatric rCPS study	Efficacy and Safety without visual perimetry testing	94 VGB 32 PBO
192	Placebo Controlled Pediatric rCPS study	Efficacy and Safety without visual perimetry testing	28 VGB 27 PBO
221	Placebo Controlled Pediatric rCPS study	Efficacy and Safety without visual perimetry testing	43 VGB 45 PBO
201	Open Label rCPS extension study continued from Studies 118 and 221	Safety with visual perimetry testing	210 VGB (53 new; 127 continued from Studies 118 and 221)
294	Open Label rCPS extension study continued from Study 192	Safety without visual perimetry testing	44 VGB (25 new; 19 continued from Study 192)
R4020	EMA rCPS study of safety	Safety by report & clinical evaluation only with visual perimetry testing	214 VGB
R003	EMA rCPS study of safety	Safety by report & clinical evaluation only with visual perimetry testing	1 VGB
0098	Open rCPS label study	Safety by report & clinical evaluation only without any vision assessment	60 VGB (continued from Study 201)
Sabril registry	REMS-required for all patients on vigabatrin for rCPS or IS	Safety with visual perimetry testing	395 VGB ages 10-16 years (260 with perimetry)
CPEN study	Randomized, double-blind IS study of add-on flunarizine to prevent the cognitive deterioration associated with infantile spasms	Duration of Therapy for IS: Post-hoc analysis of CPEN study to evaluate the relapse rate of vigabatrin responders following discontinuation of vigabatrin after 6 months of treatment for IS	38 infants treated for 6 months with VGB for IS and then followed for another 18 months after VGB discontinuation

See section 5.3 of this review for further details on each study. The relationship among the first eight of these studies is diagramed in section 7.1.1 of this review.

## 5.2 Review Strategy

Review of individual study reports for the eight clinical studies listed in section 5.1 of this review, review of the Sabril registry data, review of the publication and study report from the CPEN study, and review of the clinical and integrated summaries of efficacy and safety provided by the sponsor.

## 5.3 Discussion of Individual Studies/Clinical Trials

### Study 118

Study 118 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group design study enrolling pediatric subjects between the ages of 3 and 16 years, inclusive. The primary objective of this study was to determine the efficacy and safety of vigabatrin at doses of 20, 60, and 100 mg/kg/day when compared to placebo when added to currently prescribed AED therapy in pediatric subjects having uncontrolled CPS with or without secondary generalization. Subjects on adequate and stable AED regimens received a single-blind placebo solution during a 10-week Baseline Phase. Subjects were then randomized under double-blind conditions to receive either vigabatrin or a matching placebo.

Vision tests included fundoscopy, visual acuity, color vision testing, anterior and posterior segment examinations, visual field, ophthalmologist's assessment, VEP, and ERG. Confrontational visual fields (finger counts in all 4 quadrants and identification of red color in all 4 quadrants and centrally) were obtained for all subjects. Protocol Amendment 4 required Goldmann or Humphrey perimetry for all subjects, but the study was then prematurely discontinued.

### Study 192

Study 192 was a multicenter, randomized, double-blind, placebo-controlled study of 2 parallel groups of pediatric subjects between the ages of 3 and 16, years inclusive. The primary objective of this study was to assess, in comparison to placebo, the safety, tolerability, and efficacy of vigabatrin when added to a current AED regimen in the

treatment of CPS or partial seizures with secondary generalization in epileptic children, in the range of 0.5 to 4 g/day, depending on the subjects' individual body weight. Subjects on adequate and stable AEDs regimen were evaluated in open-label conditions during a 6-week Baseline Phase. Subjects were then randomized under double-blind conditions to receive either vigabatrin or a matching placebo.

Vision tests included fundoscopy, visual acuity, confrontational visual field (finger counts in all 4 quadrants and identification of red color in all 4 quadrants and centrally), and VEP. Perimetry was not performed

### **Study 201**

Study 201 was a multicenter, long-term, follow-up, open-label trial in pediatric subjects with CPS with or without secondary generalization who had previously participated in Study 118 or Study 221. The primary objective of this study was to continue the safety evaluation of vigabatrin as adjunctive therapy in children with uncontrolled CPS with or without secondary generalization who had previously participated in Study 118 or Study 221. Subjects participated in a 4-week double-blind Dose Adjustment Phase followed by an Open-Label Phase of 48 weeks or until marketing of vigabatrin in the United States, whichever was longer.

Vision tests included fundoscopy (with photos), full visual acuity testing, confrontational visual field (finger counts in all 4 quadrants and identification of red color in all 4 quadrants and centrally), slit lamp and color plate testing, VEP, and ERG. Protocol Amendment 4 required that subjects receive full visual field tests; perimetry testing was performed for 70 subjects.

### **Study 221**

Study 221 was a multicenter, randomized, double-blind, placebo-controlled study in 2 parallel groups of pediatric subjects between the ages of 3 and 16, inclusive. The primary objective of this study was to assess, in comparison to placebo, the efficacy, tolerability, and safety of vigabatrin, in the range of 0.5 g to 4.0 g/day, when added to currently prescribed AED therapy in pediatric subjects having uncontrolled CPS with or without secondary generalization. Subjects on adequate and stable AED regimens were evaluated in open-label conditions during a 6-week Baseline Phase. Subjects were then randomized under double-blind conditions to receive either vigabatrin or a matching placebo.

Vision tests included visual acuity, color vision, confrontational visual field (finger counts in all 4 quadrants and identification of red color in all 4 quadrants and centrally), anterior and posterior segment, fundoscopy, fundus photos (if possible), VEP, and ERG. Visual perimetry testing was not performed.

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### **Study 294**

Study 294 was a 24-week follow-up multicenter study conducted in subjects who completed Study 192. The objective of this study was to continue the evaluation of the safety and efficacy of vigabatrin, for a further 6-month period, in subjects who completed Study 192.

Depending on the dose received at the end of the previous study (Study 192), the subjects either entered this study on open-label vigabatrin for a 24-week period (if they had been on the lowest dose level per weight group), or began with a 1- to 6-week double-blind phase, followed by an 18- to 23-week open-label vigabatrin phase (if they had been on higher dose per weight group).

Vision tests included fundoscopy, visual acuity, confrontational visual field, and VEP. Visual perimetry testing was not performed.

### **Study 0098**

Study 0098 was a multicenter, open-label, flexible dose, long-term study in subjects who needed better seizure control and/or decreased adverse events from their current AED therapy. The objective of this study was to further evaluate the safety and efficacy associated with the use of vigabatrin in epilepsy subjects having partial seizures and whose lifestyle had been adversely affected by poor seizure control and/or adverse events from currently marketed AEDs.

Subjects who participated in previous vigabatrin studies were allowed to enroll to continue vigabatrin therapy. Subjects who enrolled from previous vigabatrin studies continued their maintenance dose at study entry. Dosage adjustment was allowed to achieve improvement in seizure control.

Vision was not assessed.

### **Study R4020**

Study R4020 was a multicenter, open-label, comparative, parallel-group study in adult and pediatric subjects with partial refractory epilepsy. The primary objective was to describe the epidemiology of VFDs in subjects with refractory partial epilepsy, with or without secondary generalization, and their impact on daily activities. Particularly, the prevalence, incidence, and clinical course of VFDs were investigated in subjects according to past/present AEDs, with particular reference to vigabatrin.

Subjects aged  $\geq 8$  years with refractory partial seizures were enrolled and grouped into those receiving vigabatrin for  $\geq 6$  months (Group 1); those who had received vigabatrin

for  $\geq 6$  months and then had discontinued for  $\geq 6$  months (Group 2); and those naïve to vigabatrin (Group 3). There was no investigational treatment in this study. Subjects continued the AED treatment used at inclusion, unless the physician decided that a change was in the best interest of the subject.

Potential VFDs were assessed by perimetry testing at regular intervals. The techniques used varied between centers and over time. All results were independently reviewed and classified by an international expert [REDACTED] (b) (4) and categorized as normal, abnormal of identified etiology, abnormal of unidentified etiology (sub-divided into BCPC and other pattern), technically limited, or inconclusive.

**Reviewer Note:**

***Because Study R4020 was specifically designed by the EMA to characterize the occurrence of visual field deficits in both adult and pediatric patients with rCPS who were either exposed to vigabatrin or not exposed to vigabatrin as part of their therapy and because the pediatric enrollment in this study was larger than in the other pediatric studies presented in this submission, Study R4020 is the most informative with regard to the extent of visual field loss attributable to vigabatrin in the adult vs. pediatric CPS population. (See section 7.3.5 of this review).***

**Study R003**

Study R0003 was a non-comparative, prospective and observational multicenter cohort study. The primary objective was to identify the occurrence, frequency, and clinical course of early vigabatrin-associated VFDs and related predictive factors in children and adults using electrophysiology and visual field examinations. Subjects were treated with vigabatrin according to the clinical judgment of the investigator in accordance with the indication of vigabatrin as described in the product monograph. The decision to prescribe vigabatrin was independent of the study protocol. The Health Canada, Therapeutic Products Directorate, recommends initial and periodic (approximately every 3 months) ophthalmologic examinations during vigabatrin treatment.

Visual field evaluation procedures, including static visual field examinations, field-specific VEPs and ERGs were repeated at different times during the study and the procedures employed varied according to the age of the subject. Only one pediatric patient was enrolled.

**Canadian Pediatric Epilepsy Network (CPEN) Study**

Duration of therapy for infantile spasms was evaluated in a post hoc analysis of a Canadian Pediatric Epilepsy Network (CPEN) study of developmental outcomes in

infantile spasms patients. The 38/68 infants in the study who had responded to vigabatrin therapy (complete cessation of spasms and hypsarrhythmia) continued vigabatrin therapy for a total duration of 6 months therapy. The 38 infants who responded were then followed for an additional 18 months after discontinuation of vigabatrin to determine their clinical outcome. A post hoc analysis indicated no observed recurrence of infantile spasms in any of these 38 infants.

Vision was not assessed as part of this study.

This study is further discussed in section 6.1.10 of this review.

## **6 Review of Efficacy**

### **Efficacy Summary**

#### **6.1 Indication**

Refractory complex partial seizures in pediatric patients age 10 years and above.

##### **6.1.1 Methods**

Traditional analysis and pharmacometric dose-response modeling of efficacy data from three controlled studies of vigabatrin as adjunctive therapy for pediatric patients with rCPS (Studies 118, 192, and 221) and two controlled studies of vigabatrin as adjunctive therapy for adult patients with rCPS (Studies 024 and 025). All three of the pediatric studies (Studies 118, 192, and 221) were stopped for administrative reasons before their planned enrollments were attained.

##### **6.1.2 Demographics**

The demographic characteristics for all patients were comparable across the Controlled Pediatric rCPS Studies (see Sponsor's Table 6 below from Summary of Clinical Efficacy). Most patients in each study were female and patients were predominantly Caucasian. Mean age ranged from 8.7 to 11.7 years across studies and treatment groups. Mean weight ranged from 38.7 to 51.0 kg across studies and treatment groups.



**Table 4 Baseline Characteristics for Patients in Controlled Pediatric rCPS Studies - Intent to Treat Population**

**Table 6. Baseline Characteristics for Patients in Controlled Studies – Intent-to-Treat Population**

Parameter	Study 118				Study 192		Study 221	
	Placebo N = 32	Vigabatrin			Placebo N = 27	Vigabatrin N = 28	Placebo N = 45	Vigabatrin N = 43
Age (years)		20 mg/kg/day N = 30	60 mg/kg/day N = 32	100 mg/kg/day N = 32				
Mean (SD)	9.4 (4.1)	11.0 (4.1)	11.7 (3.1)	9.2 (4.6)	10.7 (3.2)	11.2 (3.3)	8.7 (4.2)	11.0 (3.5)
Range	3, 16	4, 16	4, 16	3, 16	4, 15	5, 16	3, 16	4, 16
Gender, n (%)								
Female	16 (50.0)	16 (53.3)	15 (46.9)	20 (62.5)	14 (51.9)	16 (57.1)	27 (60.0)	19 (44.2)
Male	16 (50.0)	14 (46.7)	17 (53.1)	12 (37.5)	13 (48.2)	12 (42.9)	18 (40.0)	24 (55.8)
Race, n (%)								
Asian	0	0	1 (3.1)	1 (3.1)	NR	NR	NR	NR
Black	2 (6.3)	2 (6.7)	2 (6.3)	1 (3.1)	0	1 (3.6)	5 (11.1)	5 (11.6)
Caucasian	29 (90.6)	28 (93.3)	29 (90.6)	28 (87.5)	26 (96.3)	27 (96.4)	35 (77.8)	38 (88.4)
Other (including multiracial)	1 (3.1)	0	0	2 (6.3)	1 (3.7)	0	5 (11.1)	0
Height (cm)					n = 26			
Mean (SD)	134.7 (19.4)	145.7 (26.1)	148.7 (19.7)	133.3 (25.8)	145.2 (16.8)	148.4 (20.1)	133.8 (24.3)	144.6 (22.0)
Range	102.4, 167.6	97.8, 180.3	105.9, 180.3	95.3, 177.8	104.0, 171.0	107.0, 179.0	88.9, 179.1	101.6, 185.2
Weight (kg)								
Mean (SD)	41.2 (23.6)	51.0 (24.7)	47.5 (16.3)	39.9 (24.1)	47.7 (17.5)	49.9 (20.9)	38.7 (22.6)	47.2 (22.8)
Range	15.0, 108.9	14.5, 96.2	19.5, 80.7	13.2, 106.6	18.9, 82.4	18.0, 95.1	13.2, 96.6	14.5, 110.7

CSR = clinical study report; n = number of patients with value; NR = not reported; SD = standard deviation.

Source: Study 118 CSR Table 14, Study 192 CSR Table 13, and Study 221 CSR Table 14.

A population PK analysis of patient data was performed. This analysis evaluated the effect of patient factors, including age and sex, on the PK of vigabatrin. The rate of vigabatrin absorption was dependent on age. Younger patients were predicted to have smaller C<sub>max</sub> and longer t<sub>max</sub> values relative to an older patient with similar body weight and creatinine clearance.

No gender differences were observed for the PK parameters of vigabatrin in patients.

No specific study was conducted to investigate the effects of race on vigabatrin pharmacokinetics.

See section 7.2.1 of this review

### 6.1.3 Subject Disposition

The sponsor's Table 9 below (from Summary of Clinical Efficacy) provides a summary of patient disposition by study for each of the Controlled Pediatric rCPS Studies. The majority of patients in each treatment group completed the study (range: 71.1% to 96.3%). In Study 118, the number of patients prematurely discontinuing due to adverse events increased with vigabatrin dose. In Study 221, the number of patients prematurely discontinuing due to seizure frequency/intensity was larger in the placebo group than in the vigabatrin group.

**Table 5 Disposition of Patients in Controlled Pediatric rCPS Studies**

**Table 9. Disposition of Patients in Controlled Studies**

Parameter	Study 118				Study 192		Study 221	
	Placebo N = 32	Vigabatrin			Placebo N = 27	Vigabatrin N = 28	Placebo N = 45	Vigabatrin N = 43
		20 mg/kg/day N = 30	60 mg/kg/day N = 32	100 mg/kg/day N = 32				
Entered Baseline Period								
Randomized	32	30	32	32	27	28	45	43
Discontinued, n (%)	4 (12.5)	4 (13.3)	5 (15.6)	5 (15.6)	1 (3.7)	6 (21.4)	13 (28.9)	7 (16.3)
Failed inclusion criteria	0	1	0	0	0	0	0	0
Met exclusion criteria	0	1	1	0	0	0	0	0
Adverse event	1	0	2	4	1	3	3	1
Seizure frequency/intensity	1	2	2	1	0	0	7	2
Withdrew consent	2	0	0	0	0	3	2	2
Protocol violation	0	0	1	0	0	0	1	2
Other	0	1	0	0	0	0	0	0
Completed study, n (%)	28 (87.5)	26 (86.7)	27 (84.4)	27 (84.4)	26 (96.3)	22 (78.6)	32 (71.1)	36 (83.7)

CSR = clinical study report.

Source: Study 118 CSR Table 11 and Figure 2; Study 192 CSR Table 10 and Figure 2; and Study 221 CSR Table 11 and Figure 2.

#### 6.1.4 Analysis of Primary Endpoint(s)

The sponsor aimed to show a similar dose-response (D-R) relationship between adult patients (Study 024 and 025) and pediatric patients (Studies 118, 192, and 221).

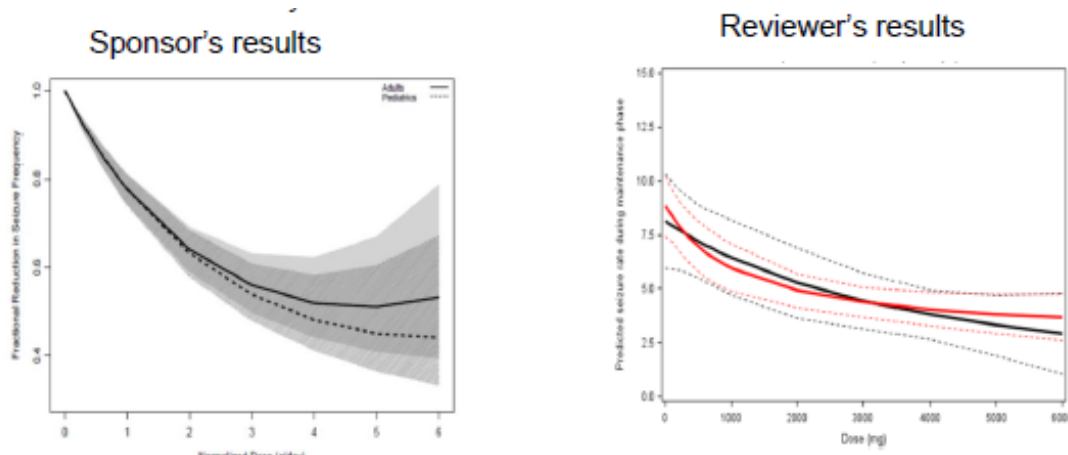
The methodology and results from this approach are reviewed in detail in the review by Dr. Atul Bhattaram.

##### Summary of Results:

- There was similarity in the dose-response relationship between adults and pediatrics from both the sponsor's analyses and reviewer's assessment.
  - Data from two adult studies (24/25) and three pediatrics studies (118/192/221) were used.
  - There were 104 patients on placebo and 165 patients on vigabatrin
  - Weight-normalized dose was used as an exposure instead of concentration.
  - Age was not found to be a significant covariate on drug effect in both the sponsor's and reviewer's analyses.

The Agency's Pharmacometrics Reviewer independently analyzed the data and found similar results.

**Figure 1 Results of Dose-Response Analysis by the Sponsor and by the Agency**



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The sponsor plotted the weight-normalized doses (in grams) vs. Fractional reduction in Seizure Frequency. The dotted curve is for the pediatric patients and the solid curve is for the adult patients. The overlapping confidence intervals are shown.

The Agency reviewer plotted the dose (in mg) vs. predicted seizure rate during the maintenance phase. The black line is for pediatric patients and the red line is for adult patients. The overlapping confidence intervals are shown.

#### 6.1.5 Analysis of Secondary Endpoints(s)

Not applicable

#### 6.1.6 Other Endpoints

The following key results support vigabatrin's efficacy for the treatment of rCPS in patients 10 to 16 years of age:

- Placebo-controlled Study 118: A statistically significant difference indicating the superiority of the vigabatrin 100 mg/kg/day dose versus placebo groups ( $p = 0.0142$ ) and a linear trend of increasing efficacy with dose ( $p = 0.0568$ ). These results,

discussed in detail in the review by the Biometrics reviewer, provide evidence of dose response, and, hence, evidence of vigabatrin's efficacy.

- Placebo-controlled Studies 192 and 221: Median decrease in seizure rate in the vigabatrin group consistent with Study 118
- Uncontrolled Studies 201 and 294: Evidence for continued efficacy for up to 24 weeks

**Reviewer comment:**

***As previously noted, all three controlled pediatric clinical studies of rCPS were discontinued prematurely for administrative reasons before full enrollment. The fact that the highest dose of vigabatrin in Study 118 demonstrated statistically significant superiority over placebo by traditional efficacy analysis despite inadequate enrollment provides reassurance that the dose-response analysis of the pooled efficacy data from all three studies is correct in concluding that the weight-normalized dose response is the same in adults and in pediatric patients age 10 years and above.***

In summary, Study 118 showed that vigabatrin 100 mg/kg was statistically significantly superior to placebo for the patient mean monthly frequency of CPS plus partial seizures secondarily generalized at end of study compared to baseline ( $p = 0.0142$ ). Vigabatrin 20 mg/kg and 60 mg/kg were not statistically different from placebo ( $p = 0.8622$  and  $0.8140$ , respectively). A trend ( $p = 0.0568$ ) toward a linear dose response was also observed. Pharmacometric bridging-type analyses provided evidence of vigabatrin's efficacy by confirming the vigabatrin dose-response in pediatric patients with rCPS and demonstrating that the dose-response relationship was similar between adults and children following a weight-based correction for exposure. Two additional double-blind, parallel group, placebo-controlled studies (studies 192 and 221) supported the finding that vigabatrin provides pediatric patients clinically important improvements from baseline in the frequency of rCPS. Low discontinuation rates and efficacy results from open-label, uncontrolled studies (Studies 201 and 294) are consistent with continued vigabatrin efficacy for up to 6 months.

In conclusion, the weight of efficacy evidence supports the use of vigabatrin as adjunctive therapy for pediatric patients 10 to 16 years of age with rCPS who have inadequately responded to alternative treatments.

**Reviewer Comment:**

***The only new indication requested in this submission is for pediatric patients age 10 years above for the adjunctive treatment of refractory complex partial seizures. The efficacy issues for rCPS are addressed in sections 6.1.1 to 6.1.9 of this review. These efficacy results, in combination with the safety finding presented in***

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***section 7 of this review, justify the conservative lowering of the lower age for proposed dosing for rCPS from 17 years of age down to 10 years of age.***

#### 6.1.7 Subpopulations

Subpopulation analysis for efficacy was not performed for the controlled clinical studies of rCPS in pediatric patients.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

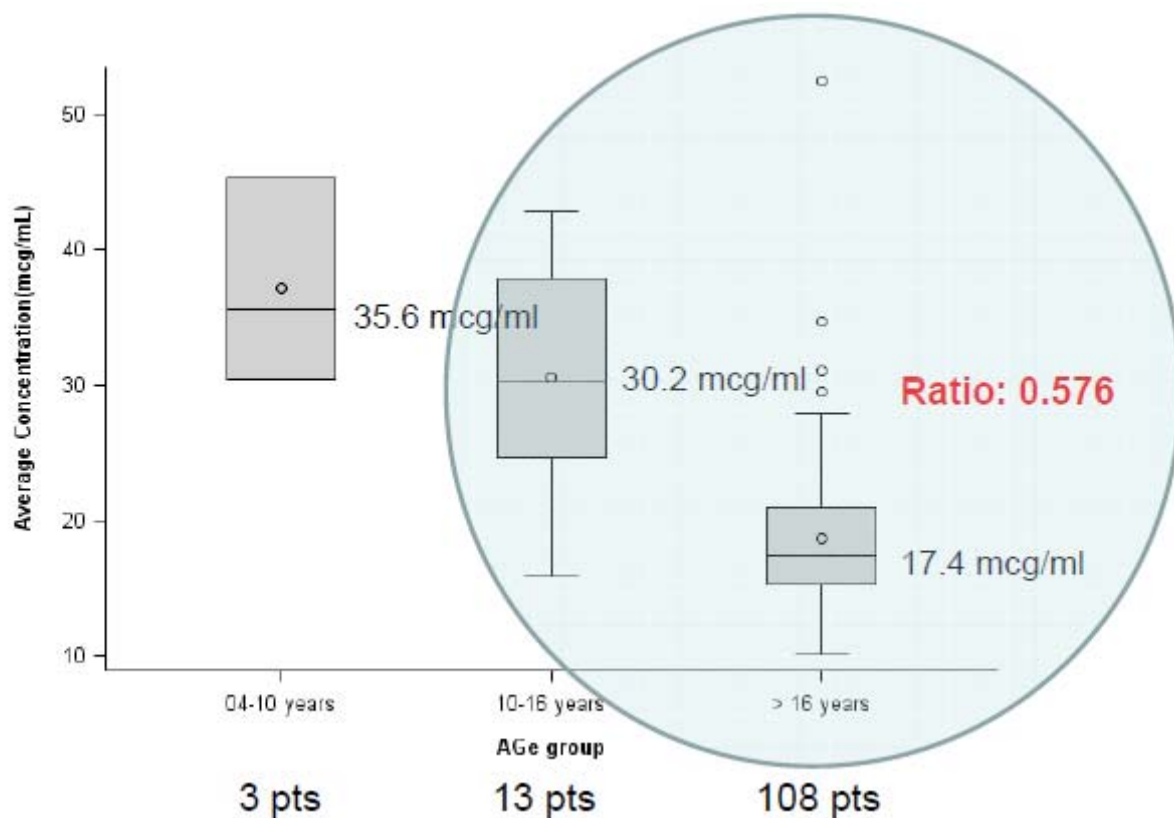
For Study 118, each patient was assigned to a vigabatrin dose group using the protocol-specified dose groups. Other than Study 118, the clinical studies (Studies 192 and 221) used flexible dosing regimens that allowed titration based on body weight and treatment response.

A population dose-response analysis included data from 3 studies in pediatric patients (Study 118, Study 192, and Study 221) and 2 studies in adult patients (Study 024 and Study 025) with rCPS. Based on the results of these analyses, a total daily normalized dose of 1, 3, and 6 g/day is predicted to reduce seizure rate by 23.2%, 45.6%, and 48.5%, respectively.

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The average concentration ( $C_{avg}$ ) at a dose of 3,000 mg/day in adults was found to be approximately 0.58 times lower than in pediatric patients age 10 years and older.

**Figure 2 Average concentration at dose of 3,000 mg/day in adults versus pediatric patients**



Using the exposure ratio of 0.576, dosing for pediatrics can be derived based on the ratio of exposure between pediatric patients and adults as shown in the table below.

**Table 6 Dosing based on exposure ratio**

		Adult Approved Dose	
		1000 mg	3000 mg
Cavg	Adults	6.2 mcg/ml	17.4 mcg/ml
	Pediatrics	10.8 mcg/ml	30.2 mcg/ml
Predicted Dose for Peds	Based on Exposure Ratio	576 mg (1000×0.576)	1728 mg (3000×0.576)
	Sponsor's Proposal	500 mg	2000 mg

Based on the final model the dosing recommendations for pediatric patients weighing 20 to 60 kilograms are as follows:

**Table 7 Pediatric Dosing Recommendations for Vigabatrin**

Body Weight	Treatment Phase	Pediatric Total Daily Dose (mg/day)	Adult Equivalent Dose (mg)
> 20-35 kg	Initiation	500	1000
> 35-60 kg	Initiation	750	1000
> 20-35 kg	Maintenance	1750	3000
> 35-60 <sup>a</sup> kg	Maintenance	2250	3000

<sup>a</sup> For patients > 60 kg, adult doses should be used.

This is in agreement with the sponsor's proposed dosing recommendations for labeling.

**Table 8 Sponsor's proposed pediatric dosing for labeling**

Body Weight [kg]	Total Daily* Starting Dose [mg/day]	Total Daily* Maintenance Dose <sup>†</sup> [mg/day]
25-60 <sup>††</sup>	500	2000
*Administered in two divided doses.		
<sup>†</sup> Maintenance dose is based on 3000 mg/day adult-equivalent dose		
<sup>††</sup> Patients weighing more than 60 kg should be dosed according to adult recommendations		

Although the effect of renal impairment has not been studied in pediatric patients, it has been shown that vigabatrin is almost entirely eliminated renally and that glomerular filtration rate remains almost constant in the range of 2 to 15 years of age. Thus, the Clinical Pharmacology reviewer has concluded that the following language concerning dose adjustments for adults and pediatric patients age 10 years and older with renal impairment will be included in the labeling under section 2.4 Dosage and Administration for Patients with Renal Impairment and cross-referenced to Clinical Pharmacology (12.3) and Use in Specific Populations (8.6).

SABRIL is primarily eliminated through the kidney.

#### Infants

Information about how to adjust the dose in infants with renal impairment is unavailable.

#### Pediatric patients 10 years and older, and adult patients

- Mild renal impairment (CL<sub>cr</sub> >50 to 80 mL/min): dose should be decreased by 25%
- Moderate renal impairment (CL<sub>cr</sub> >30 to 50 mL/min): dose should be decreased by 50%
- Severe renal impairment (CL<sub>cr</sub> >10 to 30 mL/min): dose should be decreased by 75%.



CLcr in mL/min may be estimated from a serum creatinine (mg/dL) in using the following formulas:

- Patients 10-12 years old:  $CLcr \text{ (ml/min/1.73 m}^2\text{)} = (K * Ht) / Scr$

height (Ht) in cm; serum creatinine (Scr) in mg/dl;  
K (proportionality constant): Female Child (<12 years):  
K=0.55; Male Child (<12 years): K=0.70

- Pediatric patients 12 years or older and adult patients:  
 $CLcr^* = [140 - \text{age (years)}] \times \text{weight (kg)} / 72 \times \text{serum creatinine (mg/dL)}$

\*[ $\times 0.85$  for female patients]

The effect of dialysis on SABRIL clearance has not been adequately studied.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The original two adjunctive therapy studies with adult patients with refractory complex partial seizures had treatment periods lasting 18 weeks and 16 weeks. The three controlled pediatric complex partial seizure studies had titration/maintenance periods of 14 weeks, 17 weeks, and 17 weeks. Evidence of loss of efficacy or tolerance was not observed during the controlled pediatric rCPS studies (Studies 118, 118, 192, and 221) or in the long-term open label pediatric rCPS studies (Studies 201 and 294). The presumed mechanism of action, irreversible inactivation of the GABA transaminase leading to an elevation of GABA in the central nervous system, would in theory be less likely to allow to the development of tolerance than the mechanism of a drug directly interacting with receptors such as the benzodiazepine class of antiepileptic drugs.

#### 6.1.10 Additional Efficacy Issues/Analyses (Duration of Therapy for Infantile Spasms and the CPEN Study)

**Infantile Spasms:** This submission is also the complete response to the Sabril PWR last amended on April 18, 2013. The PWR contains a requirement for a study concerning infantile spasms to address the appropriate duration of therapy which had not been addressed in labeling at the time of approval on August 21, 2009.

Originally the Agency asked the sponsor to conduct a new study comparing the long-term relapse rate after treatment for 3 months versus 6 months of therapy. However,

The Agency agreed during the June 8, 2012 Type C meeting that, due to the reluctance of clinical investigators to subject their patients to the risk of relapse after being treated for less than 6 months, a 3- versus 6-month study of vigabatrin in IS was not feasible. It was agreed that a post hoc analysis of a Canadian Pediatric Epilepsy Network (CPEN) study of developmental outcomes in infantile spasms patients could potentially be used to determine if 6 months was an appropriate minimum duration of therapy.

In the present post-hoc interim analysis of the reported relapse rate following discontinuation of Sabril (vigabatrin) in patients successfully treated with vigabatrin for 6 months in the CPEN study, 68 patients received at least 1 dose of vigabatrin. Dr. Lionel Carmant confirmed that, per protocol, all vigabatrin patients received vigabatrin 100 mg/kg/day for 3 days followed by 150 mg/kg/day. Additionally, all vigabatrin patients received vitamin B6 200 mg/day from diagnosis to the end of the 6-month treatment period. This dosing regimen reflects a faster titration method than that outlined in the current Sabril product label ("initiate therapy at 50 mg/kg/day twice daily increasing total daily dose per instructions to a maximum of 150 mg/kg/day").

In the publication based on the CPEN study, the 38 patients who responded to vigabatrin alone were reported to have remained spasm free until the end of the 6-month vigabatrin treatment and had no recurrences of spasms 18 months following discontinuation of vigabatrin. In the post-hoc analysis, among the 37 vigabatrin-treated patients with absence of hypsarrhythmic EEG pattern at Week 2, Week 4, or Month 6, none had hypsarrhythmic EEG recurrences 6 months following discontinuation of vigabatrin. Of the 28 vigabatrin-treated patients with absence of hypsarrhythmic EEG pattern at Week 4 and spasm cessation confirmed by the seizure diaries at Week 4, the post-hoc interim analyses found that one patient (3.6%) had recurrence of had a Visit 5 EEG that was presumptively positive for hypsarrhythmia; however, the Visit 6 EEG was hypsarrhythmia negative, indicating absence of relapse. Therefore, the patient was considered to have relapsed in the primary analysis, but not in the alternative methodology.

***Reviewer comment:***

***Based on these results, the following description of the post hoc analysis from the CPEN study will be included in section 14 (Clinical Studies) of labeling:***

**Duration of therapy for infantile spasms was evaluated in a post hoc analysis of a Canadian Pediatric Epilepsy Network (CPEN) study of developmental outcomes in infantile spasms patients. The 38/68 infants in the study who had responded to vigabatrin therapy (complete cessation of spasms and hypsarrhythmia) continued vigabatrin therapy for a total duration of 6 months therapy. The 38 infants who responded were then followed for an additional 18 months after discontinuation of vigabatrin to determine their clinical outcome.**

**A post hoc analysis indicated no observed recurrence of infantile spasms in any of these 38 infants.**

## **7 Review of Safety**

### **Safety Summary**

#### **7.1 Methods**

##### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

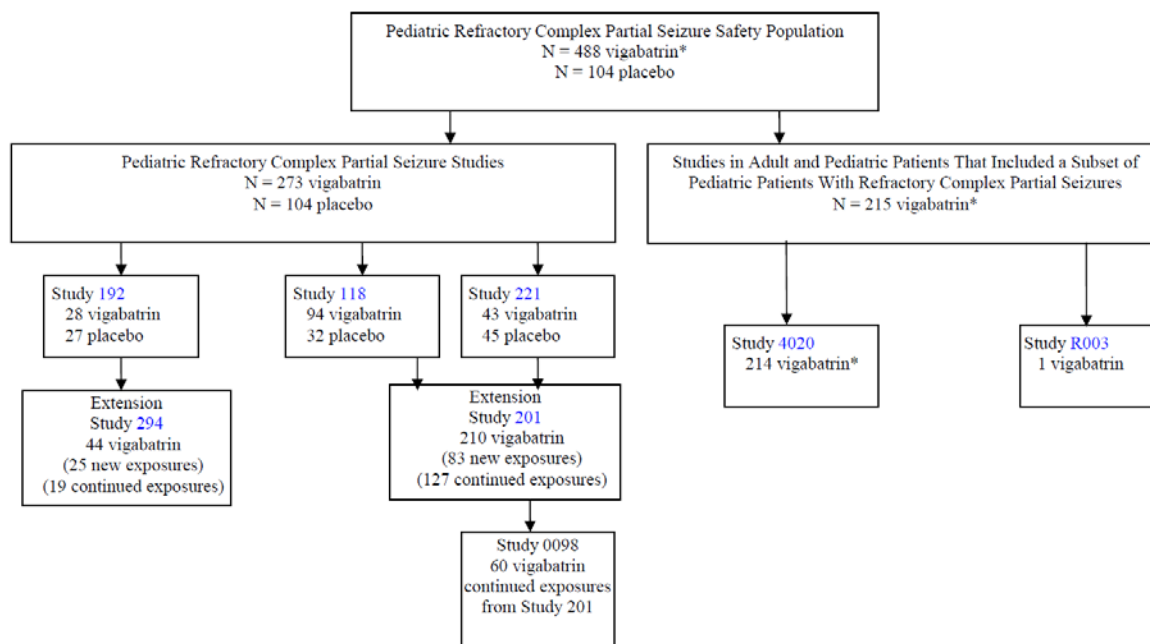
The safety data is from taken from 8 pediatric rCPS clinical studies and from the REMS-required Sabril registry. These studies and the registry are summarized in the table of studies in section 5.1 and described in detail in section 5.3 of this review.

Data for these 8 studies are summarized by the sponsor and discussed in this review according to the following categories:

- **Controlled Pediatric CPS Studies:** Studies 118, 192, and 221 (which had placebo controls)
- **All Pediatric CPS Studies:** Controlled Pediatric CPS Studies (118, 192, and 221) plus the Open- Label Extension Studies 201 and 294
- **EMA Article 12 Studies:** Studies 4020 and R003
- **Phase 3b/4 open-label Study:** Study 0098.

The relationship among these 8 studies and the number of patients included from each of the 8 studies in the Pediatric Refractory Complex Partial Seizure Safety Population are shown in the figure below, reproduced from the sponsor's Figure 3 of the Summary of Clinical Safety.

**Figure 3 Relationship Among the Eight Studies Used to Evaluate Safety**



Study 0098 also included patients from adult studies.

\* Thirty-three patients were excluded from Study 4020 exposure summaries, as they did not meet inclusion/exclusion criteria.

The clinical studies were conducted with liquid and tablet formulations of vigabatrin as follows:

- Studies 118, 192, and 221: solution
- Study 201: solution and 500-mg chewable tablet
- Studies 0098 and 294: tablet
- Studies R003 and 4020: commercial supplies at local pharmacy

### 7.1.2 Categorization of Adverse Events

The sponsor used the Medical Dictionary for Regulatory Activities (MedDRA) to code the investigator verbatim terms to preferred terms (PTs) for use in the adverse event analyses.

Available safety data of vigabatrin for adjunctive therapy in pediatric patients 3 years of age and above with rCPS are pooled from the 8 pediatric rCPS clinical studies described in section 5.3 of this review.

Treatment-emergent AEs related to anemia, edema, visual dysfunction/VFD, peripheral neuropathy, cognition/neuropsychiatric function, psychiatric function with vigabatrin, development (somatic and sexual), hepatic function, sedation, dizziness, ataxia, tremor, weight increase, suicidality, and intramyelinic edema were identified. Search methods defined in the ISS SAP were utilized to identify the PTs and/or laboratory results consistent with these AEs of special interest.

Of note, the PTs used to identify TEAEs of cognition/neuropsychiatric function and psychiatric function with vigabatrin were the same. Therefore, the results from these searches yielded identical findings and these TEAEs of special interest are discussed together.

Topics of special interest were based on discussions for the PWR with the FDA and are presented in section 7.7 of this review.

#### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Available safety data of vigabatrin for adjunctive therapy in pediatric patients 3 years of age and above with rCPS s are pooled from the 8 clinical studies described in section 5.3. Safety data from 488 unique vigabatrin-exposed patients in the vigabatrin clinical program are included.

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## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

**Table 9 General Safety Data by Age, Duration of Exposure, and Source**

Age (years)	Total Number of Patients on Drug	Number of Patients in Controlled Studies <sup>1</sup>		Number of Patients in Open Label Studies <sup>2</sup>		Number of Patients from Registry Data <sup>3</sup>	
		Patients on drug	Patients on placebo	Patient exposure ≥ 6 mos.	Patient exposure ≥ 12 mos.	Patient exposure ≥ 6 mos.	Patient exposure ≥ 12 mos.
3 ≤ 10	107	56	58	83	64	554	413
10 - 12	64	41	16	45	32	126	97
13 - 16	101	68	30	79	53	124	103
Total	272	165	104	207	149	804	613
<sup>1</sup> Studies 118, 192 and 221							
<sup>2</sup> Studies 294 and 201							
<sup>3</sup> As of 22 August 2012							

Table 10 Clinical Laboratory Safety Data by Age and Source

Analyte	Age (years)	Number of Patients in Controlled Studies <sup>1</sup>		Number of Patients in Open Label Studies <sup>2</sup>
		Patients on drug	Patients on placebo	
Albumin	3 ≤ 10	52	53	92
	10 - 12	37	14	55
	13 - 16	67	28	98
Alkaline phosphatase	3 ≤ 10	53	53	93
	10 - 12	37	14	55
	13 - 16	66	27	97
BUN	3 ≤ 10	27	39	57
	10 - 12	26	11	42
	13 - 16	36	23	64
Calcium	3 ≤ 10	53	53	92
	10 - 12	37	14	55
	13 - 16	66	27	97
Chloride	3 ≤ 10	53	53	93
	10 - 12	37	14	55
	13 - 16	66	28	97
Cholesterol	3 ≤ 10	53	53	93
	10 - 12	37	14	55
	13 - 16	66	28	97
Creatinine	3 ≤ 10	53	53	93
	10 - 12	37	14	55
	13 - 16	66	28	97
Glucose	3 ≤ 10	53	53	93
	10 - 12	37	14	55
	13 - 16	66	28	97
LDH	3 ≤ 10	53	53	93
	10 - 12	37	14	55
	13 - 16	66	28	97
Phosphorus	3 ≤ 10	48	44	88
	10 - 12	29	9	45
	13 - 16	56	20	85
Potassium	3 ≤ 10	53	53	93
	10 - 12	37	14	55
	13 - 16	66	27	97
SGOT/AST	3 ≤ 10	53	53	87
	10 - 12	37	14	47
	13 - 16	66	28	87
SGPT/ALT	3 ≤ 10	52	53	61
	10 - 12	37	13	47
	13 - 16	67	28	78
Total bilirubin	3 ≤ 10	52	53	92
	10 - 12	37	14	55

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Table: Clinical Laboratory Safety Data by Age and Source (Continued)

Analyte	Age (years)	Number of Patients in Controlled Studies <sup>1</sup>		Number of Patients in Open Label Studies <sup>2</sup>
		Patients on drug	Patients on placebo	
Total protein	13 - 16	66	26	97
	3 ≤ 10	52	53	92
	10 - 12	37	14	55
	13 - 16	66	28	97
Uric acid	3 ≤ 10	53	53	93
	10 - 12	37	13	55
	13 - 16	65	28	96
<sup>1</sup> Studies 118, 192 and 221				
<sup>2</sup> Studies 294 and 201				

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**Table 11 Hematology Safety Data**

Analyte	Age (years)	Number of Patients in Controlled Studies <sup>1</sup>		Number of Patients in Open Label Studies <sup>2</sup>
		Patients on drug	Patients on placebo	
Basophils	3 ≤ 10	49	53	89
	10 - 12	39	12	56
	13 - 16	60	26	91
Eosinophils	3 ≤ 10	50	53	90
	10 - 12	39	13	56
	13 - 16	62	26	92
Hematocrit	3 ≤ 10	54	52	93
	10 - 12	39	13	56
	13 - 16	63	26	93
Hemoglobin	3 ≤ 10	54	53	93
	10 - 12	39	13	56
	13 - 16	63	26	93
Lymphocytes	3 ≤ 10	52	53	91
	10 - 12	39	13	56
	13 - 16	62	26	92
Monocytes	3 ≤ 10	51	53	91
	10 - 12	39	13	56
	13 - 16	63	26	93
Neutrophils	3 ≤ 10	50	52	91
	10 - 12	37	12	55
	13 - 16	61	26	91
Platelet count	3 ≤ 10	48	42	88
	10 - 12	32	10	47
	13 - 16	52	17	80
RBC	3 ≤ 10	35	18	48
WBC	10 - 12	17	5	23
	13 - 16	39	7	48
	3 ≤ 10	54	53	93
	10 - 12	39	13	56
	13 - 16	63	26	93
<sup>1</sup> Studies 118, 192 and 221				
<sup>2</sup> Studies 294 and 201				

**Table 12 Vital Signs, Weight, and Height Data by Age and Source**

Analyte	Age (years)	Number of Patients in Controlled Studies <sup>1</sup>		Number of Patients in Open Label Studies <sup>2</sup>
		Patients on drug	Patients on placebo	
Systolic BP	3 ≤ 10	55	56	105
	10 - 12	41	16	63
	13 - 16	67	30	100
Diastolic BP	3 ≤ 10	55	56	105
	10 - 12	41	16	63
	13 - 16	67	30	100
Pulse	3 ≤ 10	55	56	105
	10 - 12	41	16	64
	13 - 16	67	30	100
Weight	3 ≤ 10	55	58	106
	10 - 12	41	16	64
	13 - 16	67	30	100
Baseline height	3 ≤ 10	43	28	93
	10 - 12	26	11	44
	13 - 16	52	17	84
<sup>1</sup> Studies 118, 192 and 221				
<sup>2</sup> Studies 294 and 201				

Tables of pediatric patients with available Visual perimetry data are presented in section 7.3.5 of this review.

## 7.2.2 Explorations for Dose Response

With the exception of fixed-dose Study 118, in which each patient was assigned to a vigabatrin dose group using the protocol-specified dose groups (20, 60, or 100 mg/kg/day), the clinical pediatric rCPS studies used flexible dosing regimens (over a range of 0.5 to 4 grams/day) that allowed titration based on body weight and treatment response. In the three controlled pediatric rCPS studies (Studies 118, 192, and 221), the median vigabatrin dose was 49.4 mg/kg (range of 8.0 – 105.9 mg/kg). For analysis of these studies, each patient was assigned to a vigabatrin dose group using the patient's modal dose. In order to allow for cross-study pooling of safety data, each patient was assigned to one of two vigabatrin dosing level groups: < 60 mg/kg/day and ≥ 60 mg/kg/day. The dosage of 60 mg/kg/day was chosen as the "boundary" between these two groups because drug exposure in pediatric patients from this dosing level approximately corresponds to the exposure in adults from the recommended adult dosage of 3,000 mg/day.

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Throughout the sponsor's Integrated Summary of Safety (ISS), vigabatrin dose groups for summarization are described by the sponsor as  $< 60$  mg/kg/day and  $\geq 60$  mg/kg/day.

### 7.2.3 Special Animal and/or In Vitro Testing

See section 1.4 of this review.

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## 7.2.4 Routine Clinical Testing

Table 13 Safety Parameters included in the Vigabatrin Clinical Program

**Table 2. Safety Parameters Included in the Vigabatrin Clinical Program Included in this Integrated Summary of Safety**

Safety Parameter	Controlled Pediatric CPS Studies 118, 192, and 221	Open-Label Extension Studies 201 and 294	EMA Article 12 Studies 4020 and R003	Open-label Study 0098
Disposition	X	X	n/a	n/a
Exposure				
Distribution of days	X	X	n/a	n/a
VGB modal and maximum daily dose	X	X	n/a	n/a
Cumulative VGB dose	X	X	n/a	n/a
Demographics	X	X	n/a	n/a
Concomitant medications	X	X	n/a	n/a
Treatment-emergent AEs (Section 2.4.1)				
Overview	X	X	n/a	X
≥1%, ≥2%, ≥5%, by severity, drug-related, and by age, sex, and race	X	X	n/a	n/a
Incidence and prevalence	n/a	X	n/a	n/a
Listing of patients with an outcome of death	X	X	X	X
Treatment-emergent SAEs (overall, ≥1%, drug-related, and by age, sex, and race) <sup>a</sup>	X	X	n/a	n/a
Incidence of TEAEs resulting in discontinuation of study drug	X	X	X	X
Incidence of events and clinical laboratory results of special interest	X	X	X	X
Routine clinical laboratory tests (hematology and chemistry; see Section 2.4.2)				
Change from baseline	X	X	n/a	n/a
Shift to lower or higher	X	X	n/a	n/a
Incidence of PCS (overall and by age, sex, and race)	X	X	n/a	n/a
Incidence of elevated liver enzymes	X	X	n/a	n/a
Physical examinations (see Section 2.4.3)	n/a	n/a	n/a	n/a
Vital signs (see Section 2.4.3)				
Change from baseline	X	X	n/a	n/a
Incidence of PCS	X	X	n/a	n/a
Incidence of PCS defined by previous submission criteria	X	X	n/a	n/a
Incidence of ≥ 7% weight increase from baseline	X	X	n/a	n/a
Change from baseline in height and weight Z-scores (see Section 2.4.6)	X	X	n/a	n/a
Perimetry evaluations <sup>b</sup> (see Section 2.4.4)				
By exposure, dose, and age group	X	X	n/a	n/a
By length of follow-up, dose, age group, and Sabril exposure	n/a	n/a	X	n/a
Neuropsychological assessments (see Section 2.4.5)	X	X	n/a	n/a

n/a = not applicable; PCS = potentially clinically significant

- a SAEs were collected in a pharmacovigilance database rather than a clinical database for Study 0098. For Study 4020, the collection of AEs differed by group (AEs were not collected consistently among the groups). Study R003 enrolled only 1 pediatric CPS patient. Therefore, summaries of SAEs in these studies were not prepared.
- b Perimetry evaluations were performed in Studies 118, 201, 4020, and R003 and included standard ophthalmologic evaluations (acuity, color vision, and anterior and posterior segments), assessments of possible physiological correlates of vision toxicity (electroretinogram and visual evoked potential), and tests for clinically observable loss of visual field (perimetry and confrontation) (see Report 15650A).

## 7.2.5 Metabolic, Clearance, and Interaction Workup

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Completed with original NDA submission.

## 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Vigabatrin has a unique mechanism of action. It binds irreversibly to the GABA transaminase and thus raises the level of the inhibitory neurotransmitter GABA in the central nervous system. There are other antiepileptic drugs which enhance GABAergic transmission. These include valproate, gabapentin, pregabalin, and tiagabine. The usual adverse effects associated with these other GABAergic antiepileptic drugs are typical of the whole class of antiepileptic drugs and include somnolence, sedation, and ataxia. These adverse reactions were noted in both adult and pediatric studies of vigabatrin and are included in the proposed labeling.

## 7.3 Major Safety Results

### 7.3.1 Deaths

No deaths were reported in the Controlled Pediatric CPS Studies (Studies 118, 192, 221) or in open extension Study 294.

In open extension study 201, one 17 year-old female patient (16 years old at the time of study entry) who had received 1,000 mg daily (< 60 mg/kg/day) of vigabatrin for 20 months died while being hospitalized for elective intracranial monitoring as a candidate for lobectomy for intractable epilepsy. She was on concomitant medications carbamazepine 400 mg BID (duration unknown) and fluoxetine (dose and duration unknown). On (b) (6) of her vigabatrin therapy, she underwent "surgery" [presumably surgical placement of depth electrodes] and postoperatively that same day experienced severe status epilepticus and hypotension treated with intravenous fosphenytoin, phenobarbital, levophed, dopamine, ceftazadine, clindamycin, and gentamycin. She subsequently developed multi-system organ failure with severe hepatic failure. She died as a result of these complications on (b) (6). The detailed patient narrative is presented in Appendix 9.4 of this review.

#### **Reviewer Note:**

***An attempt to determine the cause of the fatal liver failure experienced by this patient is confounded by several alternative explanations. The fact that she had been on vigabatrin at the same relatively low dose level for the prior 20 months makes vigabatrin seem less likely to be the cause. She appears to have been on the same vigabatrin dose right up to the morning of the surgical procedure, so***

***there is no suggestion of withdrawal from vigabatrin as a cause of the status epilepticus. Either an unspecified anesthetic agent possibly given at surgery or the fosphenytoin given to treat her status epilepticus may also have caused the liver failure. However, the liver failure seems most likely to have been part of multiple organ failure due to hemodynamic shock from undefined post-operative complications and from the status epilepticus.***

***Adult studies and postmarketing reports do not suggest that vigabatrin is an hepatotoxic drug. This confounded case would not be the basis for a change in labeling.***

### **Studies R4020 and R003**

No pediatric deaths occurred in EMA Article 12 Study R4020.

Only one pediatric patient was enrolled in Study R003, and this patient did not die.

### **Open-Label Study 0098**

As described previously, this study was a flexible dose, open label observational study of partial seizure patients who were poorly controlled on their standard AED therapy or patients who had rolled over from other Sabril protocols including the long-term pediatric open label extension study 201. Most of the 1264 patents were adults but 60 pediatric patients from Study 201 were included. The final study report for Study 0098 indicates that there was one pediatric death. This was a 14 year old male patient (11920014) whose cause of death is listed a seizure. There is no patient narrative available to the current sponsor because the prior sponsor did not have it.

### **Reviewer Note:**

***Because the patients in these refractory complex partial seizure studies are patients with severe seizure disorders, it is not unexpected that one of the patients would die as a result of seizures. There is no suggestion from the other safety data in adults and pediatric patients to suggest that vigabatrin exacerbates any specific seizure type. In fact, in the Controlled Pediatric rCPS Studies (118, 192, and 221) , the rate if patient discontinuation due to seizures was higher in the placebo groups than in the vigabatrin groups as noted in sections 6.1.3 and 7.3.3 of this review.***

### **CPEN Study**

Of the 69 patients with infantile spasms enrolled in the CPEN study, one infantile spasms patient died before receiving any dose of vigabatrin therapy.

A summary of all narratives of patient deaths is presented in Appendix 9.4 of this review.

### 7.3.2 Nonfatal Serious Adverse Events

Narratives for each patient who experienced an SAE in Study 118, Study 192, Study 221, Study 201, and Study 294 are presented in the individual CSRs for Study 118, Study 192, Study 221, Study 201 and Study 294, respectively. In addition, the sponsor prepared narratives for patients in Study 118 and Study 201 who experienced an SAE, but had no narrative in the CSR. For additional clarity, the sponsor also prepared narratives for select patients in Study 118, Study 201, and Study 294 who experienced an SAE and had a narrative in the CSR.

### Controlled Pediatric CPS Studies

The incidence of treatment-emergent SAEs in the Controlled Pediatric CPS Studies was low and similar across the treatment groups

Convulsion was the only treatment-emergent SAE reported by  $\geq 5.0\%$  of patients in any treatment group. Convulsion was reported by a higher percentage of patients in the placebo group (5.8%) than in the all vigabatrin group (0.6%).

### Table 14 Serious Adverse Effects in Controlled rCPS Pediatric Studies

**Table 17. Treatment-Emergent Serious Adverse Events Reported by  $\geq 1.0\%$  and at Least Two Patients in Any Treatment Group – Controlled Pediatric CPS Studies**

		< 60 mg/kg/day	$\geq 60$ mg/kg/day	
System Organ Class	Placebo	Vigabatrin	Vigabatrin	All Vigabatrin
Preferred Term	N = 104 n (%)	N = 95 n (%)	N = 68 n (%)	N = 165 n (%)
Patients with $\geq 1$ treatment-emergent SAE	8 (7.7)	5 (5.3)	3 (4.4)	8 (4.8)
Nervous system disorders	7 (6.7)	4 (4.2)	2 (2.9)	6 (3.6)
Convulsion	6 (5.8)	0	1 (1.5)	1 (0.6)
Status epilepticus	1 (1.0)	3 (3.2)	1 (1.5)	4 (2.4)

AE = adverse event; CPS = complex partial seizures; PT = preferred term; SAE = serious adverse event; SOC = system organ class

Note: An AE was considered treatment-emergent if the AE started on or after the first dose of study drug.

Note: Each patient was counted only once within each SOC and PT.

A summary of treatment-emergent SAEs reported by  $\geq 1\%$  of patients in the Controlled Pediatric CPS Studies is presented in the sponsor's Table 17. The incidence of

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treatment-related SAEs was low ( $\leq 2.1\%$ ) across all treatment groups in the Controlled Pediatric CPS Studies.

No treatment-related SAE was reported by more than one patient in any treatment group.

There were no rare SAEs such as hepatic failure (except for one confounded case narrative of fatality from Study 201 discussed above), bone marrow depression, or Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN) reported in the Controlled Pediatric CPS Studies.

**Reviewer Note:**

***Independent of this current submission, there have been five non-U.S. postmarketing reports of SJS/TEN associated with vigabatrin identified by the Agency's Office of Surveillance and Epidemiology (OSE) in the FDA Adverse Event Reporting System (FAERS) and the World Health Organization (WHO) Individual Case Safety Report Database (VigiBase). These are discussed in section 8 of this review. SJS/TEN will be added to the Post Marketing Experience section of the labeling being approved for this current submission.***

All Pediatric CPS Studies

The incidence of treatment-emergent SAEs in All Pediatric CPS Studies was 20.0% and 31.1% in the  $< 60$  mg/kg/day vigabatrin and  $\geq 60$  mg/kg/day vigabatrin treatment groups, respectively (Table 18). Convulsion, status epilepticus, and visual field defect were the only treatment-emergent SAEs reported by  $\geq 5.0\%$  of patients in either treatment group.



**Table 15 Serious Adverse Effects in All rCPS Pediatric Studies**

**Table 18. Treatment-Emergent Serious Adverse Events Reported by  $\geq 1.0\%$  and at Least Two Patients in Either Vigabatrin Group – All Pediatric CPS Studies**

	< 60 mg/kg/day Vigabatrin N = 165	$\geq 60$ mg/kg/day Vigabatrin N = 103	All Vigabatrin N = 273
System Organ Class Preferred Term	n (%)	n (%)	n (%)
Patients with $\geq 1$ treatment-emergent SAE	33 (20.0)	32 (31.1)	66 (24.2)
Nervous system disorders	28 (17.0)	25 (24.3)	54 (19.8)
Complex partial seizures	2 (1.2)	0	2 (0.7)
Convulsion	6 (3.6)	8 (7.8)	15 (5.5)
Headache	2 (1.2)	1 (1.0)	3 (1.1)
Status epilepticus	3 (1.8)	6 (5.8)	9 (3.3)
Visual field defect	17 (10.3)	8 (7.8)	25 (9.2)
Psychiatric disorders	4 (2.4)	3 (2.9)	7 (2.6)
Abnormal behaviour	1 (0.6)	2 (1.9)	3 (1.1)
Depression	1 (0.6)	2 (1.9)	3 (1.1)

AE = adverse event; CPS = complex partial seizures; PT = preferred term; SAE = serious adverse event; SOC = system organ class

Note: An AE was considered treatment-emergent if the AE started on or after the first dose of study drug.

Note: Each patient was counted only once within each SOC and PT.

A summary of treatment-emergent SAEs reported by  $\geq 1\%$  of patients in All Pediatric CPS Studies is presented in the sponsor's Table 18. The incidence of treatment-related SAEs was  $\leq 10.3\%$  in each of the vigabatrin-treatment groups in All Pediatric CPS Studies.

Convulsion and visual field defect were the only treatment-related SAEs reported by more than one patient in either treatment group.

There were no rare SAEs such as hepatic failure (except for one confounded case narrative of fatality from Study 201 discussed above), bone marrow depression, or Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN) reported in All Pediatric CPS Studies.

**Reviewer Note:**

**See the immediately previous Reviewer Note for discussion of Stevens-Johnson syndrome/ toxic epidermal necrolysis.**

**The occurrence of convulsions as a SAE requiring hospitalization is not uncommon in clinical studies with patients who have refractory CPS. There is no suggestion that vigabatrin is exacerbating the frequency of seizures in this population.**

***Visual field defects are discussed in detail in sections 7.3.5 and 7.7 of this review.***

### **EMA Article 12 Studies (Study 4020 and Study R003)**

In Study 4020, the only the visual adverse effects were classified by seriousness. No pediatric patients discontinued the study because of an adverse effect.

In Study R003, no SAEs were reported for the one pediatric patient enrolled.

### **Open-Label Study 0098**

The prior sponsor entered SAEs for Study 0098 into their post-marketing safety database but they were not included in the clinical database. Since data collected for a post-marketing safety database may differ qualitatively from data collected for a clinical trial database, SAEs for this study are not presented by the current sponsor in this submission.

### **CPEN Study**

One patient randomized to the vigabatrin group died due to a cardio-respiratory arrest that began before the patient received any dose of vigabatrin. Four additional patients (10.3%) in the vigabatrin group experienced treatment-emergent SAEs during the study, including severe status epilepticus and severe rash in 1 patient and severe kidney infection, moderate convulsion, and mild convulsion in 1 patient each.

### **Reviewer Note:**

***The patient in the CPEN study who experienced status epilepticus and later a severe rash was an 11 month old male patient who was diagnosed with infantile spasms and started on vigabatrin on September 18, 2004. He was hospitalized for status epilepticus on (b) (6). The status epilepticus resolved that day, and the patient's vigabatrin dose was subsequently increased to 1000 mg qAM and 1250 mg qPM. He remained in the CPEN study. He was started on carbamazepine in January of 2005. Three weeks later, on February 7, 2005, he experienced a rash that first appeared on his cheeks and then spread to his face, body hands, and feet. Carbamazepine was stopped. A virology work-up to rule out Kawasaki's disease was normal. The rash was considered probably related to either infection or to carbamazepine. The rash was not considered suggestive of Stevens Johnson Syndrome or toxic epidermal necrolysis, and no mucosal involvement was reported.***

***The timing of the rash does suggest that carbamazepine or infection were more likely etiologies than vigabatrin. As discussed elsewhere in this review, post marketing reports, although confounded, suggest that vigabatrin may have caused Stevens Johnson syndrome/ toxic epidermal necrolysis in several patients. See section 8 of this review.***

### 7.3.3 Dropouts and/or Discontinuations

#### Adverse Events Resulting in Premature Discontinuation of Study Drug

##### Controlled Pediatric CPS Studies

The incidence of TEAEs that led to premature discontinuation of study drug during the Controlled Pediatric CPS Studies was 4.8% in the placebo group and 8.5% in the all vigabatrin group, with a higher incidence in the < 60 mg/kg/day vigabatrin group compared to the ≥ 60 mg/kg/day vigabatrin group (10.5% and 5.9%, respectively) (See sponsor's Table 19 reproduced below).

**Table 16 Adverse Effects Leading to Premature Discontinuation in Controlled rCPS Pediatric Studies**

**Table 19. Treatment-Emergent Adverse Events Resulting in Premature Discontinuation of Study Drug by ≥ 1.0% and at Least Two Patients in Any Treatment Group – Controlled Pediatric CPS Studies**

	Placebo N = 104	< 60 mg/kg/day Vigabatrin N = 95	≥ 60 mg/kg/day Vigabatrin N = 68	All Vigabatrin N = 165
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)
Patients with ≥ 1 TEAE	5 (4.8)	10 (10.5)	4 (5.9)	14 (8.5)
Nervous system disorders	5 (4.8)	7 (7.4)	2 (2.9)	9 (5.5)
Convulsion	4 (3.8)	3 (3.2)	1 (1.5)	4 (2.4)

AE = adverse event; CPS = complex partial seizures; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event

Note: An AE was considered treatment-emergent if the AE started on or after the first dose of study drug.

Note: Each patient was counted only once within each SOC and PT.

##### All Pediatric CPS Studies

The incidence of TEAEs that led to premature discontinuation of study drug during All Pediatric CPS Studies was 23.6% in < 60 mg/kg/day vigabatrin group and 21.4% in the

≥ 60 mg/kg/day vigabatrin group (Table 20). Convulsion was the only TEAEs that led to premature discontinuation of study drug reported by ≥ 5.0% of patients in either treatment group.

### Table 17 Adverse Effects Leading to Premature Discontinuation in All rCPS Pediatric Studies

**Table 20. Treatment-Emergent Adverse Events Resulting in Premature Discontinuation of Study Drug Reported by ≥ 1.0% and at Least Two Patients in Either Vigabatrin Group – All Pediatric CPS Studies**

	< 60 mg/kg/day Vigabatrin N = 165	≥ 60 mg/kg/day Vigabatrin N = 103	All Vigabatrin N = 273
System Organ Class Preferred Term	n (%)	n (%)	n (%)
Patients with ≥ 1 TEAE	39 (23.6)	22 (21.4)	61 (22.3)
Nervous system disorders	25 (15.2)	14 (13.6)	39 (14.3)
Ataxia	2 (1.2)	0	2 (0.7)
Convulsion	10 (6.1)	12 (11.7)	22 (8.1)
Dysarthria	2 (1.2)	0	2 (0.7)
Tremor	2 (1.2)	0	2 (0.7)
Visual field defect	3 (1.8)	1 (1.0)	4 (1.5)
Psychiatric disorders	12 (7.3)	5 (4.9)	17 (6.2)
Abnormal behaviour	3 (1.8)	3 (2.9)	6 (2.2)
Aggression	3 (1.8)	0	3 (1.1)
Depression	2 (1.2)	1 (1.0)	3 (1.1)

AE = adverse event; CPS = complex partial seizures; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event

Note: An AE was considered treatment-emergent if the AE started on or after the first dose of study drug.

Note: Each patient was counted only once within each SOC and PT.

### Reviewer Note:

**Review of the patient narratives for discontinuation indicate that the other patients mostly discontinued because of a variety of mild adverse effects and that a few withdrew for administrative reasons.**

### EMA Article 12 Studies (Study 4020 and Study R003)

In Study 4020, the only the visual adverse effects were classified by seriousness. No pediatric patients discontinued the study because of an adverse effect.

For Study R003, the one pediatric patient enrolled completed the study.

### Open-Label Study 0098

Disposition was not summarized in the Study 0098 clinical study report.

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## CPEN Study

No patients dropped out or discontinued.

### 7.3.4 Significant Adverse Events

See sections 7.3.5 and 7.7 of this review.

### 7.3.5 Submission Specific Primary Safety Concerns (Visual Loss)

See section 7.7 of this review for specific safety issues (other than visual loss) identified in the PWR and individually addressed in this submission.

## Visual Loss

These two tables summarize patients with interpretable visual perimetry data from controlled rCPS clinical studies, open label rCPS studies, the Sabril registry, and EMA Article 12 Study 4020.

**Table 18 Patients with Interpretable Goldmann or Humphrey Visual Perimetry from U.S. Controlled rCPS Studies, Open Label rCPS Studies, and the Sabril Registry**

Age (years)	Total Number of Patients on Drug	Number of Patients in Controlled Studies <sup>1</sup>		Number of Patients in Open Label Studies <sup>2</sup>		Number of Patients from Registry Data <sup>3</sup>	
		Patients on drug	Patients on placebo	Patient exposure ≥ 6 mos.	Patient exposure ≥ 12 mos.	Patient exposure ≥ 6 mos.	Patient exposure ≥ 12 mos.
3 ≤ 10	11	0	0	11	11	15	13
10 - 12	12	1	1	12	12	7	6
13 - 16	27	2	1	27	26	18	17
Total	50	3	2	50	49	40	37
<sup>1</sup> Studies 118, 192 and 221							
<sup>2</sup> Studies 294 and 201							
<sup>3</sup> As of 22 August 2012							

**Table 19 Patients with Interpretable Goldmann or Humphrey Visual Perimetry from EMA Article 12 Study 4020**

Age (years)	Number of Sabril- Naïve Patients at Time of Enrollment	Number of Previous Sabril Users at Time of Enrollment		Number of Current Sabril Users at Time of Enrollment	
		Previous exposure $\geq 6$ mos.	Previous exposure $\geq 12$ mos.	Patient Follow-up $\geq 6$ mos.	Patient Follow-up $\geq 12$ mos.
3 $\leq$ 10	8	8	8	9	8
10 - 12	29	17	16	22	20
13 - 16	12	10	13	14	13
Total	49	35	37	45	41

### **Perimetry (Goldmann and Humphrey) in Pediatric Subjects:**

Perimetry testing was not performed in Controlled rCPS Studies 192 and 221. (Protocol Amendment 4 for Study 118 was added to require perimetry, but then the study was prematurely discontinued as this amendment was being implemented. Only 3 patients had perimetry performed with no baseline perimetry on any of them.).

Perimetry testing was not performed in Study 294 which was the open label follow-on study for subjects who had completed Study 192.

No visual assessment was done in Open-label Study 0098.

### **Perimetry testing was performed in 3 studies (Open label follow-on Study 201 and EMA Studies R003 and R4020).**

Perimetry results for Studies 201 and R003 were submitted with the original NDA. Analyses for Study R4020 were performed for a subset of adult and pediatric subjects who underwent kinetic perimetry testing.

Perimetry results for Studies 201, R003, and R4020 were as follows:

### **Perimetry in Study 201**

Study 201 was a multicenter, long-term, follow-up, open-label trial in pediatric subjects with CPS with or without secondary generalization who had previously participated in Study 118 or Study 221. Pediatric subjects from these two preceding placebo-controlled studies of vigabatrin were enrolled and treated with open-label vigabatrin for up to 48 or more additional weeks.

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Because the amendment to perform perimetry was implemented after most subjects had already completed 1 year of the follow-up protocol and because some of the sites had trouble performing the perimetry on children, only 70 subjects had formal visual field testing done.

Of these 70 subjects, 66 had visual fields performed using either the Humphrey or Goldman method of perimetry. Four subjects had visual fields performed using the Octopus method of perimetry (i.e., automated Goldmann).

However, the perimetry was added by protocol amendment near study termination and few subjects had baseline measurements.

All of the visual fields obtained for the 70 subjects were independently reviewed by an expert in perimetry, (b) (4). A summary of this review is presented in Sponsor's Table 4 from of the Summary of Pediatric Vision Data Report 15650A (March 29, 2013).

## **Table 20 Consultant's Evaluation of Full Visual Field Testing Results from Study 201**

**Table 4. Consultant's Evaluation of Full Visual Field Test Results (Study 201)**

Evaluation	Number of Subjects	Percent <sup>a</sup>
Normal visual fields	25	36
Vigabatrin-associated field defect	9	13 <sup>b</sup>
VFD attributable to other known cause	5	7
Unevaluable	29	41
Pending	2	3

<sup>a</sup> Denominator includes all subjects with non-missing responses within each visit and test.

<sup>b</sup> 9/41 (22%) of evaluable subjects tests

Cross-Reference: Study 201 CSR Appendix E.12.5

Of the 9 subjects with vigabatrin-associated VFDs, 2 subjects (13810010 and 13830001) had defects identified in only 1 eye and both were rated a Grade 1 out of 4 in severity by (b) (4). One subject (13970004) had a vigabatrin-associated VFD identified after approximately 1 year of vigabatrin therapy that was not present at his final visit 6 months later. The subject remained on vigabatrin the entire time.

## **Perimetry in Study R003**

In Study R003, there was one enrolled child (a white male 10 years of age with blue eyes). The subject received vigabatrin for 825 days with a total cumulative dose of 1186.75 grams. No VFD was reported for the subject.



## Perimetry in Study R4020

Study R4020 was an open-label, multicenter, comparative study conducted at 46 sites in France, South Korea, Italy, Spain, and Australia. Subjects aged  $\geq 8$  years with refractory partial seizures were enrolled and grouped: those receiving vigabatrin for  $\geq 6$  months (Group 1); those who had received vigabatrin for  $\geq 6$  months and then had discontinued for  $\geq 6$  months (Group 2); and those naïve to vigabatrin (Group 3). Subjects underwent static or kinetic perimetry, or both, every 4—6 months for  $\geq 3$  years. For kinetic perimetry, the temporal and nasal visual fields were measured along the horizontal meridian with the largest (V4e, IV4e) and smallest (I2e, I1e) isopters, respectively.

Of the 214 pediatric subjects in Study 4020, there were 98 enrolled subjects  $\geq 10$  to  $< 17$  years of age, and 132 subjects  $< 18$  years of age who had Goldmann perimetry performed. An additional 209 adult subjects ( $\geq 18$  years of age) had Goldmann perimetry performed. Of these subjects, there were 35 children  $< 18$  years of age and 54 adults who were vigabatrin-naïve at enrollment.

**Table 21 Study Groups Based on Age and Treatment History for Subjects with Goldmann Perimetry Data (Study R4020)**

Group	Description	Number of Subjects		
		Children $\geq 10$ to $< 17$ years (N = 98)	Children $< 18$ years (N = 132)	Adults $\geq 18$ years (N = 209)
1	Subjects currently being treated with vigabatrin for $\geq 6$ months	31	45	75
2	Subjects previously treated with vigabatrin for $\geq 6$ months who had discontinued for $\geq 6$ months before study entry	38	52	80
3	Subjects never treated with vigabatrin before study entry <sup>a</sup>	29	35	54

<sup>a</sup> Six subjects (5 children  $< 18$  years of age and 1 adult) in Group 3 began receiving vigabatrin during the course of the study and are included in the data analyses for both the vigabatrin-exposed and vigabatrin-naïve groups.

### Reviewer Note:

**EMA study R4020 was designed to determine the nature and incidence of visual field deficits after long-term exposures. It enrolled adequate numbers of both pediatric patients and adult patients. It included Group 3 patients who were vigabatrin-naïve at the time of enrollment in the study, although five pediatric patients in this vigabatrin-naïve group were allowed to start vigabatrin during the study (as noted in the footnote in the table above) because each patient's physician believed it was best therapy for them. Overall, despite its shortcomings, R4020 seems to be the most informative of the studies including**



***perimetry. Also, results from Studies 201 and R03 were already reviewed in the original NDA submission. Therefore, the perimetry result from R4020 will be presented in this review in greater detail than the results from Studies 201 and R03.***

Visual field defects, when they occurred in Study R4020, were most often mild or moderate and were not associated with symptoms of abnormal visual function. There was no clinically important difference between children and adults. Similar results were observed for the subset of patients  $\geq 10$  to  $< 17$  years of age.

Even among patients who were vigabatrin-naïve at baseline, there was substantial variability in extent of intact visual field at baseline and some patients had VFDs in the absence of vigabatrin exposure. There was also substantial variability upon retest of these patients.

For children, mean age varied across groups from 11.9 to 12.2 years, the majority of subjects were male, and mean duration of AED use varied across groups from 3.7 to 5.0 years (Table below). Subjects with a previous exposure to vigabatrin had a mean duration of use from 2.1 to 4.0 years across groups and mean time from first vigabatrin dose to first perimetry examination from 4.1 to 4.6 years across groups. Similar results were observed for children 10 to  $< 17$  years of age.

For adults, mean age varied across groups from 37.1 to 37.8 years, the majority of subjects were female, and mean duration of AED use varied across groups from 9.3 to 11.3 years.

Subjects with a previous exposure to vigabatrin had a mean duration of use from 2.4 to 4.1 years across groups and mean time from first vigabatrin dose to first perimetry examination from 4.2 to 5.7 years across groups.

**Table 22 Baseline Characteristics of the Study Groups (Study R4020)**

Characteristic	Children ≥10 to <17 years (n=98)			Children <18 years (n=132)			Adults (n=209)		
	Group 1 (N = 31)	Group 2 (N = 38)	Group 3 (N = 29)	Group 1 (N = 45)	Group 2 (N = 52)	Group 3 (N = 35)	Group 1 (N = 75)	Group 2 (N = 80)	Group 3 (N = 54)
Sex, n (%)									
Male	12 (38.7)	20 (52.6)	16 (55.2)	19 (42.2)	31 (59.6)	20 (57.1)	35 (46.7)	43 (53.8)	23 (42.6)
Female	19 (61.3)	18 (47.4)	13 (44.8)	26 (57.8)	21 (40.4)	15 (42.9)	40 (53.3)	37 (46.3)	31 (57.4)
Mean age, years ±SD	12.5 ± 2.0	12.2 ± 1.9	12.5 ± 2.0	12.2 ± 2.8	11.9 ± 2.7	12.1 ± 2.4	37.1 ± 14.0	37.8 ± 12.5	37.4 ± 12.4
N	31	38	NA	45	52	NA	75	79	NA
Mean duration of vigabatrin dosing at study entry, years ±SD	3.8 ± 2.9	2.3 ± 2.4	NA	4.0 ± 2.7	2.1 ± 2.2	NA	4.1 ± 2.6	2.4 ± 2.1	NA
N	31	38	NA	45	51	1	75	80	NA
Mean time from first vigabatrin dose to first perimetry examination, years ±SD	3.8 ± 2.9	5.0 ± 2.9	NA	4.1 ± 2.7	4.6 ± 2.8	NA	4.2 ± 2.6	5.7 ± 2.8	NA
N	23	36	29	35	50	35	69	79	54
Mean duration of AED use, years ±SD	4.6 ± 3.4	5.3 ± 3.3	3.8 ± 2.6	4.9 ± 4.0	5.0 ± 3.5	3.7 ± 2.4	10.4 ± 7.8	9.3 ± 8.0	11.3 ± 10.7

AED=antiepileptic drug; NA=not applicable; SD=standard deviation

Monocular temporal field at final Goldmann perimetry for vigabatrin-exposed children <18 years of age (based on the largest isopter tested) ranged from 13 to 90 degrees, and averaged 71.4 degrees (Table of Pediatric Final Perimetry and Figure 4 from Sponsor's Report 15650A reproduced below)).

When analyzed for the V4e and IV4e isopters, for which the most data were available, the mean retained temporal fields for vigabatrin-exposed children <18 years of age were 70.8 degrees (range, 11.5 to 90 degrees) and 72.4 degrees (range, 48 to 90 degrees), respectively. Similar results were observed for children ≥10 to <17 years of age.

Monocular nasal fields of vigabatrin-exposed children <18 years of age, based on the smallest isopter tested, ranged from 0 to 63.5 degrees, averaging 21.5 degrees (Final Perimetry Table below and Figure 4). When analyzed for the I2e and I1e isopters, for which the most data were available, the mean retained nasal fields were 22.2 degrees (range, 4.0 to 36.5 degrees) and 13.4 degrees (range, 3.0 to 35.0 degrees), respectively. The perimetry results from vigabatrin-exposed and vigabatrin-naïve children exhibited modest differences. Similar results were observed for children ≥10 to <17 years of age.

**Table 23 Degrees of Retained Visual Field Along the Horizontal Meridian in Children at Final Perimetry (Study 4020)**

**Table 7. Degrees of Retained Visual Field Along the Horizontal Meridian in Children at Final Perimetry (Study R4020)**

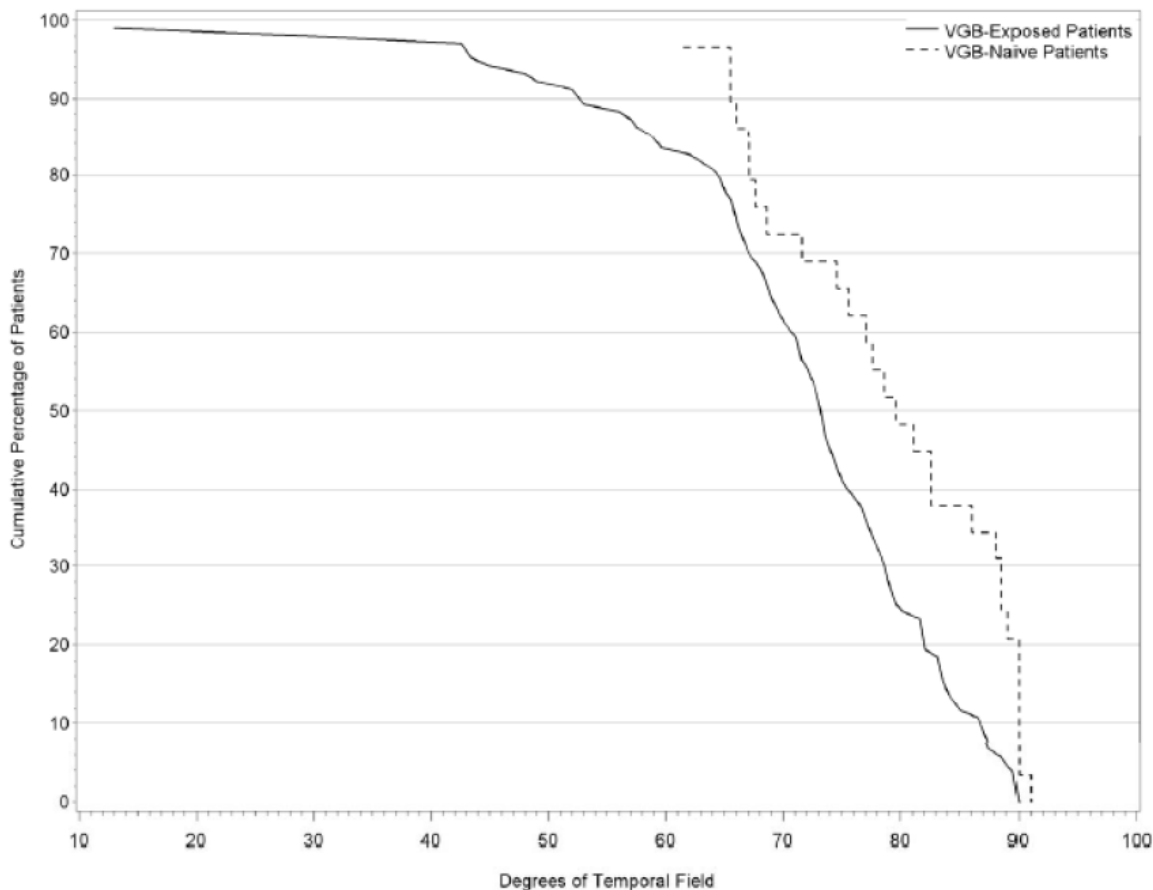
Group	Isopter	Sample Size	Mean	Median	Minimum	Maximum	SD
Children ≥10 to <17 Years							
Temporal field VGB-exposed	Largest	73	71.1	73.0	29.0	90.0	12.0
	V4e	52	69.4	72.3	11.5	90.0	16.7
	IV4e	31	73.3	73.0	53.0	90.0	9.7
VGB-naïve	Largest	25	79.3	79.5	61.5	91.0	9.4
	V4e	11	81.6	87.0	37.0	91.0	15.4
	IV4e	10	82.0	83.8	66.0	90.0	8.3
Nasal field VGB-exposed	Smallest	73	22.0	22.5	0.0	63.5	10.2
	I2e	24	22.2	23.3	10.0	36.5	6.6
	I1e	48	14.6	12.5	3.0	35.0	8.1
VGB-naïve	Smallest	25	24.1	26.0	4.5	44.5	11.8
	I2e	8	30.1	30.5	25.0	37.0	4.1
	I1e	13	15.7	15.5	4.5	40.0	9.3
Children <18 Years							
Temporal field VGB-exposed	Largest	103	71.4	73.5	13.0	90.0	13.4
	V4e	68	70.8	73.5	11.5	90.0	16.4
	IV4e	43	72.4	73.0	48.0	90.0	10.5
VGB-naïve	Largest	29	78.9	79.5	61.5	91.0	9.7
	V4e	15	80.4	86.0	37.0	91.0	15.4
	IV4e	12	79.5	79.3	66.0	90.0	9.5
Nasal field VGB-exposed	Smallest	103	21.5	22.5	0.0	63.5	10.6
	I2e	39	22.2	23.5	4.0	36.5	7.5
	I1e	66	13.4	11.5	3.0	35.0	7.7
VGB-naïve	Smallest	29	23.8	26.0	4.5	44.5	11.6
	I2e	10	29.0	29.0	19.5	37.0	4.9
	I1e	17	17.2	15.5	4.5	41.0	10.7

SD=standard deviation; VGB=vigabatrin

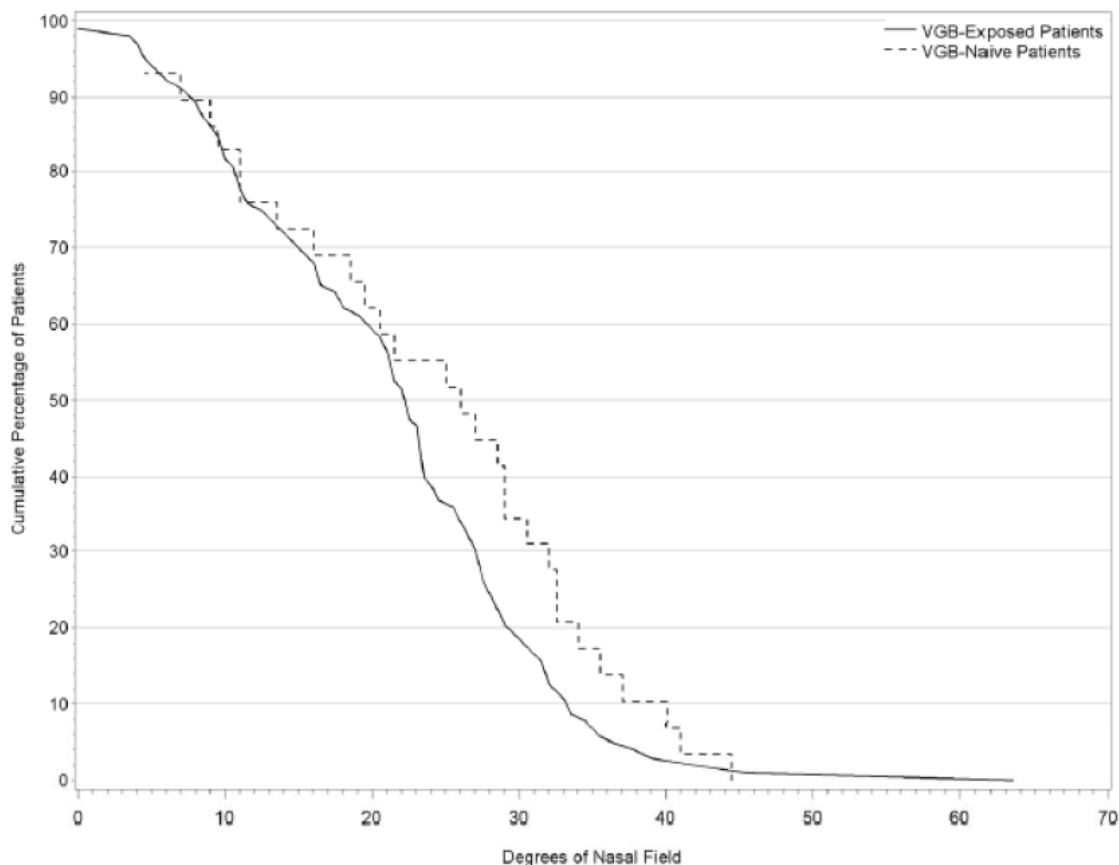
The cumulative distribution of degrees in the temporal visual field and nasal visual field at final perimetry in vigabatrin exposed and vigabatrin naïve children ≥10 to <17 years of age is provided in the Sponsor's Figure 4 (A) and (B).

**Figure 4 Cumulative Distribution of Degrees in the Temporal and Nasal Visual Fields at Final Perimetry in VGB-Exposed and VGB-Naïve Children < 18 Years of Age (Study R4020)**

**Figure 4. Cumulative Distribution of Degrees in the (A) Temporal Visual Field and (B) Nasal Visual Field at Final Perimetry in Vigabatrin-Exposed and Vigabatrin-Naïve Children <18 Years of Age (Study R4020)**



Note: Vigabatrin-Exposed(N=103) and Vigabatrin-Naïve(N=29)



Note: Vigabatrin-Exposed(N=103) and Vigabatrin-Naive(N=29)

Similar results were observed for adults. Based on the largest isopter tested, monocular 14.5 to 90 degrees, and averaged 70.8 degrees (Sponsor's Table below of Adult Final Perimetry from Report 15650A ). When analyzed for the V4e and IV4e isopters, for which the most data were available, the mean retained temporal fields for vigabatrin-exposed adults were 76.2 degrees (range, 14.5 to 90 degrees) and 67.5 degrees (range, 7 to 90 degrees), respectively.

Monocular nasal fields of vigabatrin-exposed adults, based on the smallest isopter tested, ranged from 2.5 to 52.5 degrees, averaging 18.5 degrees (Table 8). When analyzed for the I2e and I1e isopters, for which the most data were available, the mean retained nasal fields were 16.3 degrees (range, 4.5 to 31 degrees) and 13.1 degrees (range, 3.0 to 36.0 degrees), respectively. The perimetry results from vigabatrin-exposed and vigabatrin-naïve adults exhibited modest differences.

**Table 24 Degrees of Retained Visual Field Along the Horizontal Meridian in Adults at Final Perimetry (Study R4020)**

**Table 8. Degrees of Retained Visual Field Along the Horizontal Meridian in Adults at Final Perimetry (Study R4020)**

Group	Isopter	Sample Size	Mean	Median	Minimum	Maximum	SD
Temporal field VGB-exposed	Largest	155	70.8	72.5	14.5	90.0	15.5
	V4e	67	76.2	78.0	14.5	90.0	13.6
	IV4e	88	67.5	71.0	7.0	90.0	17.1
VGB-naïve	Largest	54	78.8	83.8	27.0	91.0	13.6
	V4e	25	83.5	87.5	25.0	91.0	13.1
	IV4e	26	74.4	81.3	39.5	90.0	15.2
Nasal field VGB-exposed	Smallest	153	18.5	16.5	2.5	52.5	10.7
	I2e	47	16.3	17.0	4.5	31.0	8.1
	I1e	91	13.1	11.5	3.0	36.0	6.7
VGB-naïve	Smallest	52	20.3	17.8	3.5	46.5	12.1
	I2e	18	17.8	22.5	0.0	33.5	10.7
	I1e	27	14.6	14.5	4.0	38.0	7.1

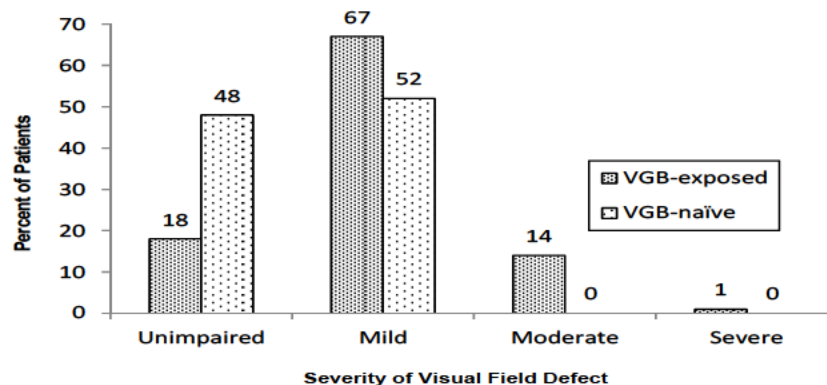
SD=standard deviation; VGB=vigabatrin

The retained temporal fields were classified as unimpaired (>80 degrees retained field, averaged for the 2 eyes), mildly impaired (60—80 degrees), moderately impaired (30—<60 degrees), and severely impaired (<30 degrees).

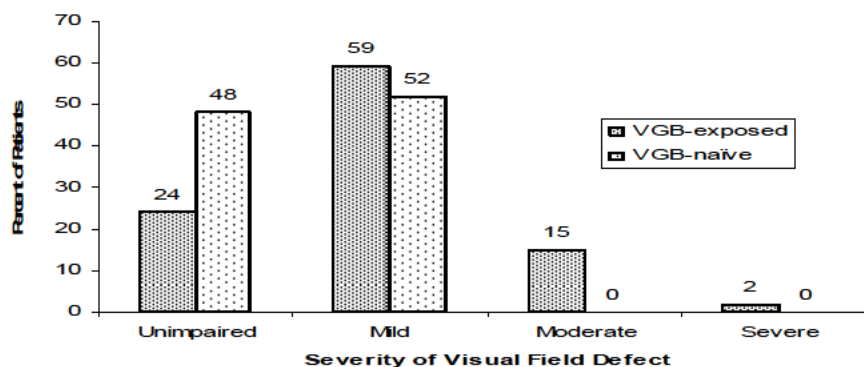
The distributions of temporal visual field impairment at the last kinetic perimetry examination for the largest isopter tested for vigabatrin-exposed and vigabatrin-naïve are shown in the Sponsor's Figure 5 for children and adults. Of vigabatrin-exposed children, the majority had unimpaired or had mild or moderate impairment of temporal visual fields, while ≤2% had severe impairment. Similar results were observed for vigabatrin-exposed and vigabatrin-naïve adults.

**Figure 5 Severity of Visual field Loss at Last Kinetic Perimetry in VGB-Exposed and VGB-Naïve Pediatric and Adult Patients (Study R4020)**

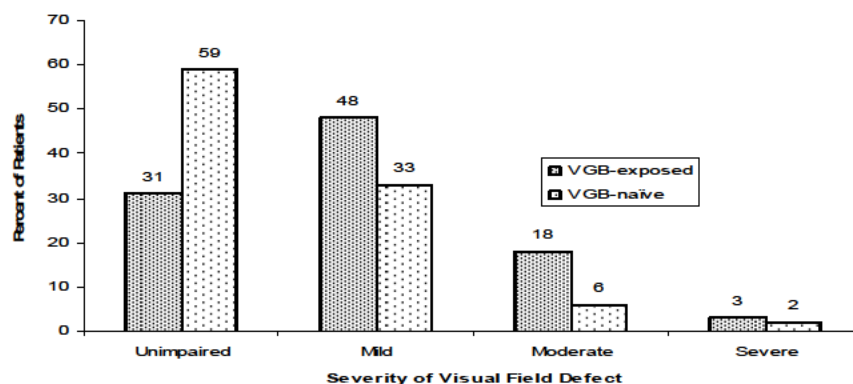
**Children  $\geq 10$  to  $< 17$  Years**



**Children  $< 18$  Years**



**Adults**



VGB=vigabatrin

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Unimpaired: >80 degrees monocular temporal field retained; mild: 60—80 degrees monocular temporal field retained; moderate: 30—<60 degrees monocular temporal field retained; severe: <30 degrees monocular temporal field retained. Measurements are of largest isopter tested at final Goldmann perimetry.

Cross-Reference: Appendix 8.6.1 Figure 9, Figure 10, Figure 11, and Figure 12; Appendix 8.6.2 Figure 3.1.1 and Figure 3.1.2

No generally agreed upon categorization of the severity of VFD exists. The severity categories chosen for the current analysis were intended to reflect the degree of resulting functional limitation. For example, 120 degrees of total width of the horizontal visual field (equivalent to 60 degrees of monocular temporal vision) is the limit for having a driver's license in many jurisdictions and was chosen as the dividing line between mild and moderate defect. The criterion of <30 degrees for a severe deficit is similar to that chosen for several published studies based on kinetic perimetry.

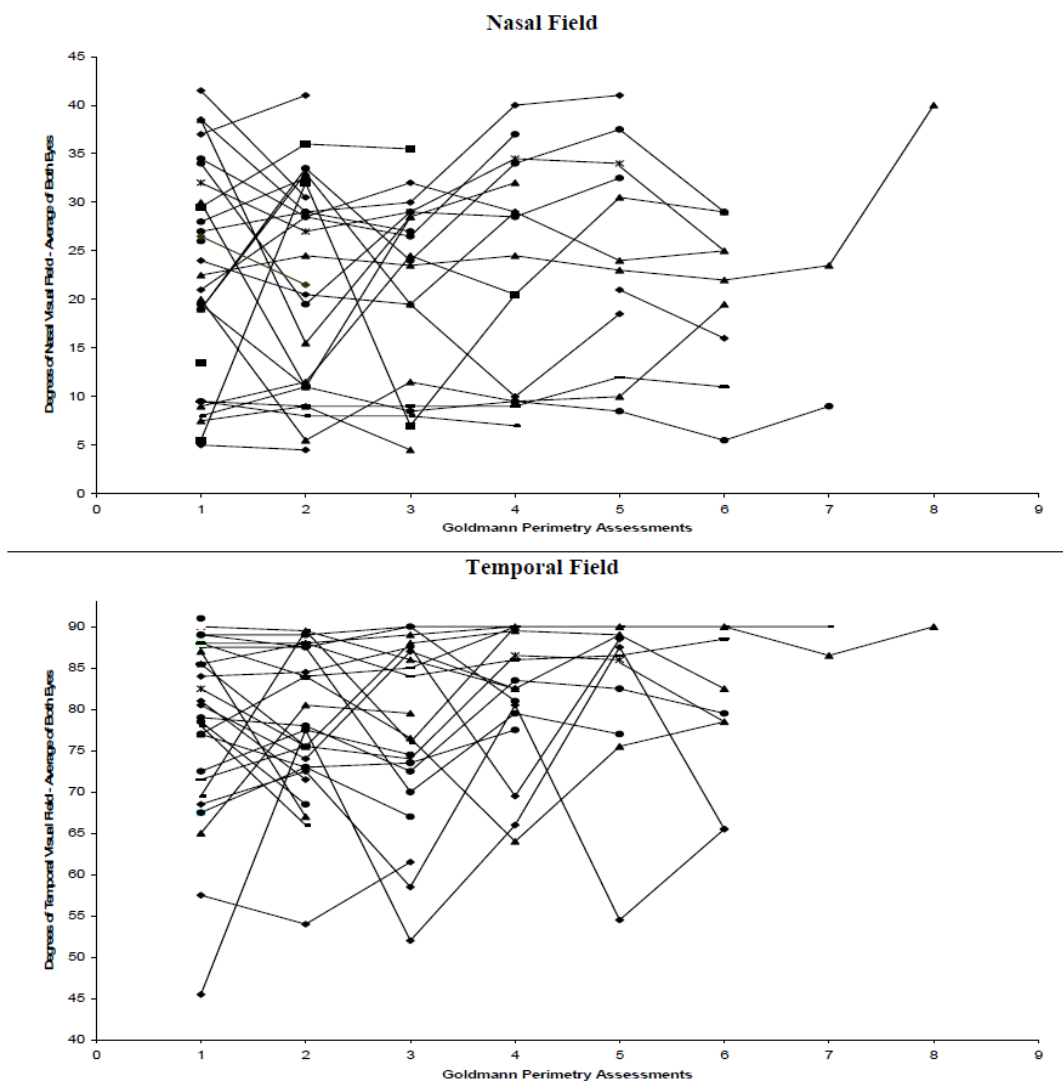
The results of Goldmann perimetry for each vigabatrin-naïve child <18 years of over time are shown in the Sponsor's Figure 6.

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**Figure 6 Results of Goldmann Perimetry Over Time for VGB-Naïve Children <18 years of Age Who Never Received VGB (Study R4020)**

**Figure 6. Results of Goldmann Perimetry Over Time for Vigabatrin-naïve Children <18 Years of Age Who Never Received Vigabatrin (Study 4020)**



Note: The time between consecutive perimetry assessments varies within and across patients.

There was substantial variability in extent of intact visual field at baseline and some patients had VFDs in the absence of vigabatrin exposure. There was also substantial variability upon retest of these patients. Similar results were observed for nasal and temporal fields in children  $\geq 10$  to  $<17$  years of age.

For Study R4020, the sponsor concludes that VFDs, when they occurred, were most often mild or moderate and were not associated with symptoms of abnormal visual function. There was no clinically important difference between children and adults. Among patients who were vigabatrin-naïve at baseline, there was substantial variability

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in extent of intact visual field at baseline and some patients had VFDs in the absence of vigabatrin exposure. There was also substantial variability upon retest of these patients.

**Reviewer Comment:**

***The variability in retesting emphasizes the difficulty in obtaining reliable visual fields in pediatric patients. .When reviewing visual fields in adult patients during the review of the original NDA 20427 submission, Dr. Ronald Farkas found the same difficulty.***

***Despite the limitations of this open label study, Study R4020 provides convincing data that the incidence and severity of visual field deficits in pediatric patients age 10 years and above are no worse than those reported in the adult population.***

**Confrontational Visual Fields in Pediatric Subjects**

Visual fields were assessed by confrontation methods (finger counts in all 4 quadrants and identification of red color in all 4 quadrants and centrally) during up to 17 weeks of vigabatrin exposure in multicenter, randomized, double-blind, parallel group, placebo controlled Studies 118, 192, and 221. Enrolled subjects had not previously received vigabatrin. Assessments by confrontation testing were also made during up to 24 weeks and 48 or more weeks of vigabatrin exposure in uncontrolled, extension Studies 294 and 201, respectively.

Confrontation visual field tests were conducted prior to vigabatrin exposure and prospectively at protocol-specified time intervals during vigabatrin exposure. Since these studies provide important visual field data in the pediatric population, The sponsor has conducted new analyses of changes in confrontation visual fields in order to integrate findings across studies. Subjects were included in these analyses only if all baseline confrontation tests were normal. Of the 99 subjects with confrontation visual field testing, 9 subjects (4 in Study 118, 3 in Study 221, 2 in Study 192) had abnormal results at baseline.

An abnormality was defined as any non-normal finding in any confrontation test. Thus, results from the new analyses can differ from summaries of results presented in the original clinical study reports (CSRs). Among pediatric subjects with normal baseline results in pooled placebo-controlled studies, 2 of 90 subjects (2.22%) in the vigabatrin group (with up to 17 weeks of vigabatrin exposure) and 1 of 44 subjects in the placebo group (2.27%) had an abnormality in confrontational visual field at the last study visit. Among 125 pediatric subjects with normal baseline results in extension Study 201 (up to 48 or more weeks of vigabatrin exposure), 7 subjects (5.60%) had at least one abnormality in confrontational visual field at any time during the study and 4 subjects

(3.20%) had an abnormality at the last visit. No subject had 2 or more consecutive abnormalities.

### **Acuity and Color Vision in Pediatric Subjects**

Acuity and color vision were assessed in placebo-controlled Studies 118, 192, and 221 as well as extension Studies 201 and 294. A grade change represents a standard 1-line change in visual acuity in either a positive or negative direction. For example, a 1 grade change represents a subject in which the baseline visual acuity was 20/20 and the final examination visual acuity was 20/25. Subjects with a 1- or 2-line change in visual acuity in either a positive or negative direction would not be unusual in this pediatric population, since the results of the examination could vary based on the subjective nature of the test, the skill of the examiner, and whether the subject's vision was best corrected.

Vigabatrin had no consistent effect on acuity and color vision.

### **Fundoscopy in Pediatric Subjects**

There was no change in any of the parameters (vessels, nervehead, macula) in Studies 192 and 294. These examinations were not summarized in clinical reports for the other studies.

### **Ophthalmologist Assessment in Pediatric Subjects**

Ophthalmological examinations in Studies 118, 192, 294, and R003 were either within normal limits or abnormal ophthalmological examination results were compatible with preexisting organic disease. These examinations were not summarized in clinical reports for the other studies.

### **Anterior and Posterior Segments in Pediatric Subjects**

Anterior and posterior segments were assessed during up to 17 weeks of vigabatrin exposure in multicenter, randomized, double-blind, parallel group Studies 118 and 221, and during up to 48 weeks of vigabatrin exposure in uncontrolled, extension Study 201. Isolated changes from normal to abnormal were observed, but there was no consistent pattern of changes in anterior and posterior segments.

### **Electroretinogram in Pediatric Subjects**

Electroretinogram measurements were obtained during up to 17 weeks of vigabatrin exposure in multicenter, randomized, double-blind, parallel group, placebo-controlled

Studies 118 and 221. Results were independently reviewed by (b) (4)

His conclusions included:

- No evidence of dysfunction in the photoreceptors or rod-mediated visual pathways was seen.
- Evidence of an effect of vigabatrin was seen on the cone inner retinal pathway.
- No concurrent changes in ophthalmologic test results were observed.
- The ERG changes represent pharmacological effects on the physiology of the inner retina rather than pathophysiologic changes.

Electroretinogram measurements were obtained during up to 48 weeks of vigabatrin exposure in uncontrolled, extension Study 201. Results were independently reviewed by (b) (4). His conclusions included:

- The decrease in 30 Hz flicker ERG amplitude over time may be a sign of retinal toxicity.
- Acute changes which occur shortly after therapy seem to reflect normal physiologic effects of elevated retinal gamma-aminobutyric acid (GABA) and are not predictive of VFDs.
- Patients who show a progression of their ERG abnormality with prolonged treatment are at risk for development of VFD.

There was one child in Study R003 (white male 10 years of age with blue eyes). No VFD was detected by ERG examination.

Results from the (b) (4) showed that ERG abnormalities associated with the vigabatrin-associated VFD in adults are also seen in infants. These are the 30 Hz flicker amplitude and cone b-wave amplitude, of which the 30 Hz flicker is the most sensitive parameter, as seen in adults. Other changes such as intrinsic time alterations or alterations of most oscillatory potentials are generally considered to be signs of reversible drug effect on retinal neurotransmission and can be seen with other anticonvulsants. The earliest observation of a specific vigabatrin-induced abnormality was observed in one subject treated for IS at 3.1 months of therapy. The earliest instance of a sustained, that is, presumed permanent 30 Hz flicker abnormality, was observed at 9.9 months of therapy.

Since there is a substantial rate of subjects with a baseline abnormality of these parameters (38% and 19% in 30 Hz flicker and cone-b wave amplitude respectively, based on the entire group), one cannot ascribe with certainty all of those with sustained abnormalities to vigabatrin exposure. An additional finding from the Toronto study is that combined use of vigabatrin and other AEDs does not exacerbate the injury.

The clinical relevance of findings for 30 Hz flicker amplitude and other ERG parameters as an indicator of retinal toxicity is not clear.

### Visual evoked potentials in Pediatric Subjects

Visual evoked potentials were assessed in placebo-controlled Studies 118, 192, and 221. Visual evoked potentials were assessed during up to 24 weeks and 48 weeks of vigabatrin exposure in uncontrolled, extension Studies 294 and 201, respectively.

Results were independently reviewed by (b) (4). There was no evidence of an effect of vigabatrin therapy on the VEP.

### Conclusions

Sabril is approved as adjunctive therapy for adult patients with rCPS who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of vision loss. It is also approved for use as monotherapy for pediatric patients from 1 month to 2 years of age with IS for whom the potential benefits outweigh the potential risk of vision loss.

The Sabril clinical development program prospectively monitored vision safety in 502 vigabatrin-treated pediatric patients from 3 to 17 years of age.

Vision tests included standard ophthalmologic evaluations (acuity, color vision, and anterior and posterior segments), assessments of possible physiological correlates of vision toxicity (ERG and VEP), and tests for clinically observable loss of visual field (perimetry and confrontation).

These safety data, supplemented by the ongoing Sabril registry and published results from independent assessments of vision in vigabatrin-treated children, demonstrate similar profiles of vision changes in the pediatric and adult populations. Current labeled warnings appropriately inform physicians and patients/guardians to evaluate closely the benefits and risks of vigabatrin treatment. Moreover, the current Sabril REMS, which includes periodic vision testing, provides a mechanism to facilitate ongoing vision monitoring of patients which will be reported annually.

### Reviewer Note:

***For further discussion of the incidence and risk of visual dysfunction in the pediatric CPS population, see the Reviewer Notes under section 7.7 of this review under the subheading Visual Dysfunction/Visual Field Defect.***

### 7.4 Supportive Safety Results

#### 7.4.1 Common Adverse Events

The safety findings from 488 unique vigabatrin-exposed patients demonstrated that vigabatrin is well tolerated at the doses studied as treatment of rCPS in pediatric patients  $\geq 3$  years of age.

The overall safety profile, including specific TEAEs and low hemoglobin and low hematocrit, was similar to that previously observed among adults in vigabatrin studies.

#### **Controlled Pediatric CPS Studies (The Controlled Studies 118, 192, 221)**

- The most common ( $\geq 10\%$  of patients) treatment-emergent adverse events (TEAEs) among all vigabatrin-treated patients were weight increased, upper respiratory tract infection, headache, convulsion, and fatigue.
  - The most common TEAEs (reported by  $\geq 10\%$  of patients in either the  $< 60$  mg/kg/day vigabatrin or  $\geq 60$  mg/kg/day vigabatrin treatment groups) were weight increased (15.8% and 14.7%, respectively), upper respiratory tract infection (13.7% and 16.2%, respectively), headache (11.6% and 13.2%, respectively), convulsion (10.5% and 10.3%, respectively), fatigue (8.4% and 11.8%, respectively), and influenza (4.2% and 10.3%, respectively).
  - A notable difference ( $\geq 5.0$  percentage points) in the incidence of TEAEs between the placebo and all vigabatrin groups was observed for weight increased and convulsion, with a higher incidence of weight increased in the all vigabatrin group compared to the placebo group (15.2% and 1.9%, respectively) and a lower incidence of convulsion in the all vigabatrin group compared to the placebo group (10.9% and 18.3%, respectively).
- Notable differences ( $\geq 5.0\%$  of patients) in the incidence of specific TEAEs across the placebo,  $< 60$  mg/kg/day vigabatrin, and  $\geq 60$  mg/kg/day vigabatrin treatment groups were observed for fatigue (6.7%, 8.4%, and 11.8%, respectively), aggression (1.9%, 3.2%, and 8.8%, respectively), influenza (2.9%, 4.2%, and 10.3%, respectively), upper respiratory tract infection (10.6%, 13.7%, and 16.2%, respectively), and weight increased (1.9%, 15.8%, and 14.7%, respectively).
- Treatment-emergent convulsion (3 placebo, 1  $< 60$  mg/kg/day vigabatrin, and 0  $\geq 60$  mg/kg/day vigabatrin), status epilepticus (0 placebo, 2  $< 60$  mg/kg/day vigabatrin, and 1  $\geq 60$  mg/kg/day vigabatrin), and abnormal behavior (1 placebo, 2  $< 60$  mg/kg/day vigabatrin, and 0  $\geq 60$  mg/kg/day vigabatrin) were the only severe AEs reported by  $\geq 2$  patients in any treatment group.

- The only TEAE that led to premature discontinuation of study drug for  $\geq 2$  patients in any treatment group was convulsion (3.8% placebo; 3.2% < 60 mg/kg/day vigabatrin; and 1.5%  $\geq$  60 mg/kg/day vigabatrin).
- The only treatment-emergent serious adverse events (SAEs) reported by  $\geq 2$  patients in any treatment group were convulsion (5.8% placebo; 0.0% < 60 mg/kg/day vigabatrin; and 1.5%  $\geq$  60 mg/kg/day vigabatrin) and status epilepticus (1.0% placebo; 3.2% < 60 mg/kg/day vigabatrin; and 1.5%  $\geq$  60 mg/kg/day vigabatrin).

The sponsor-proposed adverse reactions for labeling, identified as those that occurred in at least 2% of vigabatrin-treated pediatric patients (age 3 to 16 years) and more frequently than placebo, are presented the table below (reproduced from Table 4 in the sponsor's Clinical Overview)

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**Table 25 Treatment-Emergent Adverse Events Reported by  $\geq$  2% of Pediatric Patients with CPS Treated with Vigabatrin and Higher than Placebo**

(b) (4)


**Reviewer Note:**

***Because the proposed pediatric indication for refractory CPS is limited to pediatric patients age 10 years and above, the Agency asked the sponsor to replace the above table in labeling with a similar table restricted to pediatric patients age 10 to 16 years. The sponsor provided the following table.***



Clinical Review  
Philip H. Sheridan, MD  
NDA 20427 S011/S-012; NDA 22006 S-012/S-013  
Sabril (Vigabatrin)

**Table 26 Treatment-Emergent Adverse Effects Reported by  $\geq 2$  % of Pediatric Patients (Ages 10-16 years) on Vigabatrin with Incidence Higher than Placebo**

Treatment-Emergent Adverse Events Reported by >=2% of Patients on Vigabatrin and Incidence is Higher Than Placebo (For ages 10-16)			
System Organ Class Preferred Term	All VGB (N=109)	Placebo (N=46)	
Eye disorders Diplopia Vision blurred		(b) (4)	
Gastrointestinal disorders Diarrhoea Abdominal pain upper Constipation			
General disorders and administration site conditions Fatigue General symptom			
Infections and infestations Upper respiratory tract infection Influenza Otitis media			
Investigations Weight increased			
Nervous system disorders Somnolence Tremor Nystagmus Psychomotor hyperactivity			
Psychiatric disorders Abnormal behaviour Aggression Disorientation			
Reproductive system and breast disorders Dysmenorrhoea			
Skin and subcutaneous tissue disorders Acne			

***This table for pediatric patients age 10 to 16 years will be used in section 5 of the labeling.***

**All Pediatric CPS Studies (The Controlled Studies 118, 192, 221 plus the Open-Label Extension Studies 204 and 294)**

- The most common ( $\geq 10\%$  of patients) TEAEs among all vigabatrin-treated patients were convulsion, headache, upper respiratory tract infection, weight increased, nasopharyngitis, fatigue, pyrexia, abnormal behavior, otitis media, dizziness, vomiting, pharyngitis streptococcal, and aggression.
- The most common TEAEs (reported by  $\geq 10\%$  of patients in either the  $< 60$  mg/kg/day vigabatrin or  $\geq 60$  mg/kg/day vigabatrin treatment groups) included those reported in the Controlled Pediatric CPS Studies (weight increased [24.2% and 24.3%, respectively], upper respiratory tract infection [17.6% and 35.0%, respectively], headache [22.4% and 25.2%, respectively], convulsion [18.2% and 36.9%, respectively], fatigue [17.6% and 13.6%, respectively], and influenza [8.5% and 12.6%, respectively], as well as vomiting (10.9% and 13.6%, respectively), pyrexia (9.7% and 25.2%, respectively), nasopharyngitis (18.8% and 22.3%, respectively), otitis media (11.5% and 15.5%, respectively), pharyngitis streptococcal (9.1% and 13.6%, respectively), viral infection

(6.7% and 14.6%, respectively), sinusitis (8.5% and 10.7%, respectively), dizziness (12.7% and 11.7%, respectively), visual field defect (10.3% and 9.7%, respectively), somnolence (6.7% and 12.6%, respectively), psychomotor hyperactivity (4.8% and 11.7%, respectively), abnormal behavior (10.9% and 16.5%, respectively), aggression (7.9% and 13.6%, respectively), and rash (7.3% and 10.7%, respectively).

- Notable differences ( $\geq 5.0\%$  of patients) in the incidence of specific TEAEs between the  $< 60$  mg/kg/day vigabatrin and  $\geq 60$  mg/kg/day vigabatrin groups were observed for upper respiratory tract infection (17.6% and 35.0%, respectively), viral infection (6.7% and 14.6%, respectively), pyrexia (9.7% and 25.2%, respectively), convulsion (18.2% and 36.9%, respectively), somnolence (6.7% and 12.6%, respectively), psychomotor hyperactivity (4.8% and 11.7%, respectively), abnormal behavior (10.9% and 16.5%, respectively), and aggression (7.9% and 13.6%, respectively).

- Treatment-emergent status epilepticus (2  $< 60$  mg/kg/day vigabatrin and 5  $\geq 60$  mg/kg/day vigabatrin), abnormal behavior (3  $< 60$  mg/kg/day vigabatrin and 3  $\geq 60$  mg/kg/day vigabatrin), convulsion (3  $< 60$  mg/kg/day vigabatrin and 1  $\geq 60$  mg/kg/day vigabatrin), and headache (2  $< 60$  mg/kg/day vigabatrin and 2  $\geq 60$  mg/kg/day vigabatrin) were the only severe AEs reported by  $\geq 2$  patients in either treatment group.

- Treatment-emergent AEs that led to premature discontinuation of study drug for  $\geq 2$  patients in either the  $< 60$  mg/kg/day vigabatrin or  $\geq 60$  mg/kg/day vigabatrin treatment groups were ataxia (1.2% and 0, respectively), convulsion (6.1% and 11.7%, respectively), dysarthria (1.2% and 0, respectively), tremor (1.2% and 0, respectively), visual field defect (1.8% and 1.0%, respectively), abnormal behavior (1.8% and 2.9%, respectively), aggression (1.8% and 0, respectively), and depression (1.2% and 0, respectively).

- One patient who received  $< 60$  mg/kg/day vigabatrin in Study 201 experienced severe status epilepticus on Day 549 and severe hepatic failure on Day 553 and died as a result of these events on Day 553. Both of the events were considered related to study drug.

### **Open-Label Study 0098**

Upper respiratory tract infection and influenza were the only TEAEs reported by  $\geq 5\%$  of patients in Study 0098 (11.7% and 5.0% respectively).

### **CPEN Study**

The AE profile in the post-hoc analysis (TEAEs reported by  $\geq 5.0\%$  of vigabatrin patients were somnolence, convulsion, ear infection, constipation, decreased appetite, gastroenteritis, and vomiting) appears consistent with the current Sabril product label.

## 7.4.2 Laboratory Findings

### Hematology

#### Controlled Pediatric CPS Studies

Mean decreases from baseline to the final visit were observed for each of the vigabatrin groups for hemoglobin, hematocrit, and red blood cell count; however, these mean decreases were small overall. Mean changes from baseline to the final visit for other hematology parameters were small in the Controlled Pediatric CPS Studies.

Shifts in hematology values from normal or high at baseline to low at post-baseline were observed in  $\geq 20.0\%$  of patients in at least 2 treatment groups for the following hematology parameters: red blood cell (RBC) count, hematocrit, neutrophils, lymphocytes, monocytes, basophils, and eosinophils. Shifts from normal or low at baseline to high at post-baseline were observed in  $\geq 20.0\%$  of patients in at least 2 treatment groups for the following hematology parameters: neutrophils, lymphocytes, monocytes, basophils, and eosinophils.

An apparent difference was observed between the  $\geq 60$  mg/kg/day vigabatrin and placebo treatment groups in the percentage of patients with shifts to low hemoglobin (33.8% and 12.0%, respectively), hematocrit (36.8% and 16.5%, respectively), lymphocytes (13.8% and 27.2%, respectively), and platelet count (4.9% and 11.6%, respectively) in the Controlled Pediatric CPS Studies. In addition, an apparent difference was observed between the  $< 60$  mg/kg/day vigabatrin and placebo treatment groups in the percentage of patients with shift to high RBC count (3.9% and 13.3%, respectively) in the Controlled Pediatric CPS Studies. No other differences were observed between any of the treatment groups for the incidence of shifts from normal or high at baseline to low at post-baseline or normal or low at baseline to high at postbaseline.

The percentage of patients with a PCS high monocyte value was 3.3%, 12.3%, and 7.7% in the placebo,  $< 60$  mg/kg/day vigabatrin, and  $\geq 60$  mg/kg/day vigabatrin treatment groups, respectively. No other potentially clinically significant (PCS) hematology value was reported for  $\geq 10\%$  of patients in any treatment group in the Controlled Pediatric CPS Studies. A summary of the incidence of PCS hematology values in the Controlled Pediatric CPS Studies is provided in the sponsor's Table 24 reproduced below.

**Table 27 Incidence of PCS Hematology Values from Controlled Pediatric rCPS Studies**

**Table 24. Incidence of Potentially Clinically Significant Hematology Values – Controlled Pediatric CPS Studies**

Parameter (unit)	Placebo N = 104 n/N (%)	< 60 mg/kg/day Vigabatrin N = 95 n/N (%)	≥ 60 mg/kg/day Vigabatrin N = 68 n/N (%)	All Vigabatrin N = 165 n/N (%)
Basophils (%)				
PCS high	1/92 (1.1)	1/86 (1.2)	0	1/152 (0.7)
Eosinophils (%)				
PCS high	5/86 (5.8)	6/85 (7.1)	2/60 (3.3)	8/146 (5.5)
Hematocrit (%)				
PCS low	0	1/89 (1.1)	2/67 (3.0)	3/157 (1.9)
PCS high	1/93 (1.1)	0	0	0
Hemoglobin (g/dL)				
PCS low	0	1/89 (1.1)	2/68 (2.9)	3/158 (1.9)
PCS high	1/93 (1.1)	0	0	0
Lymphocytes (%)				
PCS high	0	1/88 (1.1)	0	1/153 (0.7)
Monocytes (%)				
PCS high	3/92 (3.3)	10/81 (12.3)	5/65 (7.7)	15/146 (10.3)
Neutrophils (%)				
PCS low	0	2/87 (2.3)	0	2/152 (1.3)
Platelet count ( $\times 10^9/L$ )				
PCS low	0	0	1/61 (1.6)	1/135 (0.7)
RBC count ( $\times 10^{12}/L$ )				
PCS low	2/31 (6.5)	0	1/40 (2.5)	1/92 (1.1)
PCS high	1/31 (3.2)	0	0	0
WBC count ( $\times 10^9/L$ )				
PCS low	0	1/87 (1.1)	0	1/156 (0.6)
PCS high	0	1/87 (1.1)	1/68 (1.5)	2/156 (1.3)

CPS = complex partial seizures; PCS = potentially clinically significant; RBC = red blood cell; WBC = white blood cell

Source: [ISS Table 9.1.2.3.2.](#)

### All Pediatric CPS Studies

Mean changes from baseline to the final visit for hematology parameters were small, with no apparent treatment-related trend in All Pediatric CPS Studies.

Shifts in hematology values from normal or high at baseline to low at post-baseline were observed in  $\geq 20.0\%$  of patients in at least 1 treatment group for the following hematology parameters: RBC count, hemoglobin, hematocrit, WBC count, lymphocytes, monocytes, neutrophils, basophils, and eosinophils. Shifts from normal or low at baseline to high at postbaseline were observed in  $\geq 20.0\%$  of patients in at least 1 treatment group for the following hematology parameters: hematocrit, WBC count, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and platelet count.

No notable differences were observed between the  $< 60$  mg/kg/day vigabatrin and  $\geq 60$  mg/kg/day vigabatrin treatment groups for the incidence of shifts from normal or high at baseline to low at post-baseline or normal or low at baseline to high at post-baseline.

The percentage of patients with a PCS high monocyte value was 12.7% and 7.7% and the percentage of patients with a PCS high eosinophil value was 7.1% and 11.4% in the  $< 60$  mg/kg/day vigabatrin and  $\geq 60$  mg/kg/day vigabatrin treatment groups, respectively. No other PCS hematology value was reported for  $\geq 10\%$  of patients in either treatment group in All Pediatric CPS Studies. A summary of the incidence of PCS hematology values in All Pediatric CPS Studies is provided in the sponsor's Table 25.

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**Table 28 Incidence of PCS Hematology Values from All Pediatric rCPS Studies**

**Table 25. Incidence of Potentially Clinically Significant Hematology Values – All Pediatric CPS Studies**

Parameter (unit)	< 60 mg/kg/day Vigabatrin N = 165 n/N (%)	≥ 60 mg/kg/day Vigabatrin N = 103 n/N (%)	All Vigabatrin N = 273 n/N (%)
Basophils (%)			
PCS high	1/145 (0.7)	1/94 (1.1)	2/243 (0.8)
Eosinophils (%)			
PCS high	10/140 (7.1)	10/88 (11.4)	20/232 (8.6)
Hematocrit (%)			
PCS low	0	4/96 (4.2)	4/248 (1.6)
PCS high	1/148 (0.7)	0	1/248 (0.4)
Hemoglobin (g/dL)			
PCS low	0	3/97 (3.1)	3/250 (1.2)
PCS high	1/149 (0.7)	0	1/250 (0.4)
Lymphocytes (%)			
PCS high	3/148 (2.0)	1/93 (1.1)	4/245 (1.6)
Monocytes (%)			
PCS high	18/142 (12.7)	7/91 (7.7)	25/236 (10.6)
Neutrophils (%)			
PCS low	4/148 (2.7)	2/93 (2.2)	6/245 (2.4)
Platelet count ( $\times 10^9/L$ )			
PCS low	0	2/91 (2.2)	2/224 (0.9)
RBC count ( $\times 10^{12}/L$ )			
PCS low	0	3/47 (6.4)	3/120 (2.5)
PCS high	1/72 (1.4)	0	1/120 (0.8)
WBC count ( $\times 10^9/L$ )			
PCS low	1/149 (0.7)	1/96 (1.0)	2/249 (0.8)
PCS high	3/149 (2.0)	0	3/249 (1.2)

CPS = complex partial seizures; PCS = potentially clinically significant; RBC = red blood cell; WBC = white blood cell

**Reviewer Note:**

***The currently approved label states in section 5.7 (Anemia):***

***“In North American controlled trials in adults, 6% of patients (16/280) receiving SABRIL and 2% of patients (3/188) receiving placebo had adverse events of anemia and/or met criteria for potentially clinically important hematology changes involving hemoglobin, hematocrit, and/or RBC indices. Across U.S. controlled***

***trials, there were mean decreases in hemoglobin of about 3% and 0% in SABRIL and placebo treated patients, respectively, and a mean decrease in hematocrit of about 1% in SABRIL treated patients compared to a mean gain of about 1% in patients treated with placebo.***

***In controlled and open label epilepsy trials in adults and pediatric patients, 3 SABRIL patients (0.06%, 3/4855) discontinued for anemia and 2 SABRIL patients experienced unexplained declines in hemoglobin to below 8 g/dL and/or hematocrit below 24%."***

***The changes noted in the pediatric studies presented in this submission are similar. No change in labeling is required.***

## **Clinical Chemistry**

A possible dose relationship was observed for the mean change from baseline to final visit for alkaline phosphatase. Dose-related reductions in ALT and AST levels have been previously observed in adult vigabatrin studies.

Mean changes from baseline to the final visit for other chemistry parameters were small in the Controlled Pediatric CPS Studies.

Shifts in chemistry values from normal or high at baseline to low at post-baseline were observed in  $\geq 20.0\%$  of patients in at least 2 treatment groups for the following chemistry parameters: glucose, AST, and ALT. Shifts from normal or low at baseline to high at post-baseline were observed in  $\geq 20.0\%$  of patients in at least 2 treatment groups for cholesterol.

A notable difference was observed between the  $< 60$  mg/kg/day vigabatrin and  $\geq 60$  mg/kg/day vigabatrin treatment groups and the placebo group in the percentage of patients with shifts to low AST (28.7% and 32.4% vs. 10.5%) and ALT (56.3% and 73.5% vs. 8.5%) in the Controlled Pediatric CPS Studies. The incidences of shifts to low ALT and AST in the vigabatrin treatment groups compared to the placebo group are consistent with the dose-related reductions from baseline and are hypothesized to be the result of nonspecific inhibition of transaminase activity by vigabatrin.

Notable differences were also observed between the  $< 60$  mg/kg/day vigabatrin and  $\geq 60$  mg/kg/day vigabatrin treatment groups and the placebo group in the percentage of patients with shifts to high AST (4.6% and 7.4% vs. 13.7%) and ALT (1.1% and 1.5% vs. 9.6%) and between the  $\geq 60$  mg/kg/day vigabatrin group and the placebo group for shift to high chloride (20.6% and 9.5%, respectively) and phosphorus (28.6% and 13.7%, respectively) in the Controlled Pediatric CPS Studies. Notable differences were also observed between the  $< 60$  mg/kg/day vigabatrin and  $\geq 60$  mg/kg/day vigabatrin treatment groups in the percentage of patients with shifts to low alkaline phosphatase

(11.5% and 4.4%, respectively) and albumin (6.9% and 0, respectively) and to high phosphorus (11.6% and 28.6%, respectively) in the Controlled Pediatric CPS Studies. No other notable differences were observed between any of the treatment groups for the incidence of shifts from normal or high at baseline to low at post-baseline or normal or low at baseline to high at post-baseline.

The percentage of patients with a PCS high alkaline phosphatase value was 4.3%, 4.0%, and 10.0% in the placebo, < 60 mg/kg/day vigabatrin, and ≥ 60 mg/kg/day vigabatrin treatment groups, respectively. No other PCS chemistry value was reported for ≥ 10% of patients in any treatment group in the Controlled Pediatric CPS Studies. A summary of the incidence of PCS chemistry values in the Controlled Pediatric CPS Studies is provided in the sponsor's Table 26.

**Table 29 Incidence of PCS Chemistry Values from Controlled Pediatric rCPS Studies**

**Table 26. Incidence of Potentially Clinically Significant Chemistry Values – Controlled Pediatric CPS Studies**

Parameter (unit)	Placebo N = 104 n/N (%)	< 60 mg/kg/day Vigabatrin N = 95 n/N (%)	≥ 60 mg/kg/day Vigabatrin N = 68 n/N (%)	All Vigabatrin N = 165 n/N (%)
Alkaline phosphatase (U/L)				
PCS high	3/70 (4.3)	2/50 (4.0)	4/40 (10.0)	6/91 (6.6)
BUN (mg/dL)				
PCS high	1/75 (1.3)	0	0	0
Calcium (mg/dL)				
PCS low	2/95 (2.1)	1/88 (1.1)	0	1/157 (0.6)
Chloride (mEq/L)				
PCS high	1/97 (1.0)	0	0	0
Glucose (mg/dL)				
PCS low	1/97 (1.0)	0	0	0
Potassium (mEq/L)				
PCS high	1/96 (1.0)	3/89 (3.4)	2/68 (2.9)	5/158 (3.2)

BUN = blood urea nitrogen; CPS = complex partial seizures; PCS = potentially clinically significant

The percentage of patients with an AST or ALT value greater than the ULN was greater in the placebo group (29.4%) compared to the < 60 mg/kg/day vigabatrin and ≥ 60 mg/kg/day vigabatrin treatment groups (8.5% and 8.8%, respectively). No patient in any treatment group had an AST or ALT value ≥ 3 × ULN or a total bilirubin value ≥ 2 × ULN.

There was an apparent dose-related change in the percentage of patients with an alkaline phosphatase value ≥ 2 × ULN (placebo [11.8%], < 60 mg/kg/day vigabatrin treatment group [14.9%], and ≥ 60 mg/kg/day vigabatrin treatment group [26.5%]). In an



effort to assess the clinical relevance of this possible trend, an exploratory analysis of the percentage of patients with  $\geq 3 \times \text{ULN}$  was performed. The relevant fold increase above the ULN reflects current clinical practice as reflected in the medical literature for this analyte. This dose-related change was no longer apparent for the percentage of patients with an alkaline phosphatase value  $\geq 3 \times \text{ULN}$  as shown in the sponsor's Table 27.

**Table 30 Incidence of Elevated Liver Enzyme Values from Controlled Pediatric rCPS Studies**

**Table 27. Incidence of Elevated Liver Enzyme Values – Controlled Pediatric CPS Studies**

Parameter	Placebo N = 104 n/N (%)	< 60 mg/kg/day Vigabatrin N = 95 n/N (%)	$\geq 60$ mg/kg/day Vigabatrin N = 68 n/N (%)	All Vigabatrin N = 165 n/N (%)
ALT or AST $> \text{ULN}$	30/102 (29.4)	8/94 (8.5)	6/68 (8.8)	14/164 (8.5)
Alkaline phosphatase $\geq 2 \times \text{ULN}$	12/102 (11.8)	14/94 (14.9)	18/68 (26.5)	32/164 (19.5)
Alkaline phosphatase $\geq 3 \times \text{ULN}$	4/102 (3.9)	2/94 (2.1)	4/68 (5.9)	6/164 (3.7)
Total bilirubin $\geq 2 \times \text{ULN}$	0	0	0	0
ALT or AST $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$	0	0	0	0

ALT = alanine transaminase; AST = aspartate transaminase; CPS = complex partial seizures; ULN = upper limit of normal

#### All Pediatric CPS Studies

A possible dose relationship was observed for the mean change from baseline to final visit for alkaline phosphatase. Mean changes from baseline to the final visit for other chemistry parameters were small in All Pediatric CPS Studies.

Shifts in chemistry values from normal or high at baseline to low at post-baseline were observed in  $\geq 20.0\%$  of patients in at least 1 treatment group for the following chemistry parameters: AST, ALT, cholesterol, and glucose. Shifts from normal or low at baseline to high at postbaseline were observed in  $\geq 20.0\%$  of patients in at least 1 treatment group for the following chemistry parameters: cholesterol, glucose, lactic dehydrogenase, phosphorus, alkaline phosphatase, chloride, and potassium.

A notable difference was observed between the  $< 60$  mg/kg/day vigabatrin and  $\geq 60$  mg/kg/day vigabatrin treatment groups in the percentage of patients with shifts to high total protein (4.8% and 13.4%, respectively) and calcium (8.8% and 2.1%, respectively) in All Pediatric CPS Studies. The percentage of patients with shifts to high alkaline phosphatase was 23.8% in the  $< 60$  mg/kg/day vigabatrin treatment group and 42.3% in the  $\geq 60$  mg/kg/day vigabatrin treatment group. No other notable differences were observed between the treatment groups for the incidence of shifts from normal or high at baseline to low at post-baseline or normal or low at baseline to high at post-baseline.

A notable difference was observed between the < 60 mg/kg/day vigabatrin and ≥ 60 mg/kg/day vigabatrin treatment groups in the percentage of patients with a PCS high alkaline phosphatase value (23.7% and 65.5%, respectively). No other PCS chemistry value was reported for ≥ 10% of patients in either treatment group in All Pediatric CPS Studies. A summary of the incidence of PCS chemistry values in All Pediatric CPS Studies is provided in the sponsor's Table 28.

**Table 31 Incidence of PCS Chemistry Values from All Pediatric rCPS Studies**

**Table 28. Incidence of Potentially Clinically Significant Chemistry Values – All Pediatric CPS Studies**

Parameter (unit)	< 60 mg/kg/day Vigabatrin N = 165 n/N (%)	≥ 60 mg/kg/day Vigabatrin N = 103 n/N (%)	All Vigabatrin N = 273 n/N (%)
Alkaline phosphatase (U/L)			
PCS high	23/97 (23.7)	38/58 (65.5)	62/159 (39.0)
Calcium (mg/dL)			
PCS low	1/150 (0.7)	0	1/251 (0.4)
Chloride (mEq/L)			
PCS low	1/150 (0.7)	0	1/252 (0.4)
Creatinine (mg/dL)			
PCS high	2/150 (1.3)	1/98 (1.0)	3/252 (1.2)
Glucose (mg/dL)			
PCS low	1/148 (0.7)	0	1/250 (0.4)
PCS high	0	1/98 (1.0)	1/250 (0.4)
Potassium (mEq/L)			
PCS low	0	1/98 (1.0)	1/252 (0.4)
PCS high	4/150 (2.7)	6/98 (6.1)	10/252 (4.0)
Uric acid (mg/dL)			
PCS high	1/150 (0.7)	0	1/251 (0.4)

CPS = complex partial seizures; PCS = potentially clinically significant

The percentage of patients with an AST or ALT value greater than the ULN was greater in the ≥ 60 mg/kg/day vigabatrin treatment group (23.3%) compared to the < 60 mg/kg/day vigabatrin treatment group (16.5%). No patient in any treatment group had an AST or ALT value ≥ 3 × ULN or a total bilirubin value ≥ 2 × ULN.

The percentage of patients with an alkaline phosphatase value ≥ 2 × ULN was greater in the ≥ 60 mg/kg/day vigabatrin treatment group (54.4%) compared to the < 60 mg/kg/day vigabatrin treatment group (26.2%). Similar to the Controlled Pediatric CPS Studies, an exploratory analysis of the percentage of patients in All Pediatric CPS Studies with ≥ 3 × ULN was performed. This dose-related change was no longer

apparent for the percentage of patients with an alkaline phosphatase value  $\geq 3 \times \text{ULN}$  as shown in the sponsor's Table 29).

**Table 32 Incidence of Elevated Liver Enzyme Values from All Pediatric rCPS Studies**

**Table 29. Incidence of Elevated Liver Enzyme Values – All Pediatric CPS Studies**

Parameter (unit)	< 60 mg/kg/day Vigabatrin N = 165 n/N (%)	$\geq 60$ mg/kg/day Vigabatrin N = 103 n/N (%)	All Vigabatrin N = 273 n/N (%)
ALT or AST $> \text{ULN}$	27/164 (16.5)	24/103 (23.3)	53/272 (19.5)
Alkaline phosphatase $\geq 2 \times \text{ULN}$	43/164 (26.2)	56/103 (54.4)	100/272 (36.8)
Alkaline phosphatase $\geq 3 \times \text{ULN}$	15/164 (9.1)	13/103 (12.6)	28/272 (10.3)
Total bilirubin $\geq 2 \times \text{ULN}$	0	0	0
ALT or AST $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$	0	0	0

ALT = alanine transaminase; AST = aspartate transaminase; CPS = complex partial seizures; ULN = upper limit of normal

**Reviewer Note:**

*The sponsor notes that, although laboratory normal ranges may vary with age and gender, laboratory PCS criteria for the sponsor's Integrated Summary of Safety (ISS) were based on normal ranges for adult patients. Normal serum alkaline phosphatase values are higher in children (20 - 150 U/L) compared to adults (20 -70 U/L) presumably due to the higher levels of new bone production during the growth spurt occurring in children age 10 to 16 years of age (Fischbach F. A Manual of Laboratory and Diagnostic Tests New York: J. B. Lippincott, 1992). This may partly explain the substantial percentages of pediatric patients with  $> 2 \times [\text{adult}] \text{ULN}$  and  $> 2 \times [\text{adult}] \text{ULN}$  values of alkaline phosphatase. Since elevations of liver enzymes are commonly seen in adult and pediatric patients on AEDs, there is no need to discuss this in labeling.*

*The dose-related reductions in ALT and AST levels observed in the pediatric studies have been previously observed in adult vigabatrin studies and are already noted in labeling.*

*The Clinical Chemistry changes observed are otherwise unremarkable.*

### 7.4.3 Vital Signs

#### Controlled Pediatric CPS Studies

Mean changes from baseline to the final visit for vital sign parameters were small and not considered clinically significant in the Controlled Pediatric CPS Studies.

No notable trend was observed for the percentage of patients with a PCS low or PCS high vital sign parameter in the Controlled Pediatric CPS Studies.

The criteria used to identify PCS vital sign values in the original NDA submission, dated August 21, 2009, were more extreme than the current PCS criteria. When the previous submission criteria were applied, no notable trend was observed for the percentage of patients with a PCS low or PCS high vital sign parameter in the Controlled Pediatric CPS Studies.

The incidences of patients with a  $\geq 7\%$  weight increase from baseline in the Controlled Pediatric CPS Studies (18.6%, 41.1%, and 55.9% in the placebo,  $< 60$  mg/kg/day vigabatrin, and  $\geq 60$  mg/kg/day vigabatrin treatment groups, respectively) are consistent with the dose-related increase in the incidence of weight increase AEs. Weight gain has been previously observed among adults in vigabatrin studies, but the use of other concomitant AEDs makes this finding difficult to interpret.

#### All Pediatric CPS Studies

Mean changes from baseline to the final visit for vital sign parameters were small in All Pediatric CPS Studies.

There was evidence of a dose-related change in the percentage of patients with a PCS high pulse ( $< 60$  mg/kg/day vigabatrin treatment group [5.5%] and  $\geq 60$  mg/kg/day vigabatrin treatment group [14.6%]). No other notable trend was observed for the percentage of patients with a PCS low or PCS high vital sign parameter in All Pediatric CPS Studies.

When the original NDA submission criteria were used to identify PCS vital sign values, no notable trend was observed for the percentage of patients with a PCS low or PCS high vital sign parameter in All Pediatric CPS Studies.

The incidence of patients with a  $\geq 7\%$  weight increase from baseline in All Pediatric CPS Studies was 70.6% and 92.1% in the  $< 60$  mg/kg/day vigabatrin and  $\geq 60$  mg/kg/day vigabatrin treatment groups, respectively. As previously noted, weight gain has been previously observed among adults in vigabatrin studies, but the use of other concomitant AEDs makes this finding difficult to interpret.

#### 7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in any of the 8 pediatric clinical studies.

#### 7.4.5 Special Safety Studies/Clinical Trials

See 7.3.5 and 7.7 of this review.

#### 7.4.6 Immunogenicity

No studies of immunogenicity were presented in this submission.

### 7.5 Other Safety Explorations

See 7.3.5 and 7.7 of this review.

#### 7.5.1 Dose Dependency for Adverse Events

Throughout the ISS, vigabatrin dose groups for summarization are described by the sponsor as  $< 60$  mg/kg/day and  $\geq 60$  mg/kg/day.

The incidence of AEs related to ataxia and cognition/neuropsychiatric function or psychiatric function was higher in the  $\geq 60$  mg/kg/day vigabatrin treatment group compared to the  $< 60$  mg/kg/day vigabatrin treatment group.

Similarly, the incidence of AEs related to sedation, dizziness, tremor, and weight increase was higher in the  $\geq 60$  mg/kg/day vigabatrin treatment group compared to the  $< 60$  mg/kg/day vigabatrin treatment group.

- An apparent dose relationship was observed for the mean decrease from baseline to final visit for AST and ALT in both the Controlled Pediatric CPS Studies and All Pediatric CPS Studies. Dose-related reductions in ALT and AST levels have been previously observed in adult vigabatrin studies.

- An apparent dose-related trend was observed in the incidence of PCS low hemoglobin and PCS low hematocrit value in both the Controlled Pediatric CPS Studies and All Pediatric CPS Studies. An apparent dose-related trend for alkaline phosphatase was also observed for the mean change from baseline to final visit, the incidence of PCS high, and the percentage of patients with a value  $\geq 2 \times$  ULN in both the Controlled Pediatric CPS Studies and All Pediatric CPS Studies; however, these dose-related changes were no longer apparent for the percentage of patients with an alkaline phosphatase value  $\geq 3 \times$  ULN. No notable differences were observed among the treatment groups for the incidence of other PCS low or PCS high hematology or clinical chemistry parameters in the Controlled Pediatric CPS Studies or All Pediatric CPS Studies.

- An analysis of pulse and blood pressure did not reveal any significant changes related to vigabatrin, nor were there any clinically meaningful mean changes from baseline to final values for weight to age Z-score or height to age Z-score between vigabatrin treatment groups.

### 7.5.2 Time Dependency for Adverse Events

Serious and common adverse events observed in the controlled and open label clinical studies of pediatric patients age 10 to 16 years were similar in character, incidence, and timing of onset to those already documented in the labeling for the adult population. No new safety issues were identified.

The incidence and prevalence of TEAEs with an incidence of  $\geq 10\%$  in All Pediatric CPS Studies were reviewed for patterns during the first 899 days of treatment ( $\geq 75$  patients in the studies). The incidence and prevalence of AEs generally decreased after the first 180 days for the following AEs: vomiting, upper respiratory tract infection, rash, nasopharyngitis, otitis media, influenza, headache, dizziness, and somnolence. No apparent trend was observed in the incidence of investigator-identified visual field defect, fatigue, and pyrexia and the prevalence increased after the first 180 days. The incidence of weight increased, convulsion, abnormal behavior, and psychomotor hyperactivity decreased after the first 180 days and no apparent trend was observed in the prevalence. No apparent trend in incidence or prevalence was observed for pharyngitis streptococcal, aggression, viral infection, and sinusitis.

Summaries of narratives for deaths, adverse events resulting in discontinuation, and serious adverse events are presented in Appendix 9.4

Review of postmarketing data from the Sabril registry and from the published literature did not identify any new safety issues.

### 7.5.3 Drug-Demographic Interactions

There were no clinically important effects on TEAEs and laboratory values when categorized by age, sex, or race.

There were no identifiable trends or patterns in the distribution of AEs across all pediatric age groups, and no new safety issues were identified.

There were no clinically important effects on TEAEs and laboratory values when summarized by age, sex, or race.

#### 7.5.4 Drug-Disease Interactions

##### Renal function:

Vigabatrin is primarily eliminated through the kidney. Clearance of vigabatrin is decreased in patients with impaired renal function. Caution should be taken in dosing patients with moderate and severe renal impairment, and in patients undergoing hemodialysis. The effect of dialysis on vigabatrin clearance has not been adequately studied. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

A study of the relationship between age (birth to 15 years of age) and renal function as measured by glomerular filtration rate found that glomerular filtration rate remained almost constant at 100 mL/min within the age range of 2 to 15 years, whereas the relationship from birth to 2 years of age was characterized by a gradual increase in renal function with increasing age, reaching a maximum at approximately 2 years of age.

For adjustment of dosing in pediatric patients with renal impairment, see section 6.1.8 of this review.

##### Hepatic function:

Because vigabatrin is excreted renally and not significantly metabolized in the liver, adjustment in dosing is probably not required for hepatic impairment. The pharmacokinetics of vigabatrin in patients with impaired liver function have not been studied.

#### 7.5.5 Drug-Drug Interactions

The sponsor references current labeling.

Vigabatrin does not have an inhibitory effect on CYP metabolizing enzymes. In vitro drug metabolism studies indicate that vigabatrin induces, to a minor extent, cytochrome P450 2C enzymes and does not induce major CYP 450 isozymes including CYP1A2 or CYP3A4/5.

##### ***Reviewer comment:***

***Because vigabatrin is excreted renally and not significantly metabolized in the liver, the drug-drug interactions are relatively few. The current labeling describes these interactions based on adult studies.***

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Philip H. Sheridan, MD  
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## 7.6 Additional Safety Evaluations

None.

### 7.6.1 Human Carcinogenicity

The sponsor references current labeling.

### 7.6.2 Human Reproduction and Pregnancy Data

The sponsor references current labeling.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

See section 7.7 of this review.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

#### **Overdose and Abuse Liability:**

These issues were addressed in the original NDA approval and are addressed in current labeling. As reported in the approved labeling, confirmed and/or suspected vigabatrin overdoses have been reported during clinical studies and in post-marketing surveillance. No vigabatrin overdoses resulted in death. When reported, the vigabatrin dose ingested ranged from 3 g to 90 g, but most were between 7.5 g and 30 g. Nearly half the cases involved multiple drug ingestions including carbamazepine, barbiturates, benzodiazepines, lamotrigine, valproic acid, acetaminophen, and/or chlorpheniramine. Coma, unconsciousness, and/or drowsiness were described in the majority of cases of vigabatrin overdose. These symptoms resolved with supportive care.

There was no documented overdose among vigabatrin patients in the Controlled Pediatric CPS Studies. There were 15 events among 15 patients (9 in the < 60 mg/kg/day vigabatrin group and 6 in the ≥ 60 mg/kg/day vigabatrin group) of overdose (based on a search using the following overdose and dosing error related strings: “\*overdos\*”, “\*error\*”, “\*toxic\*”, and “\*administ\*”) in All Pediatric CPS Studies. Of these 15 events, 1 patient experienced a severe accidental overdose that was an SAE and was considered related to study drug. All remaining overdose events were mild or moderate in severity.



## **Withdrawal**

Current approved labeling for adults recommends reducing the dose of vigabatrin gradually upon discontinuation. In controlled studies in adults, the daily dose was decreased 1 g/day on a weekly basis until discontinued. Gradual discontinuation is also recommended in pediatric patients with rCPS.

Patients in Controlled rCPS Studies (Studies 118, 192, and 221) who discontinued study drug were to have their total daily dose of study drug tapered over 3 weeks until study drug was discontinued. No explicit analyses of withdrawal effects were provided in the original clinical study reports.

Other than a few reports in the literature of exacerbation of or development of psychiatric symptoms following discontinuation of vigabatrin, most preclinical, clinical, and postmarketing evidence does not indicate that vigabatrin is associated with a discontinuation syndrome or the emergence of status epilepticus or new seizure types during discontinuation periods.

## **7.7 Additional Submissions / Safety Issues**

Topics of special interest were based on discussions for the PWR with the Agency. A. Treatment-emergent AEs related to anemia, edema, visual dysfunction/VFD, peripheral neuropathy, cognition/neuropsychiatric function, psychiatric function with vigabatrin, development (somatic and sexual), hepatic function, sedation, dizziness, ataxia, tremor, weight increase, suicidality, and intramyelinic edema were identified. Search methods defined in the ISS SAP were utilized to identify the PTs and/or laboratory results consistent with these AEs of special interest.

Of note, the PTs used to identify TEAEs of cognition/neuropsychiatric function and psychiatric function with vigabatrin were the same. Therefore, the results from these searches yielded identical findings and these TEAEs of special interest are discussed together.

### **Anemia**

One (1.5%) patient in the  $\geq 60$  mg/kg/day vigabatrin treatment group experienced an AE of anemia in the Controlled Pediatric CPS Studies. The event was mild in intensity. No patient in the placebo or  $< 60$  mg/kg/day vigabatrin treatment groups experienced an AE of anemia. The incidence of patients with an AE of anemia in All Pediatric CPS Studies was 1.2% in the  $< 60$  mg/kg/day vigabatrin treatment group and 3.9% in the  $\geq 60$  mg/kg/day vigabatrin treatment group. All patients with an AE of anemia had events that were mild or moderate in intensity.

## Edema

The incidence of patients with edema events in the Controlled Pediatric CPS Studies was 2.9% in the placebo group, 1.8% in the all vigabatrin group, 1.1% in the < 60 mg/kg/day vigabatrin treatment group, and 2.9% in the  $\geq$  60 mg/kg/day vigabatrin treatment group.

All patients with edema events had events considered mild or moderate in intensity.

The incidence of patients with edema events in All Pediatric CPS Studies was 6.1% in the < 60 mg/kg/day vigabatrin treatment group and 10.7% in the  $\geq$  60 mg/kg/day vigabatrin treatment group. All patients with edema events had events considered mild or moderate in intensity).

## Visual Dysfunction/Visual Field Defect

See section 7.3.5 of this review for a detailed discussion of visual toxicity.

The incidence of patients with visual dysfunction/visual field defect events in the Controlled Pediatric CPS Studies was 3.8% in the placebo group, 4.2% in the all vigabatrin group, 3.2% in the < 60 mg/kg/day vigabatrin treatment group, and 5.9% in the  $\geq$  60 mg/kg/day vigabatrin treatment group. All patients with visual dysfunction/visual field defect events had events considered mild or moderate in intensity.

### **Reviewer Note:**

***These results from the “Controlled Pediatric CPS Studies” seem to indicate very low incidences of visual dysfunction. These apparently low incidences can be explained as follows. None of the three Controlled Pediatric CPS Studies used visual perimetry testing because they were designed and conducted prior to the discovery of visual field loss in adults. The finger-counting confrontational fields done as part of the routine neurological examination would be unlikely to detect the insidious onset of a peripheral field deficit. The duration of the controlled studies was also relatively short compared to the open label follow-up studies which are included in the “All Pediatric CPS Studies” category discussed in the next paragraph. Thus, in the three controlled studies, only the high dose vigabatrin treatment group ( $\geq$ 60 mg/kg/day) exceeded the placebo group by 2% with regard to visual dysfunction. The studies discussed in section 7.3.5 of this review (especially R4020 which was specifically designed to determine the incidence of visual field defects in adults and children) better characterize the visual loss in the pediatric population and suggest that it is similar in incidence to that in the adult population. See the next Reviewer Note for further discussion of the issue of visual dysfunction.***

The incidence of patients with visual dysfunction/visual field defect events in All Pediatric CPS Studies was 21.8% in the < 60 mg/kg/day vigabatrin treatment group and 25.2% in the ≥ 60 mg/kg/day vigabatrin treatment group. All patients with visual dysfunction/visual field defect events had events considered mild or moderate in intensity.

***Reviewer Note: This result from “All Pediatric CPS Studies” includes all eight studies and thus includes longer studies which used the more sensitive technique of visual perimetry in their follow-up assessments. The more sensitive detection methods and longer observation periods give a higher estimate than the estimate from “Controlled Pediatric CPS Studies” of the incidence of visual dysfunction attributable to vigabatrin in the pediatric population.***

***This result again suggests that the incidence of visual field loss in the pediatric patient population is comparable to that found in the adult patient population exposed to vigabatrin.***

***As discussed in section 7.3.5 of this review, Study R4020 gives the most informative data. This study showed that the vigabatrin-naïve population also had a significant amount of visual field deficits found on perimetry testing and that these deficits (from vigabatrin-exposed or vigabatrin-naïve patients) were often not reproducible on retesting. This was true for both pediatric and adult patients as discussed in the review by Dr Ronald Farkas when the Study R4020 data were reviewed as part of the original NDA submission for vigabatrin. Thus, the estimate for the incidence of visual dysfunction may be conservatively higher than the actual incidence.***

***Therefore, it seems reasonable and prudent to estimate the risk of loss of visual function for older pediatric patients (age 10 years to 16 years) as the same as that for the adult population.***

***The Agency’s concern that the developing retina of younger pediatric patients would have a demonstrably greater incidence or severity of visual toxicity does not appear supported by the data although the restriction of vigabatrin usage for CPS to pediatric patients age 10 years and above will further protect against this theoretical possibility. (The usage of vigabatrin in infants for the treatment of infantile spasms has a different benefit-to-risk assessment given the greater severity of and paucity of treatment alternatives for the syndrome of infantile spasms. Therefore, the infantile spasm indication is approved despite greater uncertainty about the visual function outcome in the infant population). The restriction of the CPS indication to pediatric patients age 10 years or greater was also chosen to restrict the CPS indication to patients who would be old enough to follow a visual field evaluation.***

***All Sabril patients must be enrolled in the Sabril registry. The results of the REMS-required periodic visual field and acuity evaluations will be presented annually for Agency review as part of the Sabril REMS. The data from individual patients will be trackable serially as each patient is evaluated over time. This will allow further post-marketing evaluation of the true incidence and severity of loss of visual function in the older pediatric population (age 10 years to 16 years) compared to the adult patients who will also be in the registry and thus in the mandated periodic visual evaluations and the annual summary.***

### **Peripheral Neuropathy**

The incidence of patients with any patient reports suggestive of peripheral neuropathy (numbness or tingling) in the Controlled Pediatric CPS Studies was 3.8% in the placebo group, 3.0% in the all vigabatrin group, 4.2% in the < 60 mg/kg/day vigabatrin treatment group, and 1.5% in the ≥ 60 mg/kg/day vigabatrin treatment group. All patients with peripheral neuropathy events had events considered mild or moderate in intensity.

The incidence of patients with any patient reports suggestive of peripheral neuropathy (numbness or tingling) in All Pediatric CPS Studies was 4.2% in the < 60 mg/kg/day vigabatrin treatment group and 3.9% in the ≥ 60 mg/kg/day vigabatrin treatment group. All patients with peripheral neuropathy events had events considered mild or moderate in intensity.

#### ***Reviewer comment:***

***There was no objective demonstration of peripheral neuropathy reported in the pediatric studies.***

### **Cognition/Neuropsychiatric Function and Psychiatric Function with Vigabatrin**

The incidence of patients with cognition/neuropsychiatric function events or psychiatric function with vigabatrin events in the Controlled Pediatric CPS Studies was 50.0% in the placebo group, 44.8% in the all vigabatrin group, 41.1% in the < 60 mg/kg/day vigabatrin treatment group, and 48.5% in the ≥ 60 mg/kg/day vigabatrin treatment group. The majority of patients with such events had events considered mild or moderate in intensity; 9 patients (5 placebo, 4 < 60 mg/kg/day vigabatrin) had events considered severe.

The incidence of patients with cognition/neuropsychiatric function events or psychiatric function with vigabatrin events in All Pediatric CPS Studies was 63.6% in the < 60 mg/kg/day vigabatrin treatment group and 71.8% in the ≥ 60 mg/kg/day vigabatrin treatment group.

The majority of patients with such events had events considered mild or moderate in intensity; 17 patients (11 < 60 mg/kg/day vigabatrin, 6 ≥ 60 mg/kg/day vigabatrin) had events considered severe. The severe AEs were 3 abnormal behavior, 3 convulsion, and 1 each of grand mal convulsion, mood altered, somnolence, partial seizures with secondary generalization, and 1 patient with confusional state, disorientation, hallucination, and tremor in the < 60 mg/kg/day vigabatrin group and 3 abnormal behavior, 1 psychomotor hyperactivity, 1 convulsion, and 1 patient with partial seizures and somnolence in the ≥ 60 mg/kg/day vigabatrin group.

**Reviewer Note:**

***The controlled clinical study data is reassuring that the incidence of neuropsychiatric cognitive adverse events is similar for the placebo and vigabatrin groups. The pediatric CPS patient population has a higher incidence of these events compared to the general pediatric population and the pediatric CPS population is receiving concomitant AEDs and other medications that could also potentially cause neurocognitive adverse events. The longer follow-up studies included in the All Pediatric CPS Studies do not suggest that there was a change in neurocognitive function over time.***

Neuropsychological assessments were performed in Studies 118, 192, 221, 201, and 294. The measures chosen were the most commonly used in the pediatric population at the time of the studies.

The neuropsychological assessments included tests aimed at assessing neuropsychological, cognitive functions, and psychiatric status. A total of 15 neuropsychological assessments were to be performed at baseline and at least 1 post-baseline visit, including the Children's Psychiatric Rating Scale, Animal Continuous Performance, Auditory Continuous Performance, Doering Rourke Underlying Test, McCarthy Verbal Fluency Test, Logical Memory Stories for Children, Stanford-Binet Memory for Sentences, Beery Visual Motor Integration Test, Mesulam Verbal Cancellation Test, Purdue Pegboard, Rey Auditory Verbal Learning Test, Story Memory Test from the Wide Range Assessment of Memory and Learning, Stroop Test, Woodcock Johnson Cross Out Test, and Woodcock-Johnson Spatial Relation Test.

Although the clinical study reports for these pediatric rCPS studies include listings of the data, no summaries or integration of the data were performed. For the purposes of the current submission, the data were integrated and summarized by the sponsor using descriptive statistics. An external consultant and expert in neuropsychological evaluations (b) (4) reviewed the test results and provided a clinical assessment. (b) (4) findings are summarized as follows.

### Controlled Pediatric CPS Studies

No clinically meaningful changes from baseline to the final visit (duration of 98 to 119 days for controlled studies) in mean attention, memory, executive function, motor function, or Children's Psychiatric Rating Scale (CPRS) scores were noted for the vigabatrin treatment groups.

No clinically meaningful differences were observed between placebo and vigabatrin treatment groups with respect to mean changes from baseline to the final visit in attention, memory, executive function, motor function, or CPRS scores.

### All Pediatric CPS Studies

No clinically meaningful changes from baseline to the final visit (duration of approximately 1 year for patients who participated in the open-label extension studies) in mean attention, memory, executive function, motor function, or CPRS scores were noted for the vigabatrin treatment groups.

No clinically meaningful differences were observed between vigabatrin dose groups with respect to mean changes from baseline to the final visit in attention, memory, executive function, motor function, or CPRS scores.

(b) (4) notes that the review of means and standard deviations (SDs) across conditions and groups for some variables was problematic due to a low number of subjects evaluated (less than 14 for the Animal Continuous Performance, Logical Memory for Children, Stanford-Binet Memory for Sentences, Woodcock-Johnson Cross Out tests, and Section B of the CPRS) as well as a high variability in individual scores, and therefore only a limited interpretation could be made for some of the analyses.

### **Reviewer Note:**

***The summary data of the neuropsychological assessments showed no evidence for a neurocognitive deficit in pediatric patients treated with vigabatrin as compared with pediatric patients treated with placebo. There is also no evidence of a meaningful change in cognitive functioning over time (up to one year) attributable to treatment with vigabatrin.***

### **Development (Somatic and Sexual)**

One (1.0%) patient in the placebo group and 1 patient (1.5%) in the  $\geq 60$  mg/kg/day vigabatrin treatment group experienced a development event (menstruation irregular) in the Controlled Pediatric CPS Studies. The event in the placebo patient was considered moderate in intensity and the event in the  $\geq 60$  mg/kg/day vigabatrin patient was

considered mild in intensity. No patient in the < 60 mg/kg/day vigabatrin treatment group experienced a development event.

The incidence of patients with development events in All Pediatric CPS Studies was 1.8% in the < 60 mg/kg/day vigabatrin treatment group and 1.9% in the ≥ 60 mg/kg/day vigabatrin treatment group. All patients with development events had events considered mild or moderate in intensity.

## Hepatic Function

One (1.1%) patient in the < 60 mg/kg/day vigabatrin treatment group experienced a mild hepatic function event in the **Controlled Pediatric CPS Studies**. The event was considered mild in intensity. This patient (0221-1418-0002) was a 12 year old white female who received vigabatrin <60mg/kg/day from 07/05/1995 until 11/06/1995. On Day 71 (09/14/1995), the patient experienced a nonserious event of asterixis of the left hand . No treatment was administered for the event, protocol was not interrupted, and the dose of vigabatrin was not changed. The event was considered possibly related to vigabatrin and mild in severity. The outcome was reported as not recovered. The patient's hepatic function laboratory results (e.g. ALT, AST, bilirubin) were all within normal range during the study.

### **Reviewer Note:**

***Dyskinetic movements have been observed in epileptic patients on other AEDs. The sponsor has made another CBE-0 submission based on post marketing observations of dyskinesia in patients on vigabatrin. After review of this other submssion, a decision will be made on a possible addition to current labeling.***

No patient in the placebo or ≥ 60 mg/kg/day vigabatrin treatment groups experienced a hepatic function event.

Two (1.2%) patients in the < 60 mg/kg/day vigabatrin treatment group and no patients in the ≥ 60 mg/kg/day vigabatrin treatment group experienced a hepatic function event in **All Pediatric CPS Studies**. One patient experienced severe hepatic failure and died (as described in section 7.3.1 of this review).and the other patient had a hepatic function event that was considered mild in intensity as discussed in the immediately preceding paragraphs.

## Sedation

The incidence of patients with sedation events in the Controlled Pediatric CPS Studies was 25.0% in the placebo group, 22.4% in the all vigabatrin group, 16.8% in the < 60

mg/kg/day vigabatrin treatment group, and 29.4% in the  $\geq 60$  mg/kg/day vigabatrin treatment group. The majority of patients with sedation events had events considered mild or moderate in intensity; 4 patients (one placebo, one  $< 60$  mg/kg/day vigabatrin, two  $\geq 60$  mg/kg/day vigabatrin) had events considered severe.

The incidence of patients with sedation events in All Pediatric CPS Studies was 44.2% in the  $< 60$  mg/kg/day vigabatrin treatment group and 58.3% in the  $\geq 60$  mg/kg/day vigabatrin treatment group. The majority of patients with sedation events had events considered mild or moderate in intensity; 4 patients (all  $< 60$  mg/kg/day vigabatrin) had events considered severe.

### **Dizziness**

The incidence of patients with dizziness events in the Controlled Pediatric CPS Studies was 27.9% in the placebo group, 26.7% in the all vigabatrin group, 22.1% in the  $< 60$  mg/kg/day vigabatrin treatment group, and 32.4% in the  $\geq 60$  mg/kg/day vigabatrin treatment group. The majority of patients with dizziness events had events considered mild or moderate in intensity; 3 patients (one placebo, one  $< 60$  mg/kg/day vigabatrin, one  $\geq 60$  mg/kg/day vigabatrin) had events considered severe.

The incidence of patients with dizziness events in All Pediatric CPS Studies was 46.7% in the  $< 60$  mg/kg/day vigabatrin treatment group and 61.2% in the  $\geq 60$  mg/kg/day vigabatrin treatment group. The majority of patients with dizziness events had events considered mild or moderate in intensity; 4 patients (all  $< 60$  g/kg/day vigabatrin) had events considered severe.

### **Ataxia**

The incidence of patients with ataxia events in the Controlled Pediatric CPS Studies was 25.0% in the placebo group, 22.4% in the all vigabatrin group, 16.8% in the  $< 60$  mg/kg/day vigabatrin treatment group, and 29.4% in the  $\geq 60$  mg/kg/day vigabatrin treatment group.

The majority of patients with ataxia events had events considered mild or moderate in intensity; 4 patients (one placebo, one  $< 60$  mg/kg/day vigabatrin, two  $\geq 60$  mg/kg/day vigabatrin) had events considered severe.

The incidence of patients with ataxia events in All Pediatric CPS Studies was 44.2% in the  $< 60$  mg/kg/day vigabatrin treatment group and 58.3% in the  $\geq 60$  mg/kg/day vigabatrin treatment group. The majority of patients with ataxia events had events considered mild or moderate in intensity; 4 patients (all  $< 60$  mg/kg/day vigabatrin) had events considered severe).



## **Tremor**

The incidence of patients with tremor events in the Controlled Pediatric CPS Studies was 51.0% in the placebo group, 44.8% in the all vigabatrin group, 41.1% in the < 60 mg/kg/day vigabatrin treatment group, and 48.5% in the  $\geq 60$  mg/kg/day vigabatrin treatment group.

The majority of patients with tremor events had events considered mild or moderate in intensity; 9 patients (five placebo, four < 60 mg/kg/day vigabatrin) had events considered severe.

The incidence of patients with tremor events in All Pediatric CPS Studies was 63.6% in the < 60 mg/kg/day vigabatrin treatment group and 71.8% in the  $\geq 60$  mg/kg/day vigabatrin treatment group. The majority of patients with tremor events had events considered mild or moderate in intensity; 17 patients (eleven < 60 mg/kg/day vigabatrin, six  $\geq 60$  mg/kg/day vigabatrin) had events considered severe.

## **Weight Increase**

The incidence of patients with weight increase events in the Controlled Pediatric CPS Studies was 5.8% in the placebo group, 16.4% in the all vigabatrin group, 15.8% in the < 60 mg/kg/day vigabatrin treatment group, and 17.6% in the  $\geq 60$  mg/kg/day vigabatrin treatment group. All patients with weight increase events had events considered mild or moderate in intensity.

The incidence of patients with weight increase events in All Pediatric CPS Studies was 26.7% in the < 60 mg/kg/day vigabatrin treatment group and 29.1% in the  $\geq 60$  mg/kg/day vigabatrin treatment group. All patients with weight increase events had events considered mild or moderate in intensity.

## **Assessment of Growth**

### **Controlled Pediatric rCPS Studies**

A summary of change from baseline to final visit for z-scores in the Controlled Pediatric rCPS Studies is presented in the sponsor's Table 61. Mean changes from baseline were small.

**Table 33 Mean Change from Baseline to the Final Visit in Z-Scores from Controlled Pediatric rCPS Studies**

**Table 61. Mean Change From Baseline to the Final Visit in Z-Scores – Controlled Pediatric CPS Studies**

Parameter Statistic	Placebo N = 104	< 60 mg/kg/day Vigabatrin N = 95	≥ 60 mg/kg/day Vigabatrin N = 68	All Vigabatrin N = 165
Weight to age Z-score	n = 102	n = 95	n = 68	n = 163
Baseline mean (SD)	1.0 (1.16)	1.0 (1.26)	0.2 (1.17)	0.7 (1.29)
Mean change at the final visit (SD)	-0.0 (0.25)	0.1 (0.43)	0.3 (0.37)	0.2 (0.42)
Height to age Z-score	n = 25	n = 17	n = 4	n = 21
Baseline mean (SD)	0.6 (1.10)	0.7 (1.75)	0.6 (1.01)	0.7 (1.62)
Mean change at the final visit (SD)	-0.0 (1.36)	0.0 (0.22)	-0.3 (0.25)	-0.0 (0.25)

Note: Z-scores are based on growth charts from the Center for Disease Control and Prevention (2000).

CPS = complex partial seizures; SD = standard deviation

#### All Pediatric rCPS Studies

A summary of change from baseline to final visit for z-scores in All Pediatric CPS Studies is presented in the sponsor's Table 62.

Mean changes from baseline were small.

**Table 34 Mean Change from Baseline to the Final Visit in Z Scores from All Pediatric rCPS Studies**

**Table 62. Mean Change From Baseline to the Final Visit in Z-Scores –All Pediatric CPS Studies**

Parameter Statistic	< 60 mg/kg/day Vigabatrin N = 165	≥ 60 mg/kg/day Vigabatrin N = 103	All Vigabatrin N = 273
Weight to age Z-score	n = 163	n = 101	n = 266
Baseline mean (SD)	1.0 (1.27)	0.2 (1.09)	0.7 (1.27)
Mean change at the final visit (SD)	0.2 (0.53)	0.5 (0.58)	0.3 (0.56)
Height to age Z-score	n = 79	n = 43	n = 123
Baseline mean (SD)	0.2 (1.31)	-0.2 (1.25)	0.1 (1.30)
Mean change at the final visit (SD)	-0.1 (0.35)	-0.0 (0.66)	-0.1 (0.48)

Note: Z-scores are based on growth charts from the Center for Disease Control and Prevention (2000).

CPS = complex partial seizures; SD = standard deviation

#### Weight Increase

See the previous subheading of Weight Increase in this section and see section 7.4.3 for a discussion of weight increase.

## **Suicidality**

No patients in the Controlled Pediatric CPS Studies had a suicidality event.

Three (1.8%) patients (< 60 mg/kg/day vigabatrin) in All Pediatric CPS Studies had a suicidality event. Two of the events were considered moderate in severity and 1 event was considered severe. No patient in the  $\geq 60$  mg/kg/day vigabatrin treatment group had a suicidality event.

## **Intramyelinic Edema**

A white paper entitled Vigabatrin, Intramyelinic Edema, and Magnetic Resonance Imaging Abnormalities, dated November 30, 2007, reviewed the current body of knowledge concerning vigabatrin, intramyelinic edema, magnetic resonance imaging (MRI) findings and their functional and clinical significance, including evidence concerning the reversibility and long-term clinical consequences of intramyelinic edema and MRI abnormalities. Current Sabril labeling was based on findings from this white paper.

## **Summary of Safety Topics of Special Interest**

As required in the PWR, safety data from the 488 unique vigabatrin-exposed patients were evaluated with reference to specified safety issues of particular concern.

The incidence of AEs within the SMQs of ataxia and cognition/neuropsychiatric function or psychiatric function was higher in the  $\geq 60$  mg/kg/day vigabatrin treatment group compared to the < 60 mg/kg/day vigabatrin treatment group. Similarly, the incidence of AEs within the SMQs sedation, dizziness, tremor, and weight increase was higher in the  $\geq 60$  mg/kg/day vigabatrin treatment group compared to the < 60 mg/kg/day vigabatrin treatment group.

The incidences of patients with a  $\geq 7\%$  weight increase from baseline in the Controlled Pediatric CPS Studies and All Pediatric CPS Studies were consistent with the dose-related increase in the incidence of weight increase AEs. Weight gain has been previously observed among adults in vigabatrin studies, but the use of other concomitant AEDs makes this finding difficult to interpret.

Similar to the findings noted in adult vigabatrin studies, an apparent dose-related trend was observed in the incidence of PCS low hemoglobin and PCS low hematocrit value in both the Controlled Pediatric CPS Studies and All Pediatric CPS Studies. However, none of these changes was associated with an SAE or premature discontinuation from study drug.

Vision data from prospective clinical studies, supplemented by the ongoing Sabril registry and recently published results from independent assessments of vision in vigabatrin-treated children, demonstrate similar profiles of vision findings in the pediatric and adult populations. Current labeled warnings appropriately inform physicians and patients/guardians to evaluate closely the benefits and risks of vigabatrin treatment. Moreover, the current Sabril REMS, which includes periodic vision testing, provides a mechanism to facilitate ongoing vision monitoring of pediatric patients with rCPS and risk benefit discussions between patients/caregivers and physicians.

In conclusion, the overall safety profile for pediatric patients was similar to that previously observed among adults in vigabatrin studies.

## **8 Postmarket Experience**

There were no identifiable trends or patterns in the distribution of AEs across all pediatric age groups, and no new safety issues were identified from this current submission. Based on review and evaluation of the events of special interest, the information received in the pediatric age group from  $\geq 3$  to  $< 18$  years is generally consistent with the data for other postmarketing age groups.

The safety information presented in the published literature highlights what is currently known and adequately covered in the United States Package Insert for vigabatrin. The analysis of the evidence presented from this literature does not change the current benefit-risk balance or safety profile of vigabatrin in the pediatric population as compared to the adult population.

### **Stevens-Johnson syndrome and Toxic Epidermal Necrolysis**

Independent of this current submission, there have been five non-U.S. postmarketing reports of SJS/TEN associated with vigabatrin identified by the sponsor's CBE-0 submitted on November 8, 2011 and/or by the Agency's Office of Surveillance and Epidemiology (OSE) using the FDA Adverse Event Reporting System (FAERS) and the World Health Organization (WHO) Individual Case Safety Report Database (VigiBase). Three of these five reports concerned pediatric patients (ages 6 months, 2 years, and 12 years). The reports involving the 6 month old and 2 year old patients had confirmed diagnoses, but all three cases were confounded by concomitant medications which could have also caused the syndrome. The other two reports concerned adult patients, one confounded by concomitant medications and the other probably attributable to vigabatrin. Based on the sponsor's CBE-0 submitted on November 8, 2011 and on the

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OSE review of the five cases, SJS/TEN will be added to the Post Marketing Experience section of the labeling being approved for this current submission.

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## **9 Appendices**

### **9.1 Literature Review/References**

The safety information presented in the published literature highlights what is currently known and adequately covered in the United States Package Insert for vigabatrin. The analysis of the evidence presented from this literature does not change the current benefit-risk balance or safety profile of vigabatrin in the pediatric population as compared to the adult population.

### **9.2 Labeling Recommendations**

Approval of pediatric indication (age 10 years and older) for refractory complex partial seizures.

Inclusion of results of the Canadian Pediatric Epilepsy Network (CPEN) study in sections 8.4 (Pediatric Use) and 14 (Clinical Studies) of labeling to guide duration of therapy for infantile spasms (IS).

Approval of CBE-0 to include “Stevens Johnson and Toxic Epidermal Necrolysis” under section 6.2 (Post Marketing Experience) in labeling

Merging and updating of the two labeling documents for Sabril tablets and Sabril oral solution into a single labeling document

For the text of the negotiated label from this submission, see the approval letter.

### **9.3 Advisory Committee Meeting**

Not applicable.

### **9.4 Summary of Case Narratives**

#### **Deaths**

Patient Death in Study 201 Sabril

Subject 1621-0007

This 16 year-old female (16 years old in database based on age at time of study entry, 17 years old at the time of hospitalization) who had received vigabatrin 1g QD for approximately (b) (6) months prior hospitalization for elective intracranial monitoring prior to a possible lobectomy for intractable epilepsy. During treatment with vigabatrin, AST and ALT values decreased, but were still within normal limits, with the exception of a low ALT at the study visit prior to hospitalization.

The subject was admitted on (b) (6) and had surgery the following day. Her dose of vigabatrin had been reduced to 500 mg BID for this procedure and the final dose was on the day of surgery.

The evening after surgery, she was found seizing with generalized tonic clonic seizures that went into status epilepticus. The seizures lasted approximately 50 minutes. She was treated with phosphenytoin, phenobarbital, IV fluids and was intubated. Upon examination the patient was afebrile, hypotensive and unresponsive; broad spectrum antibiotics (including ceftazadine, clindamycin, gentamycin) were initiated as well as hemodynamic support with levophed and dopamine.

Her clinical course continued to decompensate with liver enzymes escalating rapidly until her death 4 days after last vigabatrin dose. Post-mortem report described the cause of death as extensive hepatic necrosis with multisystem organ failure. The investigator assessed this case as “definitely” drug related according to the CSR listings; however, it was assessed as “possibly” related on the SAE Reporting Form.

Concomitant medications included carbamazepine 400 mg BID (duration unknown) and Prozac (dose / duration unknown). The post mortem examination revealed extensive hepatocellular necrosis with prominent steatosis evident in the remaining viable parenchyma. Examination of the brain showed right hippocampal sclerosis, malrotation of the left hippocampus (findings consistent with old injury or a developmental abnormality), and diffuse acute ischemic injury in the cortex and brainstem. The acute ischemic injury was felt to be a consequence, not a cause, of her clinical course.

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<u>Liver Enzymes:</u>	<u>AST (U/L)</u>	<u>ALT (U/L)</u>	<u>GGT (U/L)</u>	<u>AlkPhos (U/L)</u>
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Clinical study:

01-Nov-96	15	12	n/a	68
21 Apr 97	13	8	n/a	276
24-Nov-97	9	4 (low)	n/a	231
Normal Values:	(not given)			

Hospital:

(b) (6)	67	41	103	125
	245	86	140	150
	4700	4609	149	183

**Reviewer comment on death of this Study 201 patient in section 7.3.1 of this review**

Open-Label Study 0098

As described previously, this study was a flexible dose, open label observational study of partial seizure patients who were poorly controlled on their standard AED therapy or patients who had rolled over from other Sabril protocols including the long-term pediatric open label extension study 201. Most of the 1264 patents were adults but 60 pediatric patients from Study 201 were included. The prior sponsor (Marion Merrell Dow Inc.) entered SAEs for Study 0098 into its post-marketing safety database, but they were not included in the clinical database. However, this final study report for Study 0098 indicates that there was one pediatric death. This was a 14 year old male patient (11920014) whose cause of death is listed a seizure. There is no patient narrative available to the current sponsor.

CPEN Study

Of the 69 patients with infantile spasms enrolled in the CPEN study, one infantile spasms patient died before receiving any dose of vigabatrin therapy.

**Patient Drop-outs and/or Discontinuations**

Study 118  
Patient 12730003

3 year old female with history of hydrocephalus was discontinued from Study 118 for slurred speech after 2.4 months of vigabatrin 100 mg//kg/day. Investigator felt event

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was mild and possibly related to vigabatrin. Concomitant medication was carbamazepine. The patient remained on vigabatrin and entered open label extension Study 201.

Study 118  
Patient 12740002

13 year old female was discontinued from Study 118 for increase in seizure frequency and increase in "post-ictal compulsion". The investigator felt event was mild and possibly related to vigabatrin. Concomitant medication were phenytoin and phenobarbital. The patient remained on vigabatrin and entered open label extension Study 201.

Study 118  
Patient 12740003

5 year old female with history of ADD and mental retardation was discontinued from Study 118 for psychotic depression after 1.2 months of vigabatrin 100 mg/kg/day.. Investigator felt event was severe and probably related to vigabatrin. Concomitant medications were carbamazepine and lamotrigine. . Not stated if vigabatrin was discontinued. The event abated.

Study 118  
Patient 12750010

4 year old female with history of autistic-like developmental problems was discontinued from Study 118 for irritability after 2.7 months of vigabatrin 100 mg/kg/day. Investigator felt event was moderate and probably related to vigabatrin. Concomitant medication was lamotrigine. Patient remained on vigabatrin and entered open label extension Study 201.

Study 118  
Patient 12770019

9 year old female was discontinued from Study 118 for "a drug interaction" after 2.7 months of vigabatrin 100 mg/kg/day. Investigator felt event was moderate and probably related to 60 vigabatrin. Concomitant medications were carbamazepine and phenytoin. Patient remained on vigabatrin and entered open label extension Study 201.

Study 118



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Patient 12790007

12 year old male with history of left hemisphere resection, cerebral malformation, and mild mental retardation and ADD was discontinued from Study 118 for increased seizure frequency after 1 month of vigabatrin 100 mg/kg/day. Investigator felt event was severe and probably related to vigabatrin. Concomitant medications were divalproex and phenytoin. Patient outcome unknown since lost to follow-up.

Study 118  
Patient 12820001

9 year old male was discontinued from Study 118 for exacerbation of behavioral problems after 1.6 months of vigabatrin 100 mg/kg/day. Investigator felt event was mild and possibly related to vigabatrin. Concomitant medications were lamotrigine, lorazepam, and gabapentin. Not stated if vigabatrin was discontinued. The event abated.

Study 118  
Patient 12780004

13 year old female was hospitalized for pseudoseizures and discontinued from Study 118 after 1.6 months of vigabatrin 20 mg/kg/day. Vigabatrin was discontinued. Investigator felt event was severe but not related to vigabatrin but rather to problems at school and in her family. . Concomitant medications were lamotrigine, and phenobarbital. . Not stated if event abated.

Study 118  
Patient 12740001

5 year old male on placebo with a history of ADD, mental retardation, and chronic encephalopathy was discontinued from Study 118 for gastroenteritis. Investigator felt event was mild and not related to vigabatrin; this may have been after the blind was broken. Concomitant medication was carbamazepine. Event abated. Patient was then started on vigabatrin and entered open label extension Study 201.

Study 118  
Patient 12950005

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15 year old male was hospitalized and discontinued from Study 118 for status epilepticus after 3.5 months of vigabatrin 60 mg/kg/day. Concomitant medications were gabapentin and primidone. Investigator felt event was severe and related to vigabatrin.. Event resolved without sequelae and the patient entered open label extension Study 201 the next day.

Site: 1295 (Study 118)  
Subject Number: 0004

Treatment group: Placebo

Narrative category: TEAE resulting in discontinuation of study drug.

Event: Convulsion

This 9-year-old (at the time of enrollment) white male with refractory complex partial seizures received his first dose of study drug on 02 February 1996. His medical history included pneumonia and chicken pox. Concomitant medications taken by the subject included carbamazepine and valproate semisodium.

On Day 82, the subject experienced a non-serious TEAE of convulsion that was considered by the investigator to be moderate in severity and related to study drug. This non-serious TEAE resulted in withdrawal of study drug and resolved on Day 85.

Information regarding any treatment the subject may have received for this event was not provided.

The subject did not experience any other TEAEs.

Study 192  
Patient 60011

10 year old male discontinued from Study 192 for agitation after 2.9 months of 1.5g/day vigabatrin. The investigator stated moderate intensity and possibly related to vigabatrin. Outcome is unknown. Concomitant medications were phenytoin and carbamazepine.

Study 192  
Patient 90026

11 year old male discontinued from Study 192 for aggressiveness and hyperactivity after 2.6 months of 1.5g/day vigabatrin. The investigator stated moderate intensity and definitely related to vigabatrin. Concomitant medications were phenytoin and carbamazepine. Outcome is unknown.

Study 192  
Patient 70040

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9 year old female discontinued from Study 192 for inability to concentrate and nightmares after 2.9 months of 2 g/day vigabatrin. The investigator stated moderate intensity and possibly related to vigabatrin. Concomitant medication was carbamazepine. Outcome is unknown.

Study 192  
Patient 140092

15 year old male on placebo discontinued from Study 192 for prolonged seizures lasting 15 minutes associated with fever and tonsillitis after 2.4 months of placebo. The investigator stated moderate intensity and not related to vigabatrin (but blind may have already been broken). Concomitant medications were not stated. Patient was not enrolled in the open label extension study.

Site: 0008 (Study 192)  
Subject Number: 0001

Treatment group: Vigabatrin < 60 mg/kg/day  
Narrative category: TEAE resulting in discontinuation of study drug  
Events: Convulsion and abdominal pain

This 12-year-old (at the time of enrollment) white male with refractory complex partial seizures received his first dose of study drug on 13 December 1993. His medical history included infantile spasms and learning disorder. Concomitant medications taken by the subject included phenytoin and nitrazepam. On Day 30, the subject experienced a non-serious TEAE of convulsion that was considered by the investigator to be moderate in severity and related to study drug. On Day 37, he developed abdominal pain that was considered by the investigator to be mild in severity and not related to study drug. These non-serious TEAEs resulted in withdrawal of study drug. The AE of convulsion resolved on Day 48 and the AE of abdominal pain resolved on Day 120. Information regarding any treatment the subject may have received for these events was not provided. The subject also experienced a non-serious TEAE of ear infection (Days 31-37, severe, not related).

Study 221  
Patient 14210011

12 year old male with history of learning disability and behavioral problems was discontinued from Study 221 for multiple seizures after 3.1 months of vigabatrin . Investigator felt the event was moderate and unlikely to be related to vigabatrin since

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the patient was missing doses of both vigabatrin and phenytoin. Concomitant medications were phenytoin and lamotrigine. Patient entered open label extension Study 201.

#### Study 221

Patient 14180006

6 year old male on placebo with history of right temporal lobe astrocytoma was discontinued from Study 221 for a prolonged post-ictal period after 3.1 months of placebo. Investigator felt the event was severe and possibly related to study drug. Concomitant medication was divalproex. Patient entered open label extension Study 201.

#### Study 221

Patient 14211006

4 year old female on placebo with history of developmental delay and ADD was discontinued from Study 221 for a prolonged post-ictal period after 2.8 months of placebo. Investigator felt the event was mild and possibly related to study drug. Concomitant medication was lamotrigine. Patient entered open label extension Study 201.

#### Study 221

Patient 14240006

9 year old male on placebo with history of learning disability and ADD was discontinued from Study 221 for inability to tandem walk after 2.8 months of placebo. Investigator felt the event was moderate mild and probably related to study drug. Concomitant medications were phenytoin and gabapentin. Patient entered open label extension Study 201.

Site: 1423 (Study 221)

Subject Number: 0010

Treatment group: Vigabatrin < 60 mg/kg/day

Narrative category: TEAE resulting in discontinuation of study drug

Events: Convulsion

This 13-year-old (at the time of enrollment) white male with refractory complex partial seizures received his first dose of study drug on 29 February 1996. His medical history included exotropia, status post divergent strabismus, scoliosis, chromosomal abnormality, allergy to penicillin and dander of animal hair, and viral chest cold. Concomitant medications taken by the subject included gabapentin, valproate semisodium, loracarbef, and poly-histine.

On Day 43, the subject experienced convulsions that were considered by the investigator to be mild in severity and not related to study drug. This non-serious TEAE

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nevertheless resulted in withdrawal of study drug and resolved on Day 53. Information regarding any treatment the subject may have received for this event was not provided. The subject also experienced a non-serious TEAE of cerebellar syndrome (Days 3-27, mild, not related).

Site: 1425 (Study 221)  
Subject Number: 0005

Treatment group: Placebo

Narrative category: TEAE resulting in discontinuation of study drug

Event: Convulsion

This 9-year-old (at the time of enrollment) white female with refractory complex partial seizures received her first dose of study drug on 18 April 1996. Her medical history included headache, allergy to dilantin and phenobarbital, and upper respiratory infection. Concomitant medications taken by the subject included lamotrigine.

On Day 104, the subject experienced a non-serious TEAE of convulsion that was considered by the investigator to be moderate in severity and related to study drug. This non-serious TEAE resulted in withdrawal of study drug and resolved the same day. Information regarding any treatment the subject may have received for this event was not provided. The subject did not experience any other TEAEs during Study 221.

Site: 1425 (Study 221)  
Subject Number: 0013

Treatment group: Placebo

Narrative category: TEAE resulting in discontinuation of study drug

Events: Sinus headache

This 13-year-old (at the time of enrollment) white female with refractory complex partial seizures received her first dose of study drug on 16 January 1997. Her medical history included menarche at 10 years, headache, refractive error, wears corrective lenses, fatigue, periodic musculoskeletal pain, chest pain, post-ictal headaches, and volatile temperament. Concomitant medications taken by the subject included valproate semisodium.

On Day 35, the subject experienced a sinus headache that was considered by the investigator to be mild in severity and not related to study drug. This non-serious TEAE resulted in withdrawal of study drug and resolved on Day 36. Information regarding any treatment the subject may have received for this event was not provided.

The subject also experienced non-serious TEAEs of constipation (Days 8-8, mild, not related) and convulsion (Days 16-76, moderate, related).

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Site: 1421 (Study 221)  
Subject Number: 0005

Treatment group: Placebo

Narrative category: TEAE resulting in discontinuation of study drug

Event: Per Study Termination Information Page: 1° reason: "substantial worsening in seizure frequency and/or intensity", 2° reason: "patient experienced an AE or had a clinically significant increase in AEs".

This 7-year-old (at the time of enrollment) white female with refractory complex partial seizures received her first dose of study drug on 25 July 1996. Her medical history included encephalitis secondary to herpes, elevated liver functions, reflux, hypotension, multiple episodes of tachycardia, hemiballismus right motor restlessness, left hemiparesis due to stroke, cortical blindness, encephalopathy, strep throat, upper respiratory infections, rhinitis, drooling, bad behavior, cognitive deficiencies, dysarthric speech, precocious puberty, GT placement and then gastric button for supplemental nutrition, headache, constipation, pneumonia, and allergies to pollen and mold. Concomitant medications taken by the subject included carbamazepine, valproate sodium, and leuprorelin acetate.

On Day 2, the subject experienced a non-serious TEAE of increased appetite that was considered by the investigator to be moderate in severity and related to study drug. The study drug dose was not changed and the event resolved on Day 105. On Day 46, the subject experienced a nonserious TEAE of congestion coded to a preferred term of unevaluable event (since legacy events cannot be clarified) that was considered by the investigator to be mild in severity and not related to study drug. The study drug dose was not changed and the event resolved on Day 49. On Day 56, the subject experienced a non-serious TEAE of blood cholesterol increased that was considered by the investigator to be moderate in severity and not related to study drug. The study drug dose was not changed and the event resolved on Day 105. On Day 69, the subject experienced a non-serious TEAE of convulsion that was considered by the investigator to be moderate in severity and related to study drug. On Day 76, the subject experienced non-serious TEAEs of convulsion and lethargy that were considered by the investigator to be moderate in severity and related to study drug. The study drug dose was reduced. Both events of convulsion and the event of lethargy resolved on Day 105. Information regarding any treatment the subject may have received for these events was not provided.

According to the Study Termination Information Page, the primary reason for discontinuation was substantial worsening in seizure frequency and/or intensity and the secondary reason for discontinuation of study drug was due to an AE; however, from the AE information provided by the prior sponsor it is not evident which event resulted in discontinuation.

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Site: 1424 (Study 221)  
Subject Number: 0008

Treatment group: Placebo

Narrative category: TEAE resulting in discontinuation of study drug

Event: Per Study Termination Information Page: 1° reason: voluntary withdrawal

2° reason: "patient experienced an AE or had a clinically significant increase in AEs".

This 4-year-old (at the time of enrollment) white female with refractory complex partial seizures received her first dose of study drug on 07 January 1997. Her medical history included tuberous sclerosis, multiple hypopigmented macules, multiple subcortical hematomas, hyperactivity, moderate irritability and aggressiveness, and stitches required after falls in 1993 and 1994.

Concomitant medications taken by the subject included clonazepam and phenytoin.

On Day 17, the subject experienced abnormal behavior that was considered by the investigator to be severe in severity and not related to study drug. The event resolved on Day 59. On Day 29, the subject experienced nasopharyngitis that was considered by the investigator to be mild in severity and not related to study drug. The study drug dose was not changed and the event resolved on the same day. Information regarding any treatment the subject may have received for these events was not provided.

According to the Study Termination Information Page, the primary reason for discontinuation was voluntary withdrawal and the secondary reason for discontinuation of study drug was due to an AE; however, from the AE information provided by the prior sponsor it is not evident which event resulted in discontinuation.

Site: 1398 (Study 201)  
Subject Number: 1003

Treatment group: Vigabatrin < 60 mg/kg/day

Narrative category: TEAE resulting in discontinuation of study drug

Events: Memory impairment and dysarthria

This 12-year-old (at the time of enrollment) white female with refractory complex partial seizures received her first dose of study drug on 18 June 1996. Her medical history included urinary tract infection, neutropenia, nystagmus, fracture of right fibula, cerebral hemorrhage, headache usually after seizure, meningitis, motor skill delay, right hemiparesis, shunted hydrocephalus and shunt, and mental retardation. Concomitant medications taken by the subject included valproate sodium.

On Day 57, the subject began experiencing mild memory impairment and on Day 95, she developed moderate dysarthria; both events were considered by the investigator to be not related to study drug. These non-serious TEAEs resulted in withdrawal of study drug. The event of memory impairment resolved on Day 95 and the event of dysarthria resolved on Day 106.

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Information regarding any treatment the subject may have received for these events was not provided.

The subject also experienced non-serious TEAEs of dyskinesia (Days 1-14, mild, related), ataxia (Days 1-106, mild, related), weight increased (Days 1-106, moderate, related), joint injury (Days 14-75, moderate, not related), and cognitive disorder and dyscalculia (Days 57-106, mild, not related).

Site: 1381 (Study 201)  
Subject Number: 0002

Treatment group: Vigabatrin  $\geq$  60 mg/kg/day  
Narrative category: TEAE resulting in discontinuation of study drug  
Event: Platelet count decreased

This 5-year-old (at the time of enrollment) white male with refractory complex partial seizures received his first dose of study drug on 08 September 1995. His medical history included cardiac arrest shortly after birth, circumcision, bilateral myringotomy tubes, frequent "hay fever" symptoms, tubes in ears, jaundice after birth, developmental delay, decreased motor coordination, delayed (slurred) speech, allergy to felbatol and lamictal. Concomitant medications taken by the subject included valproate semisodium and fluoride.

On Day 311, the subject developed a non-serious TEAE of platelet count decreased that was considered by the investigator to be mild in severity and related to study drug. This event resulted in withdrawal of study drug and resolved on Day 906. Information regarding any treatment the subject may have received for this event was not provided. The subject also experienced non-serious TEAEs of viral infection (Days 62-68, mild, not related, resolved), increased appetite (Days 78-319, mild, related), upper respiratory tract infection (Days 115-311, mild, not related), liver palpable subcostal (Days 117-227, mild, related), drooling (Days 118-343, mild, related), disturbance in attention (Days 120-343, mild, related), otitis media (Days 138-147, mild, not related), clonus (Days 143-227, mild, related), convulsion (Days 218-224, mild, related), and viral infection (Days 218-234, mild, not related).

Site: 1392 (Study 201)  
Subject Number: 0001

Treatment group: Vigabatrin  $\geq$  60 mg/kg/day  
Narrative category: TEAE resulting in discontinuation of study drug  
Event: Convulsion

This 11-year-old (at the time of enrollment) white male with refractory complex partial seizures received his first dose of study drug on 03 January 1996. His medical history included developmental delay (speech and motor) and seizures. Concomitant medications taken by the subject included mesuximide and acetazolamide.

On Day 352, the subject experienced a non-serious TEAE of convulsion that was considered by the investigator to be moderate in severity and not related to study drug.



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This event resulted in withdrawal of study drug and resolved on Day 402. Information regarding any treatment the subject may have received for this event was not provided. The subject also experienced a non-serious TEAE of weight increased (Days 183-373, mild, related).

Site: 1624 (Study 201)  
Subject Number: 0005

Treatment group: Vigabatrin  $\geq$  60 mg/kg/day

Narrative category: TEAE resulting in discontinuation of study drug

Event: Abnormal behavior

This 8-year-old (at the time of enrollment) white female with refractory complex partial seizures received her first dose of study drug on 27 March 1996. Her medical history included epilepsy, intracranial epilepsy monitoring which did not indicate a need for epilepsy surgery, nightmares, flurries increased over last 8 months, and weight gain. Concomitant medications taken by the subject included lamotrigine and diazepam. On Day 174, the subject exhibited abnormal behavior that was considered by the investigator to be moderate in severity and related to study drug. This non-serious TEAE resulted in withdrawal of study drug and resolved on Day 225. Information regarding any treatment the subject may have received for this event was not provided. The subject also experienced non-serious TEAEs of chest pain (Days 94-158, mild, related), dyspnoea (Days 94-157, mild, related), pyrexia (Days 96-99, mild, not related), headache (Days 117-119, mild, related), gastroenteritis (Days 146-147, mild, not related), headache (Days 149-175, mild, related), gastroenteritis (Days 149-149, moderate, related), and nasopharyngitis (Days 201-201, mild, not related).

Site: 1398 (Study 201)  
Subject Number: 0002

Treatment group: Vigabatrin  $<$  60 mg/kg/day

Narrative category: TEAE resulting in discontinuation of study drug

Events: Viral pharyngitis and incision site pain

This 14-year-old (at the time of enrollment) white male with refractory complex partial seizures received his first dose of study drug on 26 April 1996. His medical history included hypothyroidism, astigmatism, visual loss in the left eye following encephalitis, otitis media, basilar migraine (headache and right neck pain), encephalitis possibly due to cat scratch disease, slow speech, inability to follow a 3-step command, behavioral disorder, and attention deficit disorder with hyperactivity. Concomitant medications taken by the subject included ibuprofen and lamotrigine.

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On Day 693, the subject experienced viral pharyngitis that was considered by the investigator to be moderate in severity and not related to study drug. The event resolved on Day 698. On Day 740, the subject experienced incision site pain that was considered by the investigator to be moderate in severity and not related to study drug. The event resolved on Day 847. Both of these non-serious TEAEs resulted in withdrawal of study drug. Information regarding any treatment the subject may have received for these events was not provided.

The subject also experienced non-serious TEAEs of irritability (Days 46-768, moderate, related), nausea (Days 46-638, mild, related), cognitive disorder (Days 71-127, mild, related), visual field defect (Days 113-768, missing severity, related), disorientation (Days 127-162, mild, related), convulsion (Days 128-128, mild, not related), burning sensation (Days 135-162, moderate, not related), memory impairment (Days 162-462, moderate, related), convulsion (Days 271-768, moderate, not related), convulsion (Days 271-768, moderate, not related), weight increased (Days 279-768, moderate, related), disorientation (Days 355-638, mild, related), memory impairment (Days 355-462, mild, related), vomiting (Days 621-622, moderate, not related), memory impairment (Days 638-768, moderate, related), vomiting (Days 657-768, moderate, not related), partial seizures with secondary generalization (Days 734-735, moderate, not related), and procedural pain (Days 740-741, moderate, not related). The subject also experienced serious TEAEs of grand mal convulsion (Days 621-768, severe, not related), convulsion (Days 657-768, moderate, not related), convulsion (Days 696-768, moderate, not related), and visual field defect (Days 755-768, mild, related).

Site: 1402 (Study 201)  
Subject Number: 1005

Treatment group: Vigabatrin < 60 mg/kg/day

Narrative category: TEAE resulting in discontinuation of study drug

Event: Nystagmus (also see narrative in Study 201 CSR for this subject)

This 12-year-old (at the time of enrollment) white female with refractory complex partial seizures received her first dose of study drug on 05 June 1996. Her medical history included transient function systolic murmur, bedwetting, eye pain "pressure", multiple ophthalmological abnormalities, otitis media, sinusitis, tonsillitis, broken bone in right foot, angiomas related to Sturge-Weber syndrome, left vertebral atrophy related to Sturge-Weber syndrome, congenital nevus related to Sturge-Weber syndrome, pneumonia, mild contact dermatitis, allergy to amoxicillin and erythromycin, and laser surgeries for facial nevus. Concomitant medications taken by the subject included valproic acid and cefprozil. On Day 160, the subject experienced nystagmus that was considered by the investigator to be mild in severity and not related to study drug. This non-serious TEAE resulted in withdrawal of study drug and resolved on Day 194. Information regarding any treatment the subject may have received for this event was not provided. The subject also experienced non-serious TEAEs of neuromyopathy

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(Days 134-140, mild, not related), somnolence (Days 140-160, moderate, not related), infusion site extravasation (Days 140-194, moderate, not related), and ophthalmological examination abnormal (Days 157-157, moderate, not related). The subject also experienced a serious TEAE of complex partial seizures (Days 134-194, moderate, not related).

Site: 1389 (Study 201)

Subject Number: 0001

Treatment group: Vigabatrin < 60 mg/kg/day

Narrative category: TEAE resulting in discontinuation of study drug

Events: Polycystic ovaries, weight increased, and blood creatine increased

This 14-year-old (at the time of enrollment) white female with refractory complex partial seizures received her first dose of study drug on 07 March 1996. Her medical history included menarchial, encopresis, Rasmussen's encephalitis, cortical resection, and allergy to sulfa drugs. Concomitant medications taken by the subject included valproic acid.

On Day 477, the subject was noted to have polycystic ovaries, an event that was considered by the investigator to be moderate in severity and related to study drug. The event resolved on Day 923. On Day 646, the subject developed a TEAE of weight increased that was considered by the investigator to be moderate in severity and related to study drug. The event resolved on Day 1022. On Day 904, the subject developed a TEAE of blood creatine increased that was considered by the investigator to be mild in severity and not related to study drug. The event resolved on Day 912. All of these non-serious TEAEs resulted in withdrawal of study drug. Information regarding any treatment the subject may have received for these events was not provided.

The subject also experienced non-serious TEAEs of fatigue (Days 4-502, mild, related), respiratory disorder (Days 477-1022, moderate, not related), nausea (Days 543-544, mild, not related), nausea (Days 549-551, moderate, related), headache (Days 689-900, mild, related), pneumonia (Days 757-768, moderate, not related), convulsion (Days 798-798, mild, not related), tremor (Days 806-923, mild, not related), and convulsion (Days 832-923, moderate, related).

Site: 1400 (Study 201)

Subject Number: 0003

Treatment group: Vigabatrin < 60 mg/kg/day

Narrative category: TEAE resulting in discontinuation of study drug

Events: Optic neuropathy, visual field defect, abnormal behavior, and chest pain

This 13-year-old (at the time of enrollment) white male with refractory complex partial seizures received his first dose of study drug on 08 November 1996. His medical history included enuresis, hamartoma anterior pituitary stalk, neural glial hamartoma,

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craniotomy, right parietal scar from craniotomy. Concomitant medications taken by the subject included imipramine hydrochloride, valproate semisodium, and lamotrigine. On Day 670, the subject experienced SAEs of optic neuropathy and visual field defect that were considered by the investigator to be mild in severity. On Day 677, the subject exhibited abnormal behavior that was considered by the investigator to be moderate in severity. On Day 726, the subject experienced chest pain that was considered by the investigator to be mild in severity. These events resulted in withdrawal of study drug and were considered by the investigator to be related to study drug. All events resolved on Day 797. Information regarding any treatment the subject may have received for these events was not provided. The subject also experienced non-serious TEAEs of visual evoked potentials abnormal (Days 99-797, missing severity, related), decreased appetite (Days 99-797, missing severity, related), coma (Days 99-797, missing severity, related), aggression (Days 99-797, missing severity, related), pyrexia (Days 99-797, missing severity, related), lethargy (Days 99-797, missing severity, related), visual field defect (Days 99-797, missing severity, related), gastroenteritis viral (Days 292-292, mild, not related), and encephalitis (Days 381-398, moderate, not related). The subject also experienced serious TEAEs diarrhea (Days 382-393, severe, not related), encephalitis (Days 382-390, severe, not related), renal failure acute (Days 384-393, severe, not related), disseminated intravascular coagulation (Days 384-393, severe, not related), and hypoxia (Days 384-393, severe, not related).

Site: 1621 (Study 201)  
Subject Number: 0015

Treatment group: Vigabatrin < 60 mg/kg/day  
Narrative category: TEAE resulting in discontinuation of study drug Events: Personality change, convulsion, and general symptom

This 6-year-old (at the time of enrollment) white female with refractory complex partial seizures received her first dose of study drug on 07 June 1997. Her medical history included optic atrophy and hydrocephalus. Concomitant medications taken by the subject included lamotrigine.

On Day 107, the subject exhibited a personality change that was considered by the investigator to be moderate in severity. On Day 112, the subject experienced convulsions that were considered by the investigator to be moderate in severity. On Day 123, the subject experienced headache and vomiting, which was coded to a preferred term of general symptom (since legacy events cannot be clarified) that was considered by the investigator to be mild in severity. These non-serious TEAEs resulted in withdrawal of study drug and were considered by the investigator to be related to study drug. The events of personality change and general symptom resolved on Day 143 and the event of convulsion resolved on Day 171. Information regarding any treatment the

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subject may have received for these events was not provided. The subject also experienced a non-serious TEAE of headache (Days 106-126, mild, related).

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/s/  
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PHILIP H SHERIDAN  
10/25/2013

NORMAN HERSHKOWITZ  
10/25/2013