HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SABRIL safely and effectively. See full prescribing information for SABRIL.

Sabril® (vigabatrin) for Oral Solution
For Oral Administration Only
Initial U.S. Approval: 2009

WARNING: VISION LOSS
See full prescribing information for complete boxed warning

- SABRIL causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity.
- Risk increases with total dose and duration of use, but no exposure to SABRIL is known that is free of risk of vision loss
- Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL
- Unless a patient is formally exempted, periodic vision assessment is required for patients on SABRIL. However, this assessment cannot always prevent vision damage.Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Monitoring of Vision (5.1) 12/2012

----------INDICATIONS AND USAGE----------
SABRIL is an antiepileptic drug (AED) indicated for:
- **Infantile Spasms (IS) - 1 Month to 2 Years of Age** (1.1)

----------DOSAGE AND ADMINISTRATION----------
- Infantile Spasms: Initiate therapy at 50 mg/kg/day twice daily increasing total daily dose per instructions to a maximum of 150 mg/kg/day (2.1)
- Dose adjustment recommended in renally impaired patients (2.2)
- Reduce dose gradually upon discontinuation (2.3)

----------DOSAGE FORM AND STRENGTHS----------
Powder for Oral Solution: 500 mg (3.1)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- SABRIL causes permanent vision loss (5.1)
- Abnormal MRI signal changes have been reported in some infants with IS receiving SABRIL (5.3)
- Antiepileptic drugs, including SABRIL, increase the risk of suicidal thoughts and behavior (5.5)
- Dose should be tapered gradually to avoid withdrawal seizures (5.6)
- SABRIL causes anemia (5.7)
- SABRIL causes somnolence and fatigue (5.8)
- SABRIL causes peripheral neuropathy (5.9)
- SABRIL causes weight gain (5.10)
- SABRIL causes edema (5.11)

----------ADVERSE REACTIONS----------
Most common adverse reactions described in adults (change of ≥5% over placebo) in addition to permanent vision loss in adult controlled trials with vigabatrin were fatigue, somnolence, nystagmus, tremor, vision blurred, memory impairment, weight gain, arthralgia, abnormal coordination, and confusional state (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck at 1-800-455-1141 or www.lundbeckus.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Decreased phenytoin plasma levels have been reported (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available (8.1)
- Nursing Mothers: SABRIL is excreted in human milk (8.2)
- Renal Impairment: Dose adjustment recommended (2.2, 8.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide).

Revised: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS

WARNING: VISION LOSS

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

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

1 INDICATIONS AND USAGE

1.1 Infantile Spasms (1 Month to 2 Years of Age)

SABRIL® is indicated as monotherapy for pediatric patients with infantile spasms (IS) for whom the potential benefits outweigh the potential risk of vision loss [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Infantile Spasms (1 Month to 2 Years of Age)

Physicians should review and discuss the Medication Guide with the caregiver(s) prior to preparation and administration of SABRIL. Physicians should confirm that caregiver(s) understand how to reconstitute SABRIL and to administer the correct dose to their infants.

SABRIL should be given as twice daily oral administration with or without food. The initial dosing is 50 mg/kg/day given in two divided doses and can be titrated by 25-50 mg/kg/day increments every 3 days up to a maximum of 150 mg/kg/day [see USE IN SPECIFIC POPULATIONS, Pediatric Use (8.3)].

The entire contents of the appropriate number of packets (500 mg/packet) of powder should be emptied into an empty cup, and should be dissolved in 10 mL of cold or room temperature water per packet using the 10 mL oral syringe supplied with the medication. Discard the resulting solution if it is not clear (or free of particles) and colorless. The concentration of the final solution is 50 mg/mL. Table 1 below describes how many packets and how many mL of water will be needed to prepare each individual dose. Each individual dose should be prepared immediately before use and administered cold or at room temperature. Discard any unused portion of the solution after administering the correct dose.

Table 1. Number of Packages and mL of Water used for Each Individual Dose

Each Individual Dose (Prepared and Given Twice Daily)	Number of Packets	Number of mL of Water for Dissolving
0 to 500 mg	1 packet	10 mL
501 to 1000 mg	2 packets	20 mL
1001 to 1500 mg	3 packets	30 mL

Table 2 provides the volume that should be administered as individual doses in infants of various weights is presented below:

Table 2. Infant Dosing Table

Weight (kg)	Starting Dose 50 mg/kg/day	Maximum Dose 150 mg/kg/day
3	1.5 mL twice daily	4.5 mL twice daily
4	2 mL twice daily	6 mL twice daily
5	2.5 mL twice daily	7.5 mL twice daily
6	3 mL twice daily	9 mL twice daily

Table 2. Infant Dosing Table

7	3.5 mL twice daily	10.5 mL twice daily
8	4 mL twice daily	12 mL twice daily
9	4.5 mL twice daily	13.5 mL twice daily
10	5 mL twice daily	15 mL twice daily
11	5.5 mL twice daily	16.5 mL twice daily
12	6 mL twice daily	18 mL twice daily
13	6.5 mL twice daily	19.5 mL twice daily
14	7 mL twice daily	21 mL twice daily
15	7.5 mL twice daily	22.5 mL twice daily
16	8 mL twice daily	24 mL twice daily

2.2 Patients with Renal Impairment

SABRIL is primarily eliminated through the kidney. Information about how to adjust the dose in pediatric patients with renal impairment is unavailable.

The following dose adjustments are pertinent to the possible use of this dosage form in adults with renal impairment:

In patients with mild renal impairment (CLcr >50 to 80 mL/min), the dose should be decreased by 25%; in patients with moderate renal impairment (CLcr >30 to 50 mL/min), the dose should be decreased by 50%; and in patients with severe renal impairment (CLcr >10 to <30 mL/min), the dose should be decreased by 75%.

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

CLcr *= [140-*age* (*years*)]×*weight* (*kg*)/72×*serum creatinine* (*mg*/*dL*)]
*[×0.85 *for female patients*]

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

[See CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5)].

2.3 General Dosing Considerations

Monitoring of SABRIL plasma concentrations to optimize therapy is not helpful. If a decision is made to discontinue SABRIL, the dose should be gradually reduced. In a controlled clinical study in patients with IS, vigabatrin was tapered by decreasing the dose at a rate of 25-50 mg/kg every 3-4 days [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs) (5.6)].

3 DOSAGE FORMS AND STRENGTHS

3.1 Powder for Oral Solution

500 mg Packet.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Vision Loss (see BOXED WARNING)

Because of the risk of vision loss and because SABRIL, when it is effective, provides an observable symptomatic benefit, the patient who fails to show substantial clinical benefit within 2 to 4 weeks of initiation of treatment, should be withdrawn from SABRIL. If in the clinical judgment of the prescriber evidence of treatment failure becomes obvious earlier than 2 to 4 weeks, treatment with SABRIL should be discontinued at that time. Patient response to and continued need for treatment should be periodically assessed.

Monitoring of Vision

Because vision testing in infants and children is difficult, vision loss may not be detected until it is severe. However, monitoring of vision must be performed by an ophthalmic professional with expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina, unless a patient is formally exempted from periodic ophthalmologic assessment as documented in the Support, Help And Resources for Epilepsy (SHARE) program. For patients receiving SABRIL who are not exempted, vision assessment is required at baseline (no later than 4 weeks after starting SABRIL), at least every 3 months while on therapy and about 3-6 months after the discontinuation of SABRIL therapy.

The diagnostic approach should be individualized for the patient and clinical situation. For all patients, attempts to monitor vision periodically and/or formal exemptions must be documented under the SHARE program. In patients exempted from vision assessment, treatment may continue according to clinical judgment, with appropriate caregiver(s) counseling, and with documentation in the SHARE program of the inability to test vision. Because of variability, results from ophthalmic monitoring must be interpreted with caution, and repeat assessment is recommended if results are abnormal or uninterpretable.

The onset and progression of vision loss from SABRIL is unpredictable, and it may occur or worsen precipitously. Once detected, vision loss due to SABRIL is not reversible. It is expected that even with frequent monitoring, some SABRIL patients will develop severe vision loss. Drug discontinuation should be considered, balancing benefit and risk, if visual loss is documented.

5.2 Distribution Program for SABRIL (SHARE Program)

SABRIL is available only under a special restricted distribution program called the SHARE program. Under the SHARE program, only prescribers and pharmacies registered with the program are able to prescribe and distribute SABRIL. In addition, SABRIL may be dispensed only to patients who are enrolled in and meet all conditions of SHARE. Contact the SHARE program at 1-888-45-SHARE.

To enroll in SHARE, prescribers must understand the risks of SABRIL and complete the SHARE Prescriber Enrollment and Agreement Form indicating agreement to:

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

The prescriber may, with appropriate documentation and caregiver counseling, exempt certain patients with vision assessment, using the Ophthalmologic Assessment Form, if:

- The patient is blind (subsequent Ophthalmologic Forms do not need to be submitted to the REMS coordinating center)
- The patient's general neurological and/or mental condition permanently precludes the need for visual assessment (subsequent Ophthalmologic Forms do not need to be submitted to the REMS coordinating center)
- The patient's general neurological condition temporarily precludes the ability to assess visual function. The evaluation, however, may be performed at a later time as clinically appropriate.
- The patient's medical condition prevents visual assessment being performed safely
- For other reasons specified by the prescriber

5.3 Magnetic Resonance Imaging (MRI) Abnormalities

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with SABRIL. In a retrospective epidemiologic study in infants with IS (N=205),

the prevalence of these changes was 21.5% in SABRIL treated patients versus 4.1% in patients treated with other therapies.

In the study above, in post marketing experience, and in published literature reports, these changes generally resolved with discontinuation of treatment. In a few patients, the lesion resolved despite continued use. It has been reported that some infants exhibited coincident motor abnormalities, but no causal relationship has been established and the potential for long-term clinical sequelae has not been adequately studied.

Neurotoxicity (including convulsions and hypomyelination) was observed in rats exposed to vigabatrin during late gestation and the neonatal and juvenile periods of development. The relationship between these findings and the abnormal MRI findings in infants treated for IS with vigabatrin is unknown [see WARNINGS AND PRECAUTIONS, Neurotoxicity (5.4) and USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)].

The specific pattern of signal changes observed in IS patients was not observed in older children and adult patients treated with vigabatrin for refractory complex partial seizures (CPS). In a blinded review of MRI images obtained in prospective clinical trials in patients with refractory CPS 3 years and older (N=656), no difference was observed in anatomic distribution or prevalence of MRI signal changes between vigabatrin treated and placebo patients.

5.4 Neurotoxicity

Vacuolization, characterized by fluid accumulation and separation of the outer layers of myelin, has been observed in brain white matter tracts in adult and juvenile rats and adult mice, dogs, and possibly monkeys following administration of vigabatrin. This lesion, referred to as intramyelinic edema (IME), was seen in animals at doses within the human therapeutic range. A no-effect dose was not established in rodents or dogs. In the rat and dog, vacuolization was reversible following discontinuation of vigabatrin treatment, but, in the rat, pathologic changes consisting of swollen or degenerating axons, mineralization, and gliosis were seen in brain areas in which vacuolation had been previously observed. Vacuolization in adult animals was correlated with alterations in MRI and changes in visual and somatosensory evoked potentials (EP).

Administration of vigabatrin to rats during the neonatal and juvenile periods of development produced vacuolar changes in the 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, retinal dysplasia, and neurobehavioral abnormalities (convulsions, neuromotor impairment, learning deficits) were also observed following vigabatrin treatment of young rats. These effects occurred at doses associated with plasma vigabatrin levels substantially lower than those achieved clinically in infants and children.

In a published study, vigabatrin (200, 400 mg/kg/day) induced apoptotic neurodegeneration in the brain of young rats when administered by intraperitoneal injection on postnatal days 5-7.

Administration of vigabatrin to female rats during pregnancy and lactation at doses below those used clinically resulted in hippocampal vacuolation and convulsions in the mature offspring.

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult epilepsy patients have demonstrated no clear-cut abnormalities [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3)].

5.5 Suicidal Behavior and Ideation

The following information is pertinent to the possible use of this dosage form in adults. Antiepileptic drugs (AEDs), including SABRIL, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug treated patients in the trials and none in placebo treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by

age (5-100 years) in the clinical trials analyzed. Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing SABRIL or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregiver(s), and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, SABRIL should be withdrawn gradually.

Caregivers should be told not to suddenly discontinue SABRIL therapy. In a controlled clinical study in patients with IS, vigabatrin was tapered by decreasing the daily dose at a rate of 25-50 mg/kg every 3-4 days [see DOSAGE AND ADMINISTRATION, General Dosing Considerations (2.3), PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.5)].

5.7 Anemia

In North American controlled trials in adults, 5.7% of patients (16/280) receiving SABRIL and 1.6% 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 in hematocrit of about 1% in

Sabril treated patients compared to a 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%.

5.8 Somnolence and Fatigue

SABRIL causes somnolence and fatigue. Patients should be advised not to drive a car or operate other complex machinery until they are familiar with the effects of SABRIL on their ability to perform such activities.

Pooled data from two SABRIL controlled trials in adults demonstrated that 24% (54/222) of SABRIL patients experienced somnolence compared to 10% (14/135) of placebo patients. In those same studies, 28% of SABRIL patients experienced fatigue compared to 15% (20/135) of placebo patients. Almost 1% of SABRIL patients discontinued from clinical trials for somnolence and almost 1% discontinued for fatigue.

5.9 Peripheral Neuropathy

SABRIL has been shown to cause symptoms of peripheral neuropathy in adults. The clinical trials in pediatric patients were not adequately designed to assess whether or not these symptoms occur in the pediatric population.

In a pool of North American controlled and uncontrolled epilepsy studies, 4.2% (19/457) of SABRIL treated patients developed signs and/or symptoms of peripheral neuropathy. In the subset of North American placebo controlled epilepsy trials, 1.4% (4/280) of SABRIL treated patients and no (0/188) placebo patients developed signs and/or symptoms of peripheral neuropathy. Initial manifestations of peripheral neuropathy in these trials included, in some combination, symptoms of numbness or tingling in the toes or feet, signs of reduced distal lower limb vibration or position sensation, or progressive loss of reflexes, starting at the ankles. Clinical studies in the development program were not designed to investigate peripheral neuropathy systematically and did not include nerve conduction studies, quantitative sensory testing, or skin or nerve biopsy. There is insufficient evidence to determine if development of these signs and symptoms were related to duration of SABRIL treatment, cumulative dose, or if the findings of peripheral neuropathy were completely reversible upon discontinuation of SABRIL.

5.10 Weight Gain

SABRIL has been shown to cause weight gain in adults. The clinical trials in pediatric patients were not adequately designed to assess whether or not weight gain occurs in the pediatric population.

Data pooled from randomized controlled trials found that 17% (77/443) of SABRIL patients gained ≥ 7% of baseline body weight versus 8% (22/275) of placebo patients. In these same trials, the mean weight change among SABRIL patients was 3.5 kg compared to 1.6 kg for placebo patients. In all epilepsy trials, 0.6% (31/4855) of SABRIL patients discontinued for weight gain. The long term effects of SABRIL related weight gain are not known. Weight gain was not related to the occurrence of edema.

5.11 Edema

SABRIL has been shown to cause edema in adults. The clinical trials in pediatric patients were not adequately designed to assess whether or not edema occurs in the pediatric population.

Pooled data from controlled trials demonstrated increased risk among SABRIL patients compared to placebo patients for peripheral edema (SABRIL 2%, placebo 1%), and edema (SABRIL 1%, placebo 0%). In these studies, one SABRIL and no placebo patients discontinued for an edema related AE. There was no apparent association between edema and cardiovascular adverse events such as hypertension or congestive heart failure. Edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

6 ADVERSE REACTIONS

SABRIL causes permanent damage to vision in a high percentage of patients [see BOXED WARNING: VISION LOSS and WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Events in U.S. and Primary Non-U.S. Clinical Studies

In U.S. and primary non-U.S. clinical studies of 3139 adult and 999 pediatric patients treated with SABRIL, the most commonly observed (≥ 5%) adverse events associated with the use of SABRIL in combination with other AEDs were headache (18%), somnolence (17%), fatigue (16%), dizziness (15%), convulsion (11%), nasopharyngitis (10%), weight increased (10%), upper respiratory tract infection (10%), visual field defect (9%), depression (8%), tremor (7%), nystagmus (7%), nausea (7%), diarrhea (7%), memory impairment (7%), insomnia (7%), irritability (7%), coordination abnormal (7%), vision blurred (6%), diplopia (6%), vomiting (6%), influenza (6%), pyrexia (6%), and rash (6%).

The adverse reactions most commonly associated with SABRIL treatment discontinuation in ≥ 1% of IS patients were infections (1.5%), status epilepticus

(1.2%), developmental coordination disorder (1.2%), dystonia (1.2%), hypotonia (1.2%), hypertonia (1.2%), weight increased (1.2%), and insomnia (1.2%).

Most Common Adverse Reactions in Controlled Clinical Trials

Infantile Spasms

In a randomized, placebo-controlled IS study with a 5 day double-blind treatment phase (n=40), the adverse events reported by >5% of SABRIL patients and that occurred more frequently than in placebo patients were somnolence (SABRIL 45%, placebo 30%), bronchitis (SABRIL 30%, placebo 15%), ear infection (SABRIL 10%, placebo 5%), and otitis media acute (SABRIL 10%, placebo 0).

In a dose response study of low-dose (18-36 mg/kg/day) versus high-dose (100-148 mg/kg/day) vigabatrin, no clear correlation between dose and incidence of adverse events was observed. The treatment emergent adverse reactions (≥ 5% in either dose group) are summarized in Table 4.

Table 4. Treatment Emergent Adverse Events Occurring in ≥5% of Patients (Study 1A)

Body System Event	SABRIL Low Dose [N = 114] %	SABRIL High Dose [N = 108] %
Eye Disorders (other than field or acuity changes)		
Strabismus	5	5
Conjunctivitis	5	2
Gastrointestinal Disorders		
Vomiting	14	20
Constipation	14	12
Diarrhea	13	12
General Disorders		
Fever	29	19
Infections		
Upper respiratory tract infection	51	46
Otitis media	44	30
Viral infection	20	19
Pneumonia	13	11
Candidiasis	8	3
Ear infection	7	14
Gastroenteritis viral	6	5
Sinusitis	5	9
Urinary tract infection	5	6
Influenza	5	3
Croup infectious	5	1
Metabolism & Nutrition Disorders		
Decreased appetite	9	7
Nervous System Disorders		
Sedation	19	17
Somnolence	17	19

Table 4. Treatment Emergent Adverse Events Occurring in ≥5% of Patients (Study 1A)

Status epilepticus	6	4
Lethargy	5	7
Convulsion	4	7
Hypotonia	4	6
Psychiatric Disorders		
Irritability	16	23
Insomnia	10	12
Respiratory Disorders		
Nasal congestion	13	4
Cough	3	8
Skin & Subcutaneous Tissue Disorders		
Rash	8	11

Refractory Complex Partial Seizures in Adults

Because controlled trials in infants were of short duration and enrolled few patients, the adverse events from clinical trials in adults are presented. Table 5 lists the treatment emergent adverse reactions that occurred in ≥2% of SABRIL patients and that occurred more frequently than in placebo patients from 2 U.S. add-on clinical studies of refractory complex partial seizures in adults.

Table 5. Treatment Emergent Adverse Reactions Occurring in ≥2% of SABRIL Patients and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	SABRIL [N=222] %	Placebo [N=135] %
Eye Disorders		
Vision blurred	11	5
Diplopia	3	0
Eye disorder (other than field or acuity changes)	3	0
Asthenopia	2	0
Gastrointestinal Disorders		
Diarrhea	10	7
Nausea	9	8
Vomiting	7	6
Constipation	6	3
Abdominal pain upper	5	2
Dyspepsia	4	3
Stomach discomfort	3	1
Hemorrhoids	2	0
General Disorders		
Fatigue	27	16
Asthenia	5	2
Peripheral edema	5	1
Fever	5	3
Infections		
Nasopharyngitis	13	10
Upper respiratory tract infection	9	5
Influenza	5	4

Table 5. Treatment Emergent Adverse Reactions Occurring in ≥2% of SABRIL Patients and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	SABRIL [N=222] %	Placebo [N=135] %
Urinary tract infection	4	0
Injury		
Contusion	4	2
Metabolism and Nutritional Disorders		
Fluid retention	2	0
Increased appetite	2	0
Weight increased	8	3
Musculoskeletal Disorders		
Arthralgia	8	3
Back pain	6	2
Pain in extremity	5	4
Myalgia	3	2
Joint swelling	2	0
Muscle spasms	2	1
Shoulder pain	2	1
Nervous System Disorders		
Somnolence	22	13
Dizziness	21	17
Nystagmus	15	9
Tremor	14	8
Memory impairment	10	3
Coordination abnormal	9	2
Disturbance in attention	5	1
Sensory disturbance	5	2
Hyporeflexia	5	1
Parasthesia	5	1
Lethargy	4	2
Hypoaesthesia	3	2
Sedation	2	0
Status epilepticus	2	0
Dysarthria	2	1
Psychiatric Disorders		
Irritability	10	7
Depression	7	3
Confusional state	6	1
Depressed mood	4	1
Anxiety	4	3
Thinking abnormal	3	0
Abnormal behavior	3	1
Aggression	2	0
Reproductive System		
Dysmenorrhea	7	3
Respiratory and Thoracic Disorders		
Pharyngolaryngeal pain	9	5
Dyspnea	2	0
Sinus headache	4	1

6.2 Post Marketing Experience

The following serious adverse events have been reported since approval and use of SABRIL worldwide. All serious adverse events that are not listed above as adverse events reported in clinical trials, that are not relatively common in the population and are not too vague to be useful are listed in this section. These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Events are categorized by system organ class.

Birth Defects: Congenital cardiac defects, congenital external ear anomaly, congenital hemangioma, congenital hydronephrosis, congenital male genital malformation, congenital oral malformation, congenital vesicoureteric reflux, dentofacial anomaly, dysmorphism, fetal anticonvulsant syndrome, hamartomas, hip dysplasia, limb malformation, limb reduction defect, low set ears, renal aplasia, retinitis pigmentosa, supernumerary nipple, talipes

Ear: Deafness

Endocrine: Delayed puberty

Gastrointestinal: Gastrointestinal hemorrhage, esophagitis

***General*:** Developmental delay, facial edema, malignant hyperthermia, multi-organ failure

Hepatobiliary: Cholestasis

Nervous System: Dystonia, encephalopathy, hypertonia, hypotonia, muscle spasticity, myoclonus, optic neuritis

Psychiatric: Acute psychosis, apathy, delirium, hypomania, neonatal agitation, psychotic disorder

Respiratory: Laryngeal edema, pulmonary embolism, respiratory failure, stridor

Skin and Subcutaneous Tissue: Angioedema, maculo-papular rash, pruritus

7 DRUG INTERACTIONS

For detailed information about Drug Interactions see CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug Interactions (12.3).

7.1 Phenytoin

A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies.

7.2 Other AEDs

There are no clinically significant pharmacokinetics interactions between SABRIL and either phenobarbital or sodium valproate. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin.

7.3 Clonazepam

In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the mean C_{max} of clonazepam by 30% and decreases the mean t_{max} by 45%.

7.4 Oral Contraceptives

SABRIL is unlikely to affect the efficacy of steroid oral contraceptives.

7.5 Drug-Laboratory Test Interactions

SABRIL decreases alanine transaminase (ALT) and aspartate transaminase (AST) plasma activity in up to 90% of patients. In some patients, these enzymes become undetectable. The suppression of ALT and AST activity by SABRIL may preclude the use of these markers, especially ALT, to detect early hepatic injury.

SABRIL may increase the amount of amino acids in the urine, possibly leading to a false positive test for certain rare genetic metabolic diseases (e.g., alpha aminoadipic aciduria).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The following information is pertinent to the possible use of this dosage form in adults.

Pregnancy Category C. Vigabatrin produced developmental toxicity, including teratogenic and neurohistopathological effects, when administered to pregnant animals at clinically relevant doses. In addition, developmental neurotoxicity was observed in rats treated with vigabatrin during a period of postnatal development corresponding to the third trimester of human pregnancy. There are no adequate and well-controlled studies in pregnant women. SABRIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of vigabatrin (oral doses of 50 to 200 mg/kg) to pregnant rabbits throughout the period of organogenesis was associated with an increased incidence of malformations (cleft palate) and embryo-fetal death; these findings were observed in two separate studies. The no-effect dose for teratogenicity and embryolethality in rabbits (100 mg/kg) is approximately 1/2 the maximum recommended human dose (MRHD) of 3 g/day on a body surface area (mg/m^2) basis for adults treated for refractory complex partial seizures with vigabatrin. In rats, oral administration of vigabatrin (50, 100, or 150 mg/kg) throughout

organogenesis resulted in decreased fetal body weights and increased incidences of fetal anatomic variations. The no-effect dose for embryo-fetal toxicity in rats (50 mg/kg) is approximately 1/5 the MRHD in adults on a mg/m^2 basis. Oral administration of vigabatrin (50, 100, 150 mg/kg) to rats from the latter part of pregnancy through weaning produced long-term neurohistopathological (hippocampal vacuolation) and neurobehavioral (convulsions) abnormalities in the offspring. A no-effect dose for developmental neurotoxicity in rats was not established; the low-effect dose (50 mg/kg) is approximately 1/5 the MRHD in adults on a mg/m^2 basis.

In a published study, vigabatrin (300 or 450 mg/kg) was administered by intraperitoneal injection to a mutant mouse strain on a single day during organogenesis (day 7, 8, 9, 10, 11, or 12). An increase in malformations (including cleft palate) was observed at both doses.

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The early postnatal period in rats is generally thought to correspond to late pregnancy in humans in terms of brain development. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 of those measured in pediatric patients receiving an oral dose of 50 mg/kg.

Pregnancy Registry: To provide information regarding the effects of *in utero* exposure to SABRIL, physicians are advised to recommend that pregnant patients taking SABRIL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

8.2 Nursing Mothers

The following information is pertinent to the possible use of this dosage form in adults.

Vigabatrin is excreted in human milk. Because of the potential for serious adverse reactions from vigabatrin in nursing infants [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)], a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

SABRIL is indicated as monotherapy for pediatric patients with IS (1 month to 2 years of age) for whom the potential benefits outweigh the potential risk for developing permanent vision loss.

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with vigabatrin. In a retrospective epidemiologic study in infants with IS (N=205), the prevalence of these changes was 21.5% in vigabatrin treated patients versus 4.1% in patients treated with other therapies. A dose-dependent relationship may exist, as children with IS who were exposed to a higher vigabatrin dose (≥125 mg/kg/day) had a prevalence of 29.5%, while those exposed to lower doses of vigabatrin had a prevalence of 12.5%; however, these differences were not statistically significant (p=0.099).

In the study above, in post marketing experience, and in published literature reports, these changes generally resolved with discontinuation of treatment, although in a few patients, the lesion resolved despite continued use. It has been reported that some infants exhibited coincident motor abnormalities, but no causal relationship has been established and the potential for long-term clinical sequelae has not been adequately studied [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)].

The specific pattern of signal changes observed in IS patients was not observed in older children and adult patients treated with vigabatrin for refractory CPS. In a blinded review of MRI images obtained in prospective clinical trials in patients with refractory CPS 3 years and older (N=656), no difference was observed in anatomic distribution or prevalence of MRI signal changes between vigabatrin treated and placebo patients.

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4-65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The no-effect dose for developmental neurotoxicity in juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 of those measured in pediatric patients receiving an oral dose of 50 mg/kg.

8.4 Geriatric Use

The following information is pertinent to the possible use of this dosage form in adults.

Clinical studies of vigabatrin did not include sufficient numbers of patients aged 65 and over to determine whether they responded differently from younger patients.

Vigabatrin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal

function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Oral administration of a single dose of 1.5 g of vigabatrin to elderly (>65 years) patients with reduced creatinine clearance (<50 mL/min) was associated with moderate to severe sedation and confusion in 4 of 5 patients, lasting up to 5 days. The renal clearance of vigabatrin was 36% lower in healthy elderly subjects (>65 years) than in young healthy males. Adjustment of dose or frequency of administration should be considered. Such patients may respond to a lower maintenance dose [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.5 Renal Impairment

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

The following dose adjustments are pertinent to the possible use of this dosage form in adults with renal impairment:

In adults, dose adjustment, including initiating treatment with a lower dose, is necessary in patients with mild (creatinine clearance >50-80 mL/min), moderate (creatinine clearance >30-50 mL/min) and severe (creatinine clearance >10-30 mL/min) renal impairment [see CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Impairment (12.3) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance Class

Vigabatrin is not a controlled substance.

9.2 Abuse

Vigabatrin did not produce adverse events or overt behaviors associated with abuse when administered to humans or animals. It is not possible to predict the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of vigabatrin (e.g., incrementation of dose, drug-seeking behavior).

9.3 Dependence

Following chronic administration of vigabatrin to animals, there were no apparent withdrawal signs upon drug discontinuation. However, as with all AEDs, vigabatrin should be withdrawn gradually to minimize increased seizure frequency [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs) (5.6) and PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.5)].

10 OVERDOSAGE

10.1 Signs, Symptoms, and Laboratory Findings of Overdosage

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. Other less commonly reported symptoms included vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation, irritability, confusion, headache, hypotension, abnormal behavior, increased seizure activity, status epilepticus, and speech disorder. These symptoms resolved with supportive care.

10.2 Treatment or Management for Overdosage

There is no specific antidote for SABRIL overdose. Standard measures to remove unabsorbed drug should be used, including elimination by emesis or gastric lavage. Supportive measures should be employed, including monitoring of vital signs and observation of the clinical status of the patients.

In an *in vitro* study, activated charcoal did not significantly adsorb vigabatrin.

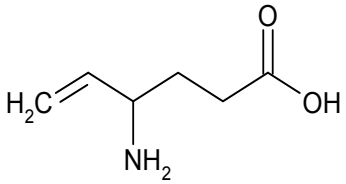
The effectiveness of hemodialysis in the treatment of SABRIL overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

11 DESCRIPTION

Table 6. Description

Proprietary Name:	SABRIL®
Established Name:	Vigabatrin for Oral Solution

Table 6. Description

Dosage Form:	Packet
Route of Administration:	Oral
Pharmacologic Class of Drug:	Antiepileptic
Chemical Name:	(±) 4-amino-5-hexenoic acid
Structural Formula:	

SABRIL (vigabatrin) is available as a white granular powder for oral administration. Each packet contains 500 mg vigabatrin. Each packet also contains the inactive ingredient povidone. Vigabatrin is an oral antiepileptic drug with the chemical name (±) 4-amino-5-hexenoic acid. It is a racemate consisting of two enantiomers. The molecular formula is $C_6H_{11}NO_2$ and the molecular weight is 129.16.

Vigabatrin is a white to off-white powder which is freely soluble in water, slightly soluble in methyl alcohol, very slightly soluble in ethyl alcohol and chloroform, and insoluble in toluene and hexane. The pH of a 1% aqueous solution is about 6.9. The n-octanol/water partition coefficient of vigabatrin is about 0.011 (log *P*=-1.96) at physiologic pH. Vigabatrin melts with decomposition in a 3-degree range within the temperature interval of 171°C to 176°C. The dissociation constants (pK_a) of vigabatrin are 4 and 9.7 at room temperature (25°C).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to be dependent on the rate of enzyme re-synthesis rather than on the rate of elimination of the drug from the systemic circulation.

12.2 Pharmacodynamics

Effects on Electrocardiogram

There is no indication of a QT/QTc prolonging effect of SABRIL in single doses up to 6.0 g. In a randomized, placebo-controlled, crossover study, 58 healthy adult subjects were administered a single oral dose of SABRIL (3 g and 6 g) and placebo. Peak concentrations for 6.0 g SABRIL were approximately 2-fold higher than the peak concentrations following the 3.0 g single oral dose.

12.3 Pharmacokinetics

Vigabatrin displayed linear pharmacokinetics after administration of single doses ranging from 0.5 g to 4 g, and after administration of repeated doses of 0.5 g to 2.0 g twice daily. Bioequivalence has been established between the oral solution and tablet formulations.

Absorption

Following oral administration, vigabatrin is essentially completely absorbed. Time to maximum concentration (t_{max}) is approximately 2.5 hours in infants and about 1 hour in children following a single dose. There was little accumulation with multiple dosing. A food effect study involving administration of vigabatrin to healthy adult volunteers under fasting and fed conditions indicated that the C_{max} was decreased by 33%, t_{max} increased to 2 hours, and AUC was unchanged under fed conditions [see DOSAGE AND ADMINISTRATION, Infantile Spasms (2.1)].

Distribution

Vigabatrin does not bind to plasma proteins. Vigabatrin is widely distributed throughout the body; mean steady-state volume of distribution is 1.1 L/Kg (CV = 20%).

Metabolism and Elimination

Vigabatrin is not significantly metabolized; it is eliminated primarily through renal excretion. The half-life of vigabatrin in adults is about 7.5 hours and about 5.7 hours in infants. Following administration of $^{[14]}$C-vigabatrin to healthy adult male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing about 80% of this. Vigabatrin induces CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.

Pharmacokinetics in Special Populations

Geriatric

The renal clearance of vigabatrin in healthy elderly patients (≥ 65 years of age) was 36% less than those in healthy younger patients. A population PK analysis of patient data also confirmed these differences in age.

Pediatric

The clearance of infants and children were 2.4±0.8 and 5.7±2.5 L/h, respectively compared to 7 L/h in adults.

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

Race
No specific study was conducted to investigate the effects of race on SABRIL pharmacokinetics. A cross study comparison in adults between 23 Caucasian and 7 Japanese patients who received 1, 2, and 4 g of vigabatrin indicated that the AUC, $C_{max,}$ and half-life were similar for the two populations. However, the mean renal clearance of Caucasians (5.2 L/hr) was about 25% higher than the Japanese (4.0 L/hr). Inter-subject variability in renal clearance was 20% in Caucasians and was 30% in Japanese.

Renal Impairment

There is no information available about the pharmacokinetics of vigabatrin in pediatric patients with renal impairment.

In adult patients with mild renal impairment (CLcr from >50-80 mL/min), mean AUC increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in comparison to the normal subjects. Mean AUC increased by two-fold and the terminal half-life increased by two-fold in patients with moderate renal impairment (CLcr from >30-50 mL/min) in comparison to the normal subjects. Mean AUC increased by 4.5-fold and the terminal half-life increased by 3.5-fold in patients with severe renal impairment (CLcr from >10-30 mL/min) in comparison to the normal subjects.

While dose adjustments are warranted in renally impaired pediatric patients, no data is available to guide dose adjustments in this patient population. Dosage adjustment in adults with renal impairment is recommended [see USE IN SPECIFIC POPULATIONS, Renal Impairment (8.5) and DOSAGE AND ADMINISTRATION, Patients with Renal Impairment (2.2)].

Hepatic Impairment
Vigabatrin is not significantly metabolized. The pharmacokinetics of vigabatrin in patients with impaired liver function have not been studied.

Drug Interactions

Phenytoin
A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies. *In vitro* drug metabolism studies indicate that decreased phenytoin concentrations upon addition of vigabatrin therapy are

likely due to induction of cytochrome P450 2C enzymes in some patients. Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated.

Other AEDs
When co-administered with vigabatrin, phenobarbital concentration (from phenobarbital or primidone) was reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of 8%. These reductions did not appear to be clinically relevant. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin.

Clonazepam
In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no effect on SABRIL (1.5 g twice daily) concentrations. SABRIL increases the mean C_{max} of clonazepam by 30% and decreases the mean t_{max} by 45%.

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

Oral Contraceptives
In a double-blind, placebo-controlled study using a combination oral contraceptive containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel, vigabatrin (3 g/day) did not interfere significantly with the cytochrome P450 isoenzyme (CYP3A)-mediated metabolism of the contraceptive tested. Based on this study, vigabatrin is unlikely to affect the efficacy of steroid oral contraceptives. Additionally, no significant difference in pharmacokinetic parameters (elimination half–life, AUC, C_{max}, apparent oral clearance, time to peak, and apparent volume of distribution) of vigabatrin were found after treatment with ethinyl estradiol and levonorgestrel.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Vigabatrin showed no carcinogenic potential in mouse or rat when given in the diet at doses up to 150 mg/kg/day for 18 months (mouse) or at doses up to 150 mg/kg/day for 2 years (rat). These doses are less than the maximum recommended human dose (MRHD) for IS (150 mg/kg/day) and for refractory complex partial seizures in adults (3 g/day) on a mg/m^2 basis.

Vigabatrin was negative in *in vitro* (Ames, CHO/HGPRT mammalian cell forward gene mutation, chromosomal aberration assay in rat lymphocytes) and in *in vivo* (mouse bone marrow micronucleus) assays.

No adverse effects on male or female fertility were observed in rats at oral doses up to 150 mg/kg/day (approximately 1/2 the MRHD of 3 g/day (on a mg/m^2 basis) for adults treated for refractory complex partial seizures with vigabatrin.

14 CLINICAL STUDIES

14.1 Infantile Spasms

The effectiveness of SABRIL as monotherapy was established for IS in two multicenter controlled studies. Both studies were similar in terms of disease characteristics and prior treatments of patients and all enrolled infants had a confirmed diagnosis of IS.

Study 1

Study 1 (N=221) was a multicenter, randomized, low-dose high-dose, parallel group, partially-blinded (caregivers knew the actual dose but not whether their child was classified as low or high dose; EEG reader was blinded but investigators were not blinded) study to evaluate the safety and efficacy of vigabatrin in patients <2 years of age with new-onset Infantile Spasms. Patients with both symptomatic and cryptogenic etiologies were studied. The study was comprised of two phases. The first phase was a 14 to 21 day partially-blind phase in which patients were randomized to receive either low-dose (18-36 mg/kg/day) or high-dose (100-148 mg/kg/day) vigabatrin. Study drug was titrated over 7 days, followed by a constant dose for 7 days. If the patient became spasm-free on or before day 14, another 7 days of constant dose was administered. The primary efficacy endpoint of this study was the proportion of patients who were spasm-free for 7 consecutive days beginning within the first 14 days of vigabatrin therapy. Patients considered spasm-free were defined as those patients who remained free of spasms (evaluated according to caregiver response to direct questioning regarding spasm frequency) and who had no indication of spasms or hypsarrhythmia during 8 hours of CCTV EEG recording (including at least one sleep-wake-sleep cycle) performed within 3 days of the seventh day of spasm freedom and interpreted by a blinded EEG reader. Seventeen patients in the high dose group achieved spasm freedom compared with 8 patients in the low dose group. This difference was statistically significant (p=0.0375). Primary efficacy results are shown in Table 7.

Table 7. Spasm Freedom by Primary Criteria (Study 1A)

	SABRIL Treatment Group	
	18-36 mg/kg/day [N=114] n (%)	100-148 mg/kg/day [N=107] n (%)
Patients who Achieved Spasm Freedom	8 (7.0)	17 (15.9)

p=0.0375
Note: Primary criteria were evaluated based on caregiver assessment plus CCTV EEG confirmation within 3 days of the seventh day of spasm freedom.

Study 2

Study 2 (N=40) was a multicenter, randomized, double-blind, placebo-controlled, parallel group study consisting of a pre-treatment (baseline) period of 2-3 days, followed by a 5-day double-blind treatment phase during which patients were treated with vigabatrin (initial dose of 50 mg/kg/day with titration allowed to 150 mg/kg/day) or placebo. The primary efficacy endpoint in this study was the average percent change in daily spasm frequency, assessed during a pre-defined and consistent 2-hour window of evaluation, comparing baseline to the final 2 days of the 5-day double-blind treatment phase. No statistically significant differences were observed in the average frequency of spasms using the 2-hour evaluation window. However, a post-hoc alternative efficacy analysis, using a 24-hour clinical evaluation window found a statistically significant difference in the overall percentage of reductions in spasms between the vigabatrin group (68.9%) and the placebo group (17.0%) (p=0.030).

15 REFERENCES

None

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 SABRIL Packet

Each SABRIL packet contains 500 mg vigabatrin as a white to off-white granular powder.

NDC 67386-211-65: Packages of 50.

Store at 20-25°C (68-77°F). See USP controlled room temperature.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.6)

Caregivers must be informed of the availability of a Medication Guide. They must be instructed to read the Medication Guide prior to initiating treatment with SABRIL and with each prescription refill. Doctors must review the SABRIL Medication Guide with every caregiver prior to initiation of treatment. Caregivers should be instructed to administer SABRIL only as prescribed.

Physicians should confirm that caregiver(s) understand how to reconstitute SABRIL for Oral Solution and to administer the correct dose to their infants.

17.1 Vision Loss

Caregiver(s) should be informed of the risk of permanent vision loss, particularly loss of peripheral vision from SABRIL, and the need for monitoring vision [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

Although vision testing in infants is insensitive, vision must be assessed to the extent possible at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months during therapy. Caregiver(s) should understand that vision testing is insensitive in infants and may not detect vision loss before it is severe. Caregiver(s) should also understand that if vision loss is documented, such loss is irreversible [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)].

Caregiver(s) should be informed that if changes in vision are suspected, they should notify their physician immediately.

17.2 MRI Abnormalities

Caregiver should be informed of the possibility of developing abnormal MRI signal changes of unknown clinical significance.

17.3 Suicidal Thinking and Behavior

The following information is pertinent to the possible use of this dosage form in adults.

Patients, their caregiver(s), and families should be counseled that AEDs, including SABRIL, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Behaviors of concern should be reported immediately to healthcare providers [see WARNINGS AND PRECAUTIONS, Suicidal Behavior and Ideation (5.5)].

17.4 Use in Pregnancy

The following information is pertinent to the possible use of this dosage form in adults.

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1), Nursing Mothers (8.2)].

Patients should be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 [see USE IN SPECIFIC POPULATIONS, Pregnancy (8.1)]. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

17.5 Withdrawal of SABRIL Therapy

Caregiver(s) should be told not to suddenly discontinue SABRIL therapy in their infant. As with all AEDs, withdrawal should be gradual. In a controlled clinical

study in patients with IS, vigabatrin was tapered by decreasing the daily dose at a rate of 25-50 mg/kg every 3-4 days.

17.6 FDA-Approved Medication Guide

Manufactured by: Patheon
Cincinnati, OH 45237, U.S.A.

For: Lundbeck
Deerfield, IL 60015, U.S.A.

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