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) Tablets **On**
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
- Periodic vision testing is required for patients on SABRIL, but cannot reliably prevent vision damage
- Because of the risk of permanent vision loss, SABRIL is available only through a special restricted distribution program

----------INDICATIONS AND USAGE----------
SABRIL is an antiepileptic drug (AED) indicated for:
- **Refractory Complex Partial Seizures in Adults** (1.1). It should be used as adjunctive therapy in patients who have responded inadequately to several alternative treatments.

----------DOSAGE AND ADMINISTRATION----------
- Refractory Complex Partial Seizures in Adults: Initiate therapy at 500 mg twice daily, increasing total daily dose per instructions. The recommended dose is 1.5 grams twice daily (2.1).
- Dose adjustment recommended in renally impaired patients (2.2)
- Reduce dose gradually upon discontinuation (2.3)

----------DOSAGE FORM AND STRENGTHS----------
Tablet: 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 (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 Inc. at 1-800-455-1141 or www.lundbeckinc.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).

Issued: 08/2009

FULL PRESCRIBING INFORMATION: CONTENTS

WARNING: VISION LOSS

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

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

1 INDICATIONS AND USAGE

1.1 Refractory Complex Partial Seizures in Adults

SABRIL® is indicated as adjunctive therapy for adult patients with refractory complex partial seizures (CPS) who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of

vision loss [see WARNINGS AND PRECAUTIONS, Vision Loss (5.1)]. SABRIL is not indicated as a first line agent for complex partial seizures.

2 DOSAGE AND ADMINISTRATION

2.1 Refractory Complex Partial Seizures in Adults

SABRIL 500 mg tablets should be given as twice daily oral administration with or without food. Therapy should be initiated at 1 g/day (500 mg twice daily). Total daily dose may be increased in 500 mg increments at weekly intervals depending on response. The recommended dose of SABRIL in adults is 3 g/day (1.5 g twice daily). A 6 g/day dose has not been shown to confer additional benefit compared to the 3 g/day dose and is associated with an increased incidence of adverse events.

2.2 Patients with Renal Impairment

SABRIL is primarily eliminated through the kidney. In patients with renal impairment, dose adjustments should be made as follows:

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

SABRIL should be withdrawn gradually. In controlled clinical studies in adults with CPS, vigabatrin was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued [see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs) (5.6)].

3 DOSAGE FORMS AND STRENGTHS

3.1 Tablet

500 mg Tablet.

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, a patient who fails to show substantial clinical benefit within 3 months 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 3 months, treatment with SABRIL should be discontinued at that time. Patient response to and continued need for treatment should be periodically assessed.

Monitoring of Vision

Monitoring of vision by an ophthalmic professional with expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina is required. Vision testing at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months is required for adults on SABRIL. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy.

The diagnostic approach should be individualized for the patient and clinical situation, but for all patients attempts to monitor vision periodically must be documented under the SHARE program. Perimetry is recommended, preferably by automated threshold visual field testing. Additional testing may also include electrophysiology (e.g., electroretinography [ERG]), retinal imaging (e.g., optical coherence tomography [OCT]), and/or other methods appropriate for the patient. In patients in whom vision testing is not possible, treatment may continue according to clinical judgment, with appropriate patient 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 testing is recommended if results are abnormal or uninterpretable. Repeat testing in the first few weeks of treatment is recommended to establish if, and to what degree, reproducible results can be obtained, and to guide selection of appropriate ongoing monitoring for the patient.

The onset and progression of vision loss from SABRIL is unpredictable, and it may occur or worsen precipitously between tests. 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.

5.2 Distribution Program for SABRIL

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 patient
- Educate patients on the risks of SABRIL, including the risk of vision loss [see BOXED WARNING: VISION LOSS]
- Order and review vision assessments at initiation of SABRIL treatment and every 3 months during therapy
- Remove patients from SABRIL therapy if the patients do not experience meaningful reduction in seizures
- Counsel patients who fail to comply with the program requirements
- Remove patients from SABRIL therapy who fail to comply with the program requirements after appropriate counseling

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 Infantile Spasms (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.

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 CPS. In a blinded review of MRI images obtained in prospective clinical trials in patients with 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.

For adults treated with SABRIL, routine MRI surveillance is unnecessary as there is no evidence that vigabatrin causes MRI changes in this population.

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

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 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. 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 caregivers, 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. In controlled clinical studies in adults with CPS, SABRIL was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued [see DOSAGE AND ADMINISTRATION, General Dosing Considerations (2.3), PATIENT COUNSELING INFORMATION, Withdrawal of SABRIL Therapy (17.4)].

5.7 Anemia

In North American controlled trials, 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, 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 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 causes symptoms of peripheral neuropathy. In a pool of North American controlled and uncontrolled epilepsy studies, 4.2% (19/457) of SABRIL 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 causes weight gain. Data pooled from randomized controlled trials found that 17% (77/443) of SABRIL patients versus 8% (22/275) of placebo patients gained ≥ 7% of baseline body weight. 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 causes edema. 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 Reactions in U.S. and Primary Non-U.S. Clinical Studies

In U.S. and primary non-U.S. clinical studies of 4,079 SABRIL treated patients, the most commonly observed (≥ 5%) adverse reactions 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 patients were convulsion (1.4%) and depression (1.5%).

Most Common Adverse Reactions in Controlled Clinical Trials

Refractory Complex Partial Seizures in Adults

Table 2 lists the treatment emergent adverse reactions that occurred in ≥ 2% and more than one patient per SABRIL-treated group and that occurred more frequently than in placebo patients from 2 U.S. add-on clinical studies of refractory CPS in adults.

Table 2. Treatment Emergent Adverse Reactions Occurring in ≥ 2% and More than One Patient per SABRIL-Treated Group and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	**SABRIL 3 g/day (N=134) n(%)**	**SABRIL 6 g/day (N=43) n(%)**	**Placebo (N=135) n(%)**
Ear Disorders			
Tinnitus	3 (2)	0 (0)	2 (1)
Vertigo	3 (2)	2 (5)	2 (1)
Eye Disorders			
Vision blurred	18 (13)	7 (16)	7 (5)
Diplopia	9 (7)	7 (16)	4 (3)
Asthenopia	3 (2)	1 (2)	0 (0)
Eye pain	0 (0)	2 (5)	0 (0)
Gastrointestinal Disorders			
Diarrhoea	14 (10)	7 (16)	10 (7)
Nausea	13 (10)	1 (2)	11 (8)
Vomiting	9 (7)	4 (9)	8 (6)
Constipation	11 (8)	2 (5)	4 (3)
Abdominal pain upper	7 (5)	2 (5)	2 (1)

Table 2. Treatment Emergent Adverse Reactions Occurring in ≥ 2% and More than One Patient per SABRIL-Treated Group and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	**SABRIL 3 g/day (N=134) n(%)**	**SABRIL 6 g/day (N=43) n(%)**	**Placebo (N=135) n(%)**
Dyspepsia	6 (4)	2 (5)	4 (3)
Stomach discomfort	5 (4)	1 (2)	1 (1)
Abdominal pain	4 (3)	1 (2)	2 (1)
Toothache	3 (2)	2 (5)	3 (2)
Abdominal distension	3 (2)	0 (0)	1 (1)
General Disorders			
Fatigue	31 (23)	17 (40)	21 (16)
Gait disturbance	8 (6)	5 (12)	9 (7)
Asthenia	7 (5)	3 (7)	2 (1)
Oedema peripheral	7 (5)	3 (7)	1 (1)
Fever	6 (4)	3 (7)	4 (3)
Chest pain	2 (1)	2 (5)	2 (1)
Thirst	3 (2)	0 (0)	0 (0)
Malaise	0 (0)	2 (5)	0 (0)
Infections			
Nasopharyngitis	19 (14)	4 (9)	14 (10)
Upper respiratory tract infection	10 (7)	4 (9)	8 (6)
Influenza	7 (5)	3 (7)	5 (4)
Urinary tract infection	5 (4)	2 (5)	0 (0)
Bronchitis	0 (0)	2 (5)	2 (1)
Injury			
Contusion	4 (3)	2 (5)	3 (2)
Joint sprain	2 (1)	1 (2)	1 (1)
Muscle strain	1 (1)	1 (2)	2 (1)
Wound secretion	0 (0)	1 (2)	0 (0)
Metabolism and Nutrition Disorders			
Increased appetite	2 (1)	2 (5)	1 (1)
Weight increased	8 (6)	6 (14)	4 (3)
Musculoskeletal Disorders			
Arthralgia	14 (10)	2 (5)	4 (3)
Back pain	6 (4)	3 (7)	3 (2)
Pain in extremity	8 (6)	1 (2)	5 (4)
Myalgia	4 (3)	2 (5)	2 (1)
Muscle twitching	1 (1)	4 (9)	2 (1)
Muscle spasms	4 (3)	0 (0)	1 (1)
Nervous System Disorders			
Headache	44 (33)	11 (26)	42 (31)
Somnolence	29 (22)	11 (26)	18 (13)
Dizziness	32 (24)	11 (26)	23 (17)
Nystagmus	17 (13)	8 (19)	12 (9)
Tremor	20 (15)	7 (16)	11 (8)
Memory impairment	9 (7)	7 (16)	4 (3)
Coordination abnormal	10 (7)	7 (16)	3 (2)
Disturbance in attention	12 (9)	0 (0)	1 (1)

Table 2. Treatment Emergent Adverse Reactions Occurring in ≥ 2% and More than One Patient per SABRIL-Treated Group and More Frequently than in Placebo Patients (Studies 024 and 025)

Body System Preferred Term	**SABRIL 3 g/day (N=134) n(%)**	**SABRIL 6 g/day (N=43) n(%)**	**Placebo (N=135) n(%)**
Sensory disturbance	6 (4)	3 (7)	3 (2)
Hyporeflexia	6 (4)	2 (5)	1 (1)
Paraesthesia	9 (7)	1 (2)	1 (1)
Lethargy	6 (4)	3 (7)	3 (2)
Hyperreflexia	5 (4)	1 (2)	4 (3)
Hypoaesthesia	5 (4)	2 (5)	2 (1)
Sedation	5 (4)	0 (0)	0 (0)
Status epilepticus	3 (2)	2 (5)	0 (0)
Dysarthria	3 (2)	1 (2)	1 (1)
Postictal state	3 (2)	0 (0)	1 (1)
Sensory loss	0 (0)	2 (5)	0 (0)
Psychiatric Disorders			
Irritability	10 (7)	10 (23)	10 (7)
Depression	8 (6)	6 (14)	4 (3)
Confusional state	5 (4)	6 (14)	1 (1)
Anxiety	6 (4)	0 (0)	4 (3)
Depressed mood	7 (5)	0 (0)	1 (1)
Thinking abnormal	4 (3)	3 (7)	0 (0)
Abnormal behaviour	4 (3)	2 (5)	1 (1)
Expressive language disorder	2 (1)	3 (7)	1 (1)
Nervousness	3 (2)	2 (5)	3 (2)
Abnormal dreams	2 (1)	2 (5)	1 (1)
Reproductive System			
Dysmenorrhoea	12 (9)	2 (5)	4 (3)
Erectile dysfunction	0 (0)	2 (5)	0 (0)
Respiratory and Thoracic Disorders			
Pharyngolaryngeal pain	10 (7)	6 (14)	7 (5)
Cough	3 (2)	6 (14)	9 (7)
Pulmonary congestion	0 (0)	2 (5)	1 (1)
Sinus headache	8 (6)	1 (2)	1 (1)
Skin and Subcutaneous Tissue Disorders			
Rash	6 (4)	2 (5)	6 (4)

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 pharmacokinetic 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

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. 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 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 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

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

The safety and efficacy of SABRIL in pediatric patients (<16 years of age) with CPS has not been established.

Abnormal MRI signal changes were observed in infants [see WARNINGS AND PRECAUTIONS, MRI Abnormalities (5.3) and Neurotoxicity (5.4)].

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

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

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 (17.4)].

10 OVERDOSAGE

10.1 Signs, Symptoms, and Laboratory Findings of Overdosage

Confirmed and/or suspected vigabatrin overdoses have been reported during clinical trials 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.

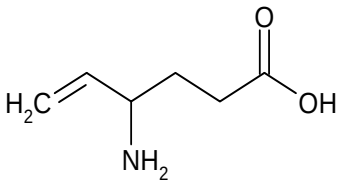
The effectiveness of hemodialysis in the treatment of SABRIL overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

11 DESCRIPTION

Table 3. Description

Proprietary Name:	SABRIL®
Established Name:	Vigabatrin Tablet
Dosage Form:	White, film-coated tablet
Route of	

Table 3. Description

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

SABRIL (vigabatrin) is available as a white, film-coated tablet for oral administration. Each tablet contains 500 mg vigabatrin. Tablets also contain as inactive ingredients: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycols, povidone, sodium starch glycolate, and titanium dioxide. 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 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 and 2.0 g twice daily with a half-life of about 7.5 hours. 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 1 hour following single and multiple doses. There was little accumulation with multiple dosing. A food effect study involving administration of vigabatrin to healthy volunteers under fasting and fed conditions indicated that the C_{max} was decreased by 33%, t_{max} was increased to 2 hours, and AUC was unchanged under fed conditions [see DOSAGE AND ADMINISTRATION (2)].

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 is about 7.5 hours. Following administration of $^{[14]}$C-vigabatrin to healthy 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. This finding is confirmed by an analysis of data from a controlled clinical trial.

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 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

Mean AUC increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in patients with mild renal impairment (CLcr from >50-80 mL/min) in comparison to 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 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 normal subjects.

Dosage adjustment, including starting at a lower dose, is recommended for patients with any degree of renal impairment [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 to be the result of 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 µg ethinyl estradiol and 150 µg 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) of 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 in rat lymphocytes) and in *in viv*o (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 on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Complex Partial Seizures in Adults

The effectiveness of SABRIL as adjunctive therapy in adult patients with CPS was established in two U.S. multicenter, double-blind, placebo-controlled, parallel-group clinical studies. A total of 357 adults (age 18 to 60 years) with CPS, with or without secondary generalization were enrolled (Studies 1 and 2). Patients were required to be on an adequate and stable dose of an anticonvulsant, and have a history of failure on an adequate regimen of carbamazepine or phenytoin. Patients had a history of about 8 seizures per month (median) for about 20 years (median) prior to entrance into the study. These studies were not capable by design of demonstrating direct superiority of SABRIL over any other anticonvulsant added to a regimen to which the patient had not adequately responded. Further, in these studies patients had previously been treated with a limited range of anticonvulsants.

The primary measure of efficacy was the patient's reduction in mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized at end of study compared to baseline.

Study 1

Study 1 (N=174) was a randomized, double-blind, placebo-controlled, dose-response study consisting of an 8-week baseline period followed by an 18-week treatment period. Patients were randomized to receive placebo or 1, 3, or 6 g/day vigabatrin administered twice daily. During the first 6 weeks following randomization, the dose was titrated upward beginning with 1 g/day and increasing by 0.5 g/day on days 1 and 5 of each subsequent week in the 3 g/day and 6 g/day groups, until the assigned dose was reached.

Results for the primary measure of effectiveness, reduction in mean monthly frequency of Complex Partial Seizures, are shown in Table 4. The 3 g/day and 6 g/day dose groups were statistically significantly superior to placebo, but the 6 g/day dose was not superior to the 3 g/day dose.

Table 4. Median Monthly Frequency of Complex Partial Seizures+

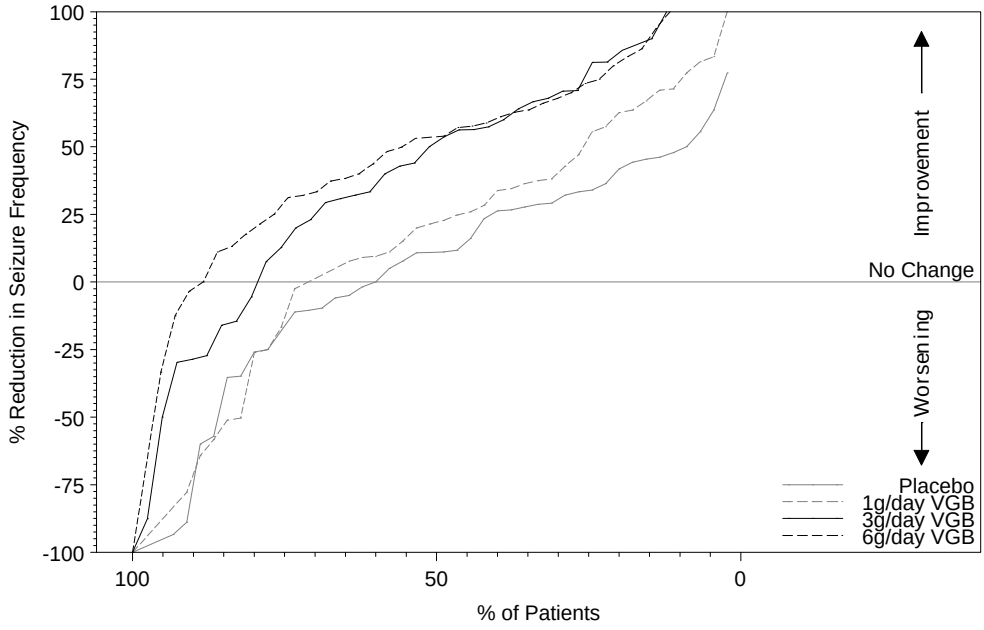
	N	Baseline	Endstudy
Placebo	45	9.0	8.8
1 g/day SABRIL	45	8.5	7.7
3 g/day SABRIL	41	8.5	3.7*
6 g/day SABRIL	43	8.5	4.5*

*P<0.05 compared to placebo
+Including one patient with simple partial seizures with secondary generalization only

Figure 1 presents the percentage of patients (X-axis) with a percent reduction in seizure frequency (responder rate) from baseline to the maintenance phase at least as great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in complex partial seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in complex partial seizure frequency). Thus, in a display of this

type, a curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in complex partial seizure frequency was consistently higher for the SABRIL 3 and 6 g/day groups compared to the placebo group. For example, 51% of patients randomized to SABRIL 3 g/day and 53% of patients randomized to Sabril 6 g/day experienced a 50% or greater reduction in seizure frequency, compared to 9% of patients randomized to placebo. Patients with an increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than -100%.

Figure 1. Percent Reduction from Baseline in Seizure Frequency



Study 2

Study 2 (N=183 randomized, 182 evaluated for efficacy) was a randomized, double-blind, placebo-controlled, parallel study consisting of an 8-week baseline period and a 16-week treatment period. During the first 4 weeks following randomization, the dose of vigabatrin was titrated upward beginning with 1 g/day and increased by 0.5 g/day on a weekly basis to the maintenance dose of 3 g/day.

Table 5. Median Monthly Frequency of Complex Partial Seizures

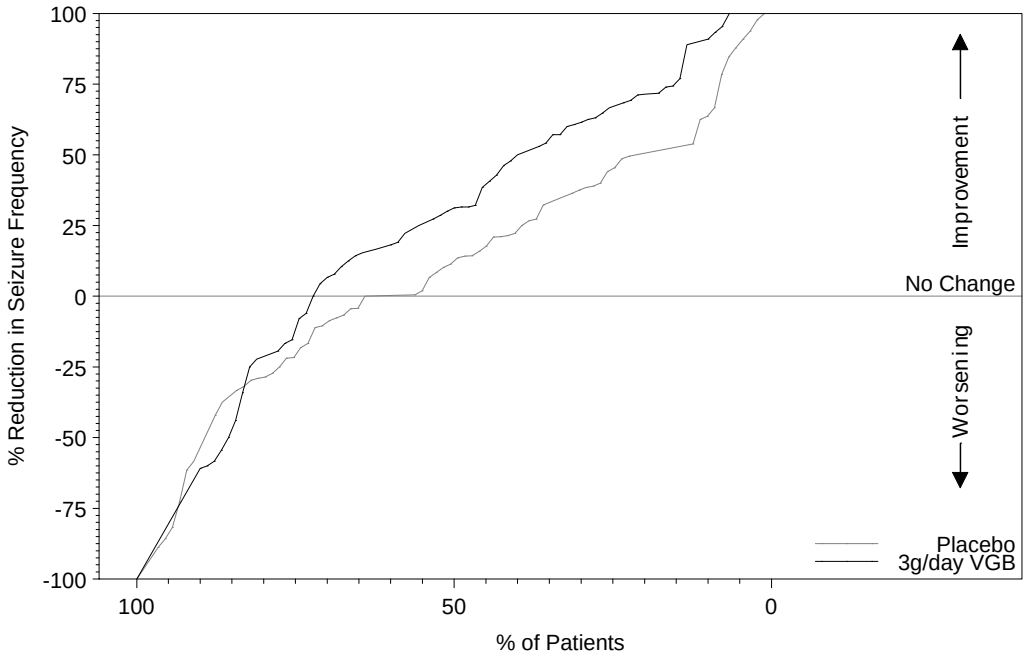
	N	Baseline	Endstudy
Placebo	90	9.0	7.5
3 g/day SABRIL	92	8.3	5.5*

*P<0.05 compared to placebo

Results for the primary measure of effectiveness, reduction in mean monthly complex partial seizure frequency, are shown in Table 5. Vigabatrin 3 g/day was statistically significantly superior to placebo in reducing seizure frequency.

Figure 2 presents the percentage of patients (X-axis) with a percent reduction in seizure frequency (responder rate) from baseline to the maintenance phase at least as great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in complex partial seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in complex partial seizure frequency). Thus, in a display of this type, a curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in seizure frequency was consistently higher for the SABRIL 3 g/day group compared to the placebo group. For example, 39% of patients randomized to SABRIL (3 g/day) experienced a 50% or greater reduction in complex partial seizure frequency, compared to 21% of patients randomized to placebo. Patients with an increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than -100%.

Figure 2. Percent Reduction from Baseline in Seizure Frequency



For both studies, there was no difference in the effectiveness of vigabatrin between male and female patients. Analyses of age and race were not possible as nearly all patients were between the ages of 18 to 65 and Caucasian.

15 REFERENCES

None

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 SABRIL Tablet

Each SABRIL film-coated tablet contains 500 mg vigabatrin and is white, film-coated, oval, biconvex, scored on one side, and debossed with OV 111 on the other.

NDC 67386-111-01: Bottles of 100.

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.5)

Patients must be informed of the availability of a Medication Guide. Patients 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 patient prior to initiation of treatment. Patients should be instructed to take SABRIL only as prescribed.

17.1 Vision Loss

Patients 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)].

Monitoring of vision, including assessment of visual fields and visual acuity, is required for adults at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy unless after repeated attempts it is not possible. In those patients in whom vision testing is not possible, treatment may continue according to clinical judgment with appropriate patient counseling and with documentation in the SHARE program of the inability to test vision. Patients should be informed that if baseline or subsequent vision is not normal, SABRIL should only be used if the benefits of SABRIL treatment clearly outweigh the risks of additional vision loss.

Patients should understand that vision testing may be insensitive and may not detect vision loss before it is severe. Patients should also understand that if vision loss is documented, such loss is irreversible.

Patients should be informed that if changes in vision are suspected, they should notify their physician immediately.

17.2 Suicidal Thinking and Behavior

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)].

17.3 Use in Pregnancy

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), and 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/.

17.4 Withdrawal of SABRIL Therapy

Patients should be told not to suddenly discontinue SABRIL therapy. As with all AEDs, withdrawal should be gradual. In controlled clinical studies in adults with CPS, vigabatrin was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued.

17.5 FDA-Approved Medication Guide

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

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

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