FDA-approved labeling 8/21/09

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
For Oral Administration Only
Initial U.S. Approval: Pending

℞ **Only**

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: 08/07/09

FDA-approved labeling 8/21/09

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 theses 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)

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(%)**
Constipation	11 (8)	2 (5)	4 (3)
Abdominal pain upper	7 (5)	2 (5)	2 (1)
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)

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(%)**
Coordination abnormal	10 (7)	7 (16)	3 (2)
Disturbance in attention	12 (9)	0 (0)	1 (1)
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 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 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.

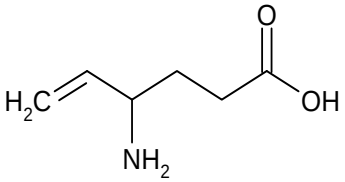
The effectiveness of hemodialysis in the treatment of SABRIL overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

11 DESCRIPTION

Table 3. Description

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

Table 3. Description

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, 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 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 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+

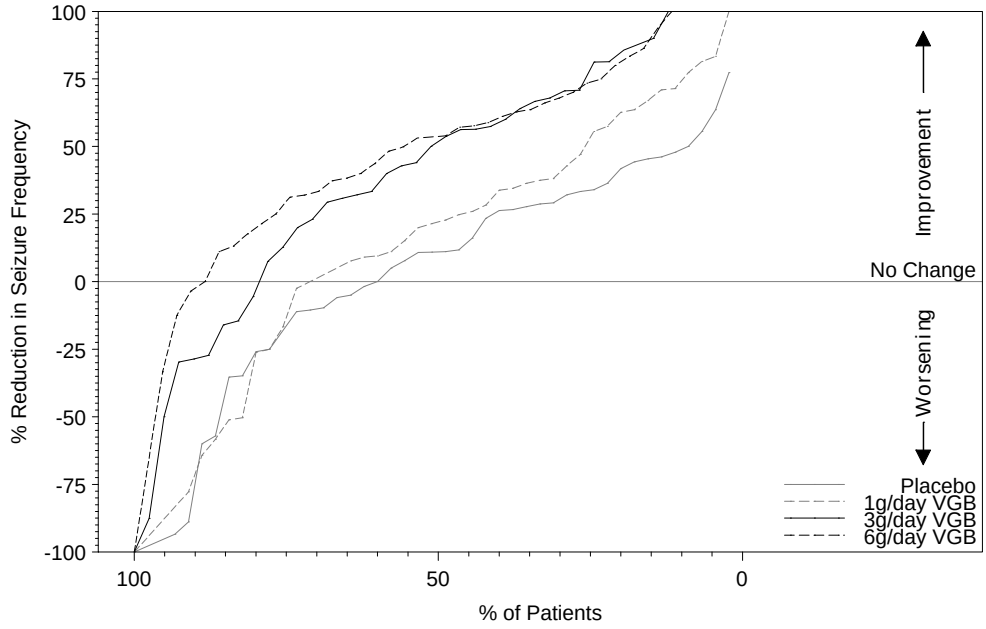
	N	Baseline	Endstudy
Placebo	45	9.0	8.8
1 g/day SABRIL	45	8.5	7.7
3 g/day SABRIL	41	8.5	3.7*
6 g/day SABRIL	43	8.5	4.5*

*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 SABRIL3 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

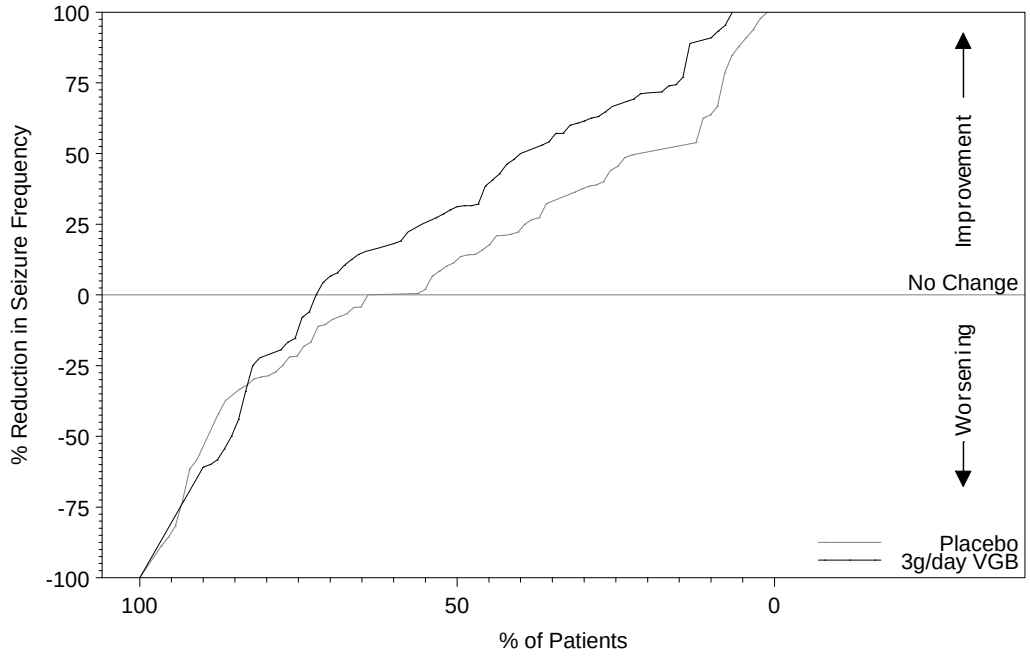
	N	Baseline	Endstudy
Placebo	90	9.0	7.5
3 g/day SABRIL	92	8.3	5.5*

*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

MEDICATION GUIDE

SABRIL® (*SAY-bril*)
(vigabatrin) Tablet

SABRIL® (*SAY-bril*)
(vigabatrin) for Oral Solution

Read the Medication Guide that comes with SABRIL before you or your baby starts taking SABRIL and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your or your baby's medical condition or treatment.

What is the most important information I should know about SABRIL?

SABRIL can cause serious side effects, including:

- **Permanent vision damage:**
  SABRIL can damage the vision of anyone who takes it. The most noticeable loss is in your ability to see to the side when you look straight ahead (peripheral vision). If this happens, it will not get better. People who take SABRIL do not lose all of their vision, but some people can have severe loss particularly to their peripheral vision. With severe vision loss you may only be able to see things straight in front of you (sometimes called 'tunnel vision'). You may also have blurry vision.

- **Vision loss and use of SABRIL in adults:** Because of the risk of vision loss, SABRIL is used to treat complex partial seizures (CPS) only in people who do not respond well enough to several other medicines.

Tell your doctor right away if you:

- think you are not seeing as well as before you started taking SABRIL
- start to trip, bump into things, or are more clumsy than usual
- are surprised by people or things coming in front of you that seem to come out of nowhere

These changes can mean that you have damage to your vision. Your doctor will test your visual fields (including peripheral vision) and visual acuity (ability to read an eye chart) before you start SABRIL or within 4 weeks after starting SABRIL, and at least every 3 months after that until SABRIL is stopped. Even if your vision seems fine, it is important that you get these regular vision tests because damage can happen to your vision before you notice any changes. These vision tests cannot prevent the vision damage that can happen with SABRIL, but they do allow you to stop SABRIL if vision has gotten worse, which usually will lessen further damage. If you do not have these vision tests regularly, your doctor may stop prescribing SABRIL for you. You should also have a vision test after SABRIL is stopped.

If you drive and your vision is damaged by SABRIL, driving might be more dangerous, or you may not be able to drive safely at all. You should discuss this with your doctor.

- **Vision loss in babies:** Because of the risk of vision loss, SABRIL is used in babies (1 month to 2 years old) with infantile spasms (IS) only when you and your doctor decide that the possible benefits of SABRIL are more important than the risks. Parents or caregivers are not likely to recognize the symptoms of vision loss in babies until it is severe. Doctors may not find vision loss in babies until it is severe. It is difficult to test vision in babies, but all babies should have a vision test before starting SABRIL or within 4 weeks after starting SABRIL, and every 3 months after that until SABRIL is stopped. You should have a vision test for your baby after SABRIL is stopped.

Tell your doctor right away if you think that your baby is:

- not seeing as well as before taking SABRIL
- acting differently than normal

Even if your baby's vision seems fine, it is important to get regular vision tests because damage can happen before your baby acts differently. Even these regular vision exams may not show the damage to your baby's vision before it is serious and permanent. If your baby does not have these vision tests regularly, your doctor may stop prescribing SABRIL for your baby. If your baby is not able to complete vision testing, your doctor may continue prescribing SABRIL for your baby. But, your doctor will not be able to watch for vision loss in your baby.

In all people who take SABRIL:

- You are at risk for vision loss with any amount of SABRIL
- Your risk of vision loss may be higher the more SABRIL you take daily and the longer you take it
- It is not possible for your doctor to know when vision loss will happen. It could happen soon after starting SABRIL or any time during treatment. It may even happen after treatment has stopped.

Because Sabril might cause vision loss, it is available to doctors and patients only under a special program called SHARE. As part of the SHARE program, among other things, your doctor will have to test your or your baby's vision frequently while you or your baby are being treated with Sabril, and even after you or your baby stops treatment. You also have to agree to be in the SHARE program, and agree to have your or your baby's vision tested regularly. Your doctor will explain the details of the SHARE program to you.

MRI changes. Brain pictures taken by magnetic resonance imaging (MRI) show changes in some babies after they are given SABRIL. It is not known if these changes are harmful.

Risk of suicidal thoughts or actions. Like other antiepileptic drugs, SABRIL may cause suicidal thoughts or actions in a very small number of people, about 1 in 500 people taking it. Call a doctor right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your doctor as scheduled.
- Call your doctor between visits as needed, especially if you are worried about symptoms.

Do not stop SABRIL without first talking to a healthcare provider.

- Stopping SABRIL suddenly can cause serious problems. Stopping a seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures.

SABRIL can be prescribed only to people who are enrolled in a program called SHARE. Before you or your baby can begin taking SABRIL, you must read and agree to all of the instructions in the SHARE program.

What is SABRIL?

SABRIL Tablets is a prescription medicine used along with other treatments to treat adults with CPS if:

- The CPS does not respond well enough to several other treatments, and
- You and your doctor decide the possible benefit of taking SABRIL is more important than the risk of vision loss.

SABRIL should not be the first medicine used to treat your CPS.

SABRIL for Oral Solution is a prescription medicine used to treat babies, one month to two years old who have IS, if you and your doctor decide the possible benefits of taking SABRIL are more important than the possible risk of vision loss.

If you are an adult with CPS, you must sign an agreement form before you can receive SABRIL.

If you are the parent or caregiver of a baby with IS, you must sign an agreement form before your baby can receive SABRIL.

What should I tell my doctor before starting SABRIL?

If you are an adult with CPS, before taking SABRIL tell your doctor if you have or had:

- depression, mood problems or suicidal thoughts or behavior
- an allergic reaction to SABRIL, such as hives, itching, or trouble breathing
- any vision problems
- any kidney problems
- low red blood cell counts (anemia)
- any nervous or mental illnesses, such as depression, thoughts of suicide, or attempts at suicide
- any other medical conditions
- are breastfeeding or planning to breastfeed. SABRIL can pass into breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take SABRIL.
- are pregnant or plan to become pregnant. It is not known if SABRIL will harm your unborn baby. You and your healthcare provider will have to decide if you should take SABRIL while you are pregnant.

Pregnancy Registry:

If you become pregnant while taking SABRIL, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy.

Before giving SABRIL to your baby, tell the doctor about all of your baby's medical conditions, including if your baby has or ever had:

- an allergic reaction to SABRIL, such as hives, itching, or trouble breathing
- any vision problems
- any kidney problems

Tell your doctor about all the medicines you or your baby take, including prescription and non-prescription medicines, vitamins, and herbal supplements. SABRIL and other medicines may affect each other causing side effects.

How should I take SABRIL?

If you are an adult with CPS:

- Your doctor will explain the SHARE Program to you
- You will receive SABRIL from a specialty pharmacy
- Take SABRIL tablets exactly as prescribed by your doctor. SABRIL tablets are usually taken two times each day.
- You may take SABRIL tablets with or without food
- Before you start taking SABRIL, talk to your doctor about what you should do if you miss a dose of SABRIL
- **Do not stop taking SABRIL suddenly.** This can cause serious problems. Stopping SABRIL or any seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures. You should follow your doctor's instructions on how to stop taking SABRIL.
- Tell your doctor right away about any increase in seizures while you are stopping SABRIL
- If SABRIL does not improve your seizures enough within 3 months, your doctor will stop prescribing SABRIL for you
- **Do not stop taking SABRIL without talking to your doctor.** If SABRIL improves your seizures, you and your doctor should talk about whether the benefit of taking SABRIL is more important than the risk of vision loss, and decide if you will continue to take SABRIL.

If you are giving SABRIL to your baby for IS:

- Your doctor will explain the SHARE program to you
- You will receive SABRIL for oral solution from a specialty pharmacy
- Mix SABRIL for oral solution and give it to your baby exactly as prescribed by your doctor. Do not stop giving SABRIL for oral solution to your baby unless your doctor tells you to.
- SABRIL for oral solution is usually given two times each day

- SABRIL for oral solution can be given to your baby at the same time as their food, but the powder should not be mixed with their food. SABRIL for oral solution powder should be mixed with water only.
- See the end of this Medication Guide for detailed instructions for how to mix SABRIL for oral solution and give the medicine to your baby
- Before your baby starts taking SABRIL, speak to your baby's doctor about what to do if your baby misses a dose, vomits, spits up, or only takes part of the dose of SABRIL
- **Stopping SABRIL suddenly can cause serious problems**. Stopping SABRIL or any seizure medicine suddenly can cause seizures that will not stop. You should follow your doctor's instructions on how to stop giving SABRIL to your baby. SABRIL does not work in all babies. If your baby's seizures do not improve enough within 2 to 4 weeks, the doctor will stop SABRIL.
- **Tell your doctor right away about any increase in your baby's seizures while stopping SABRIL**

What should I avoid while taking SABRIL?

SABRIL causes sleepiness and tiredness. Adults taking SABRIL should not drive, operate machinery, or perform any hazardous task, unless you and your doctor have decided that you can do these things safely.

What are the possible side effects of SABRIL?

SABRIL can cause serious side effects. See "What is the most important information I should know about SABRIL?"

These other serious side effects happen in **adults**. It is not known if these side effects also happen in babies who take SABRIL.

- Low red blood cell counts (anemia)
- Sleepiness and tiredness. See "What should I avoid while taking SABRIL?"
- Nerve problems. Symptoms of a nerve problem can include numbness and tingling in your toes or feet. It is not known if nerve problems will go away after you stop taking SABRIL.
- Weight gain that happens without swelling
- Swelling

If you are an adult with CPS, SABRIL may make certain types of seizures worse. Tell your doctor right away if your seizures get worse.

The most common side effects of SABRIL in adults include:

- problems walking or feel uncoordinated
- feel dizzy
- shaking (tremor)
- joint pain
- memory problems and not thinking clearly
- eye problems: blurry vision, double vision and eye movements that you cannot control

If you are giving SABRIL to your baby for IS

SABRIL may make certain types of seizures worse. You should tell your baby's doctor right away if your baby's seizures get worse. Tell your baby's doctor if you see any changes in your baby's behavior.

The most common side effects of SABRIL in **babies and young children** include:

- sleepiness - SABRIL may cause your baby to be sleepy. Sleepy babies may have a harder time suckling and feeding, or may be irritable.
- ear infection
- irritability

Tell your doctor if you or your baby have any side effect that bother you or that does not go away. These are not all the possible side effects of SABRIL. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SABRIL?

Store SABRIL tablets and SABRIL packets at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep SABRIL tablets and SABRIL powder in the container they come in.

Keep SABRIL and all medicines out of the reach of children.

General information about SABRIL

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SABRIL for a condition for which it was not prescribed. Do not give SABRIL to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about SABRIL. If you would like more information about SABRIL, talk with your doctor. You can ask your pharmacist or doctor for information about SABRIL that is written for health professionals. For more information, go to **www.SABRIL.net or call 1-800-455-1141.**

What are the ingredients in SABRIL?

Active Ingredient: vigabatrin

Inactive Ingredients in **SABRIL tablets**: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycols, povidone, sodium starch glycolate, and titanium dioxide.

Inactive Ingredient in **SABRIL powder**: povidone.

Instructions for mixing and giving SABRIL for oral solution to your baby

Sabril®
vigabatrin
500 mg tablet
500 mg powder for oral solution

Be sure to read, understand, and follow these instructions for the right way to mix SABRIL for oral solution to give to your baby. Talk to your doctor if you have any questions about the right dose of medicine to give your baby or how to mix it.

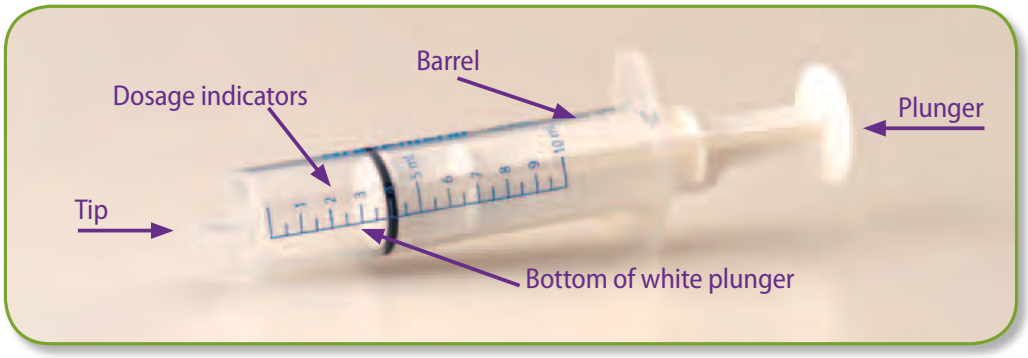
- SABRIL for oral solution comes as a powder
- Each packet contains 500 mg of SABRIL for oral solution
- The powder in the packets must be mixed with **water only.** The water may be cold or at room temperature
- Your baby's doctor will tell you:
  - how many packets of SABRIL for oral solution your baby will need for each dose
  - how many milliliters (mLs) of water to use to mix a dose of SABRIL for oral solution for your baby
  - how many milliliters (mLs) of the mixture you will need to give to your baby after the powder is mixed with water. This is the amount of medicine to give your baby for one dose of SABRIL for oral solution
- SABRIL for oral solution should be given to your baby right away after it is mixed

Supplies needed to mix a dose of SABRIL for oral solution:

- The number of packets of SABRIL for oral solution needed for your baby's dose
- 2 clean cups: 1 for mixing and 1 for water. The cup used for mixing SABRIL for oral solution should be clear so you can see if the powder is dissolved
- Water to mix with the SABRIL for oral solution
- Small 3 mL oral syringe and large 10 mL oral syringe provided
- Small spoon or other clean utensil to stir with
- Scissors

S·H·A·R·E®
Support, Help And Resources for Epilepsy

Oral syringe detail



1. Get **1** of the empty cups and the number of packets you will need for 1 dose.

2. Before you open the packet, tap it to settle all the powder at the bottom of the packet.

3. Use a pair of scissors to cut open the SABRIL for oral solution packet along the dotted line.

4. Empty the entire contents of the SABRIL for oral solution packet into **1** of the clean empty cups (Figure A).

Figure A

5. Repeat steps 2 through 4 above to open all of the packets needed for 1 dose of SABRIL for oral solution.

6. Get the **other** cup and fill it half way with water (Figure B). Do not mix SABRIL for oral solution with anything other than water.

Figure B

7. You will use the larger oral syringe (10 mL) to draw up the water needed to mix with the powder from the packets. **Each packet of SABRIL for oral solution needs to be mixed with 10 mL of water.**

   For example:

   - If you are using 1 packet of SABRIL for oral solution, you will need to use 10 mL of water (fill the 10 mL oral syringe 1 time)
   - If you are using 2 packets of SABRIL for oral solution, you will need to use 20 mL of water (fill the 10 mL oral syringe 2 times)
   - If you are using 3 packets of SABRIL for oral solution, you will need to use 30 mL of water (fill the 10 mL oral syringe 3 times)

8. Get the **larger** oral syringe (the 10 mL oral syringe). Use the oral syringe to draw up 10 mL of water. To do this, put the **tip** of the oral syringe all the way into the water in your cup. Then pull the plunger up towards you until the black ring of the white plunger is at the 10 mL line on the barrel of the oral syringe (Figure C).

Figure C

9. If you see bubbles of air in the oral syringe after drawing up the water, turn the oral syringe so the tip is pointing up (Figure D). The air will move to the top of the oral syringe. Pull the plunger back towards you and then push it back gently into the oral syringe to get rid of the bubbles. Tiny bubbles are normal.

Figure D

10. Make sure the oral syringe is full of water up to the 10 mL line (Figure E).

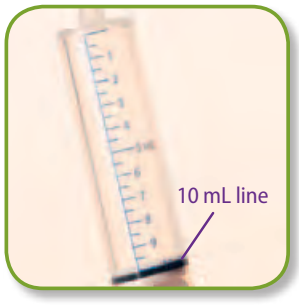


Figure E

11. Empty the water from the oral syringe directly into the cup with the SABRIL for oral solution. This is done by pushing the plunger of the oral syringe down **slowly** while the tip of the oral syringe is in the cup (Figure F).

Repeat steps 8 through 11 until all of the water that is needed to mix 1 dose of SABRIL for oral solution has been added to the cup containing the powder.

Figure F

12. Stir the mixture with the small spoon or other clean utensil until the solution is clear (Figure G). This means that all of the powder is dissolved.

Figure G

13. Use the oral syringe to draw up the number of mLs of the mixture told to you by your doctor. If you are giving **3 mL or less** of the mixture, use the smaller oral syringe (3 mL oral syringe). If you are giving **more than 3 mL** of the mixture, use the 10 mL oral syringe. (This is the oral syringe that you just used to add the water.)

14. Put the **tip** of the oral syringe all the way into the mixture. Pull the plunger up towards you to draw up the mixture. Stop when the black ring of the white plunger lines up with the marking on the barrel of the oral syringe that matches the number of mLs of mixture your doctor told you to give your baby (Figure H).

Figure H

15. If you see bubbles or air in the oral syringe after drawing up the mixture, turn the oral syringe so the tip is pointing up (Figure I). The air will move to the top of the oral syringe. Pull the plunger back towards you and then gently push it back in the oral syringe in order to get rid of the bubbles. Tiny bubbles are normal.

Figure I

16. Place the tip of the oral syringe into your baby's mouth and point the oral syringe towards either of the baby's cheeks (Figure J). Push on the plunger slowly, **a small amount at a time,** until all of the mixture in the oral syringe is given.

Figure J

17. If the dose you are giving your baby is larger than 10 mL, repeat steps 14 through 16 until you give the total dose of mixture prescribed by the doctor.

18. Throw away any mixture that is left over. Do not save and reuse leftover mixture.

19. Wash the oral syringes and mixing cups in warm water. To clean the oral syringes, remove the plunger by gently pulling it straight out of the barrel. The barrel and plunger can be hand washed with soap and water, rinsed, and allowed to dry, or the barrel and plunger can be placed in a dishwasher utensil rack, machine washed, and dried.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Marketed by:
Insert Lundbeck Inc. logo
Lundbeck Inc.
Deerfield, IL 60015, U.S.A.

Insert Lundbeck Inc. logo

Issued August 2009

APPENDIX A

RISK EVALUATION & MITIGATION STRATEGY (REMS)

Title:	Risk Evaluation & Mitigation Strategy (REMS): Support, Help and Resources for Epilepsy (SHARE)
Product Name:	Sabril (vigabatrin) NDAs 20-427, 22-006
Sponsor:	Lundbeck Inc. Four Parkway North Deerfield, Illinois 60015 Jenny Swalec, Sr. Director, Global Regulatory Affairs 847-282-1066
Date:	21 August 2009

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

The goals of the REMS are:

1) To reduce the risk of a Sabril-induced vision loss while delivering benefit to the appropriate patient populations;

2) To ensure that all patients receive a baseline ophthalmologic evaluation; 50% of patients will receive within 2 weeks of starting Sabril and 100% within 4 weeks;

3) To discontinue Sabril therapy in patients who experience an inadequate clinical response;

4) To detect Sabril-induced vision loss as early as possible;

5) To ensure regular vision monitoring to facilitate ongoing benefit-risk assessments; and

6) To inform patients/parent or legal guardian of the serious risks associated with Sabril, including vision loss and increased risk of suicidal thoughts and behavior.

II. REMS ELEMENTS

A. Medication Guide

Lundbeck will ensure that a Medication Guide is dispensed with each prescription of Sabril and in accordance with 21CFR 208.24. The Medication Guide will be included in the Sabril Starter Kit to be reviewed with the patient/parent or legal guardian by the physician prior to starting the patient on Sabril therapy.

Please see appended Medication Guide.

B. Communication Plan

At product launch (that is, during the first 6 months after product approval) and yearly for 3 years thereafter Lundbeck will send a Dear Healthcare Professional Letter via direct mail to all registered ophthalmologists. The Sabril package insert will accompany the letter. Additionally, Lundbeck Inc. field representatives will call on neuro-ophthalmologists and/or ophthalmologists at key epilepsy centers at product launch to disseminate the Sabril package inserts.

The Dear Healthcare Professional Letter is part of the REMS and is appended.

C. Elements To Assure Safe Use

1) Healthcare providers who prescribe Sabril will be specially certified under 505-1 (f)(3)(A).
   a) Lundbeck Inc. will ensure that prescribers enrolled in the REMS program are specially certified. Lundbeck Inc. will ensure that, to become certified, prescribers attest to their understanding of the REMS program requirements and the risks associated with Sabril, and that prescribers commit to the following:
      i) Reading the full prescribing information (PI) and Medication Guide;
      ii) Having knowledge of the approved indications for Sabril;
      iii) Having experience in treating epilepsy;
      iv) Having knowledge of the risks of Sabril, especially vision loss;
      v) If prescribing for infantile spasms, having knowledge of the risk of MRI abnormalities with use of Sabril;
      vi) Assessing the effectiveness of Sabril within 2-4 weeks in infants and within 12 weeks in adults; in the case that insufficient clinical benefit has occurred, Sabril will be discontinued; for patients discontinuing Sabril at this evaluation, a Treatment Maintenance Form will not be completed; for patients continuing

treatment, a Treatment Maintenance Form will be completed and faxed to the REMS coordinating center;

vii) Ordering and reviewing visual assessment at the time of initiation of Sabril using the Ophthalmologic Assessment Form (with the baseline assessment to be conducted within 4 weeks of starting Sabril), and every 3 months after initiating Sabril therapy; the Ophthalmologic Assessment Form will be faxed to the REMS coordinating center;

viii) Educating patients on the risks and benefits of Sabril;

ix) Enrolling all patients who take Sabril in the REMS program by completing and submitting the Treatment Initiation Form and the Patient/Parent/Legal Guardian-Physician Agreement Form;

x) Reviewing the Sabril Medication Guide with every patient;

xi) Counseling the patient if the patient is not complying with the required vision monitoring beyond the baseline test, and removing the patient from therapy if the patient still fails to comply with required vision monitoring;

(1) Should discontinuation be required, discontinuation will be accomplished by tapering the patient from therapy as described in the therapy by tapering the patient from therapy as described in the Dear HCP Medication Taper Letter; and

xii) Reporting to the Sponsor at 1-800-455-1141 any serious adverse events with Sabril and providing all known details of the event.

b) The prescriber may exempt certain patients from vision assessment, using the Ophthalmologic Assessment form, if:

i) The patient is blind

ii) The patient's general neurological condition precludes the need for visual assessment

iii) The patient's medical condition prevents visual assessment being performed safely, documented by the prescriber.

iv) For other reasons documented by the prescriber.

c) The following materials are part of the REMS and are appended

(1) Dear Healthcare Professional (HCP) Letter

(2) Dear HCP Medication Taper Letter

(3) Prescriber Enrollment and Agreement Form

(4) Treatment Initiation Form

(5) Treatment Maintenance Form

(6) Ophthalmologic Assessment Form

(7) Patient-Physician Agreement- Refractory CPS

(8) Parent/Legal Guardian –Physician Agreement-IS

Lundbeck Inc. will maintain a database of certified prescribers in the REMS program. Lundbeck Inc. will ensure that prescribers comply with the requirements of the REMS and may de-enroll noncompliant prescribers.

2) Pharmacies that dispense Sabril will be specially certified by Lundbeck Inc, under 505-1(f)(3)(B).

Lundbeck Inc. will ensure that to be certified, each pharmacy does the following; pharmacies not complying may be de-enrolled by Lundbeck Inc:

a) designates a representative who is trained on the REMS program

b) dispenses Sabril only to patients who are enrolled in the REMS program, and whose continued eligibility has been established within the REMS

c) obtains treatment forms and prescriptions only from the REMS coordinating center.

d) obtains a dispensing authorization from the REMS coordinating center before dispensing the first Sabril prescription and before dispensing each refill.

e) trains pharmacy staff on the REMS program procedures and REMS materials for dispensing

f) agrees that the certified pharmacy may be audited by the FDA, Lundbeck Inc, or a third party designated by Lundbeck Inc.

3) Sabril will be dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D):

a) Lundbeck Inc. will ensure that each patient treated with Sabril is enrolled in the Sabril REMS before Sabril is dispensed to him or her. Lundbeck Inc. will ensure that, to become enrolled, each patient or parent/legal guardian must sign a Patient/Parent/Legal Guardian-Physician Agreement Form indicating that:

i) they have read the Medication Guide;

ii) the prescriber has explained the risk of visual loss;

iii) vision loss, should it occur, is irreversible;

iv) that prescribed vision assessments must be obtained;

v) periodic vision assessment, although it does not protect against all vision loss, is required for the duration of therapy, and after stopping Sabril; and

vi) response to Sabril will be assessed after a short trial period (3 months for complex partial seizures and 1 month for infantile spasms); should the patient's response to Sabril be insufficient, therapy with Sabril will be stopped

b) The following materials are part of the REMS and are appended

(1) Patient-Physician Agreement- Refractory CPS

(2) Parent/Legal Guardian –Physician Agreement-IS

(3) Treatment Maintenance Form

(4) Ophthalmologic Assessment Form

4) Each patient using the drug will be enrolled in a registry under 505-1(f)(3)(F) The registry will collect prescriber specialty, patient demographics, diagnosis, prior and concurrent anti-seizure medications, periodic ophthalmologic assessment data (i.e., the results of every 3-month monitoring), and the proportion of patients receiving Sabril for refractory complex partial seizures and infantile spasms who respond/do not respond to Sabril during the treatment initiation phase.

D. Implementation System

The Implementation System will include the following. Lundbeck Inc. will:

1) maintain a validated and secured (21 CFR Part 11 compliant) database of certified pharmacies, certified prescribers and enrolled patients.

2) monitor distribution data to ensure that only certified pharmacies are distributing and dispensing Sabril.

3) train all personnel working for the REMS coordinating center (TheraCom) directly responsible for the Sabril REMS program and site managers at all certified pharmacies. Lundbeck Inc. will audit all certified pharmacies and the REMS coordinating center on an annual basis.

4) ensure that the REMS coordinating center receives each enrolled patient's completed Treatment Maintenance Form documenting an assessment of risk-benefit prior to authorizing the maintenance phase of therapy.

5) ensure that the REMS coordinating center obtains the completed Ophthalmologic Assessment Form for all registered patients at 3-month intervals (plus a 90-day grace period, as detailed in the REMS Supporting Document) prior to authorizing continued dispensing of refills

6) ensure that certified pharmacies dispense Sabril only if they receive authorization for each dispensing from the REMS coordinating center.

7) ensure that patients who do not comply with the vision monitoring requirements of the REMS are tapered from Sabril.

8) monitor and evaluate the implementation of the elements provided for under Sections C1, C.2, C.3, and C.4, above, in the manner described in the REMS supporting document, and take reasonable steps to work to improve implementation of these elements.

E. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA every 6 months from the date of approval of the REMS for 1 year, and then annually thereafter. The assessment period will close no earlier than 60 days prior to the date the respective assessment is due. The assessment is to be received by the FDA on the due date.

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Dear Healthcare Professional:

Lundbeck Inc. is writing to inform you of the approval of SABRIL® (vigabatrin), pronounced say-bril, by the Food and Drug Administration (FDA) for the following indications: As adjunctive therapy in adult patients with refractory complex partial seizures (CPS) who have inadequately responded to several alternative treatments and as monotherapy for pediatric patients with infantile spasms (IS).

Decisions to use SABRIL to treat refractory CPS and IS must balance the potential benefits with the risks of therapy.

SABRIL causes irreversible bilateral concentric constriction of the visual field in 30 percent or more of adult patients, and, therefore, has a Risk Evaluation and Mitigation Strategy (REMS) associated with its use. Information on how patients and physicians can gain access to SABRIL and guidance on how to evaluate SABRIL-induced vision loss can be found through the SHARE Program which is discussed at the end of this letter.

Copies of the full Prescribing Information and Medication Guide are enclosed for your reference. Two specific effects of SABRIL are highlighted below:

Vision Loss
SABRIL causes permanent bilateral concentric constriction of the visual field in 30 percent or more of adult patients. Vision loss can range in severity from mild to severe, including tunnel vision to within about 10 degrees of visual fixation and can result in disability. In some cases, SABRIL can also 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, although the risk of vision loss may increase with increasing duration of exposure. There is no dose known to be free of risk of vision loss, although the risk of vision loss may increase with increasing dose and cumulative exposure. The possibility that vision loss can worsen despite discontinuation of SABRIL has not been excluded.

Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before vision loss is severe; therefore, appropriate vision monitoring is needed for detection. Monitoring of vision by an ophthalmic professional (defined as having expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina) is required.

Vision monitoring is mandatory in adults receiving SABRIL for refractory CPS at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy.

Assessing vision loss is difficult in children and therefore the frequency and extent of vision loss in infants and children is poorly characterized. Vision monitoring is required to the extent possible in infants receiving SABRIL at baseline (no later than 4 weeks after starting SABRIL) and at least every 3 months while on therapy. Vision testing is also required about 3 to 6 months after the discontinuation of SABRIL therapy. This assessment should include visual acuity and visual field whenever possible. The appropriate diagnostic approach should be individualized for the patient and clinical situation, but for all patients attempts to monitor periodically must be documented under the SHARE program. In those patients in whom vision testing is not possible, treatment may continue according to clinical judgment, with appropriate caregiver counseling, and

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with documentation in the SHARE program of the inability to test vision. Results from ophthalmic monitoring must be interpreted with caution, as reliability and predictive value are variable

Please read the full Prescribing Information for additional details.

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 with SABRIL. The potential for long-term clinical sequelae and the need for monitoring have not been adequately studied. In animals that received vigabatrin, similar MRI abnormalities were correlated histologically with microvacuoles, consistent with a process of intramyelinic edema in those animals. Vacuolar changes considered distinct from intramyelinic edema, as well as other neurotoxicity and neurobehavioral abnormalities have also been observed in animals.

Brain MRI abnormalities, attributable to SABRIL have not been observed in adult or older pediatric patients treated with SABRIL for CPS.

Please read the full Prescribing Information for additional details.

S.H.A.R.E Program

To support patients and prescribers in their evaluation of the benefits and risks of SABRIL and their decision to initiate therapy, and to support the evaluators of SABRIL induced vision loss, Lundbeck Inc. has established the SHARE program which stands for Support, Help and Resources for Epilepsy. SHARE administers the SABRIL Risk Evaluation & Mitigation Strategy (REMS) program and the associated distribution and reimbursement services. All physicians who prescribe SABRIL and all patients who take SABRIL must be registered in the SHARE program. Ophthalmologists do not need to be registered.

Please visit the Lundbeck SHARE website at www.lundbeckshare.com or call SHARE at 1-888-45-SHARE for registration information. Medical inquiries should be directed to the Medical Information Department at 1-866-402-8520. Adverse drug events or product complaints should be directed to the Patient Safety Department at 1-800-455-1141.

Sincerely,

Lundbeck Inc.

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Dear Healthcare Professional:

Based on our conversation with you on *(insert date),* you indicated that you wish to continue treating patient, *(insert name)* with SABRIL after their completed Evaluation Phase of SABRIL therapy. We are writing to inform you that since we have not received a Treatment Maintenance Form for your patient, *(insert name)* which is mandatory for continued treatment with SABRIL, your next prescription must be written to taper (*insert name)* off of SABRIL, as no additional refills will be provided following completion of the taper.

This letter serves to remind you of the potential issues surrounding the abrupt withdrawal of SABRIL and provides the medication tapering recommendations from the Withdrawal of SABRIL Therapy Section of the approved labeling.

- SABRIL should not be discontinued abruptly and suddenly.
- As with all antiepileptic drugs, SABRIL should be withdrawn gradually to minimize increased seizure frequency.

An example of a tapering schedule employed in controlled clinical studies in adults with complex partial seizures is as follows: Vigabatrin was tapered by decreasing the daily dose 1 g/day on a weekly basis until discontinued. For example, if a patient was taking 3 g/day, the taper schedule was:

- Week 1: 2 g/day = two tablets twice per day = 28 tablets total
- Week 2: 1 g/day = one tablet twice per day = 14 tablets total
- Week 3: Sabril completely discontinued

This example tapering schedule would require a total of 42 tablets of SABRIL.

An example of a tapering schedule employed in a controlled clinical study in patients with infantile spasms is as follows: Vigabatrin was tapered by decreasing the daily dose at a rate of 25-50 mg/kg every 3-4 days. For example if a patient was taking 150 mg/kg/day (75 mg/kg BID), the taper schedule was:

- Days 1-3: 100 mg/kg/day (50 mg/kg BID)
- Days 4-6: 50 mg/kg/day (25 mg/kg BID)
- Days 7-10: 25 mg/kg/day (12.5 mg/kg BID)
- Day 11: Vigabatrin completely discontinued.

Read the full Prescribing Information in the approved labeling for additional details.

Please call the SHARE call center at 1-888-45-SHARE with any questions, concerns, or updates regarding this patient.

Other medical inquiries should be directed to the Lundbeck Medical Information Department at 1-866-402-8520. Adverse drug events or product complaints should be directed to the Lundbeck Patient Safety Department at 1-800-455-1141.

Sincerely,

Lundbeck Inc.

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Dear Healthcare Professional:

We are writing to inform you that we have not received documentation that your patient, *(insert name)*, has obtained vision monitoring that is required in order to continue receiving SABRIL (vigabatrin). According to the Risk Management and Evaluation Strategy (REMS) program requirements, this patient will need to be tapered off of SABRIL.

Unless verification of vision monitoring is received via the Ophthalmology Assessment Form**,** your next prescription must be written to taper (*insert name)* off of SABRIL, as no additional refills will be provided following completion of the taper.

This letter serves to remind you of the potential issues surrounding the abrupt withdrawal of SABRIL and provides the medication tapering recommendations from the Withdrawal of Sabril Therapy Section of the approved labeling.

- SABRIL should not be discontinued abruptly and suddenly.
- As with all antiepileptic drugs, SABRIL should be withdrawn gradually to minimize increased seizure frequency.

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- Days 1-3: 100 mg/kg/day (50 mg/kg BID)
- Days 4-6: 50 mg/kg/day (25 mg/kg BID)
- Days 7-10: 25 mg/kg/day (12.5 mg/kg BID)
- Day 11: Vigabatrin completely discontinued

Read the full Prescribing Information in the approved labeling for additional details.

Please provide SHARE Call Center with your patient's Ophthalmology Assessment Form as soon as possible. The Ophthalmology Assessment form is available through S.H.A.R.E. program at www.lundbeckshare.com or the S.H.A.R.E Central Call Center. Please call the S.H.A.R.E call center at 1-888-45-SHARE with any questions, concerns, or updates regarding this patient.

Other medical inquiries should be directed to the Lundbeck Medical Information Department at 1-866-402-8520. Adverse drug events or product complaints should be directed to the Lundbeck Patient Safety Department at 1-800-455-1141.

April 7, 2009

Lundbeck Inc.
Four Parkway North **Tel 847-282-1000**
Deerfield, IL 60015 **Fax 847-282-1001**
USA **www.lundbeckinc.com**

Sincerely,

Lundbeck Inc.

April 7, 2009

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

PRESCRIBER ENROLLMENT AND AGREEMENT FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

Attestation of Knowledge of Sabril

By signing below and completing the form below and on page 2, I acknowledge that I have read and understand the information in the Sabril Prescribing Information, and I agree to be registered in the SHARE program.

- Sabril is only approved for pediatric patients with infantile spasms (IS) 1 month to 2 years of age or for adults with refractory complex partial seizures (CPS) who have responded inadequately to several alternative treatments. Sabril is not a first-line treatment for refractory CPS.
- I have experience in treating epilepsy.
- I know the risks of Sabril treatment, specifically vision loss.
- *For physicians who prescribe Sabril for IS:* I have knowledge of the risk of T2 MRI abnormality in infants with IS.
- I understand that the effectiveness of Sabril in treating seizures can be assessed within 2 to 4 weeks of initiating therapy in infants and within 12 weeks of initiating therapy in adults. The possibility that vision loss can worsen despite discontinuation of Sabril has not been excluded. In patients with no meaningful improvement in seizure control, Sabril must be discontinued. For patients with meaningful seizure improvement, clinicians and patients need to have continuing discussions of benefit-risk for the duration of therapy.
- I must order and review visual assessment testing at baseline (within 4 weeks of Sabril initiation), at least every 3 months after initiation while on Sabril, and approximately 3 to 6 months after discontinuation of Sabril.
- I will educate patients/parents/legal guardians considering treatment with Sabril on the benefits and risks of the drug, give them a copy of the *Medication Guide*, instruct them to read it, and encourage them to ask questions.
- After reviewing the *Medication Guide* with the patient/parent/legal guardian and prior to the initial prescription, I may use the *Patient/Parent/Legal Guardian-Physician Agreement Form* to reinforce the education provided.
- I will counsel patients who fail to comply with the SHARE program requirements.
- I will remove patients from Sabril therapy who fail to comply with SHARE program requirements after appropriate counseling.
- I understand that Sabril is not available at retail pharmacies. Sabril is only available through select specialty pharmacies.
- I understand that all initial prescriptions for Sabril must go through the SHARE Call Center (1-888-45-SHARE [1-888-457-4273]) and will then be fulfilled by a specialty pharmacy.
- Prior to dispensing any Sabril prescription, I understand that SHARE will verify that I have a signed copy of this *Prescriber Enrollment and Agreement Form* on file.
- I will report all serious adverse events with Sabril to Lundbeck Inc. at 1-800-455-1141 or to the US Food and Drug Administration at 1-800-FDA-1088.

Prescriber Name _____ _____ _____
Last First MI

Prescriber Degree ☐ **MD** ☐ **DO** **Signature** _____ **Date** _____
month/day/year

Attestation continues on page 2

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

PRESCRIBER ENROLLMENT AND AGREEMENT FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

Attestation continued from page 1

Attestation of Knowledge of Sabril

For additional information, please visit www.LundbeckSHARE.com or call the SHARE Call Center at 1-888-45-SHARE (1-888-457-4273).

Prescriber Name _____

Institution Name (if applicable) _____

Prescriber Address _____ _____ _____ _____
Street City State ZIP Code

Telephone Number _____
Area Code Telephone Number

Alternative Telephone Number _____
Area Code Telephone Number

Office Fax _____
Area Code Fax Number

E-mail _____

Prescriber NPI# _____

Specialty
☐ **Epileptology** ☐ **Pediatric Neurology** ☐ **Other** _____
☐ **Neurology** ☐ **Internal Medicine** _____

Office Contact Name _____ _____
Last First

Second Contact Name _____ _____
Last First

By completing and submitting this form, you will be registered in the SHARE program and may begin prescribing Sabril.

For additional information, please visit www.LundbeckSHARE.com or call the SHARE Call Center at 1-888-45-SHARE (1-888-457-4273).

Once registered in the SHARE program, you will receive a copy of the *Sabril Starter Kit*, which will contain the complete Prescribing Information, information on the SHARE program, the *Medication Guide*, and the *Patient/Parent/Legal Guardian-Physician Agreement* to be used when initiating Sabril therapy. Additional copies of the *Sabril Starter Kit* can be obtained by contacting your Lundbeck Account Manager or contacting the SHARE Call Center (1-888-45-SHARE).

You only need to register in the SHARE program once, and you are under no obligation to prescribe Sabril.

To complete your registration, fax both pages of your completed *Prescriber Enrollment and Agreement Form* to SHARE at 1-877-742-1002.

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

TREATMENT INITIATION FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

STEP ONE: Patient Profile

Name (First, Middle, Last): _____ Sex: ❑ Male ❑ Female DOB: _____ month/day/year

Address: _____ City: _____ State: _____ Zip Code: _____

SSN: _____-_____-_____ Phone: _____ Today's Date: _____ month/day/year

Sabril Administration Site: ❑ Home ❑ Hospital ❑ I/DD Facility

I authorize my healthcare providers and health plans to disclose personal and medical information related to my use or potential use of Sabril (vigabatrin) to Lundbeck and its agents and contractors and I authorize Lundbeck to use and disclose this information to: 1) establish my benefit eligibility; 2) communicate with my healthcare providers and health plans about my benefit and coverage status and my medical care; 3) provide support services, including facilitating the provision of Sabril to me; 4) evaluate the effectiveness of Sabril's education programs; and 5) participate in the Sabril Patient Registry. I agree that using the contact information I provide, Lundbeck may get in touch with me for reasons related to the SHARE program and may leave messages for me that disclose that I take Sabril.

I understand that once my health information has been disclosed to Lundbeck, privacy laws may no longer restrict its use or disclosure; however, Lundbeck agrees to protect my information by using and disclosing it only for the purposes described above or as required by law. I may also cancel this authorization in the future by notifying Lundbeck in writing and submitting it by fax to 1-877-742-1002 or by calling 1-888-45-SHARE (1-888-457-4273). If I cancel, Lundbeck will cease using or disclosing my information for the purposes listed above, except as required by law or as necessary for the orderly termination of my participation in the SHARE program. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me. I also certify that the information provided about the insurance status is complete and accurate and will update the SHARE Call Center promptly if such status should change.

Power of Attorney: ❑ Yes ❑ No ❑ N/A Power of Attorney (First, Middle, Last): _____

Patient / Parent / Legal Guardian Signature: _____ Date: _____ month/day/year

STEP TWO: Patient Insurance Profile

Name of Primary Payer: _____ Phone Number: _____

Relationship to Cardholder: ❑ Self ❑ Spouse ❑ Child ❑ Other

Cardholder Name: _____ Plan Number: _____

Group Number: _____ ID Number: _____

Name of Secondary Payer: _____ Phone Number: _____

Relationship to Cardholder: ❑ Self ❑ Spouse ❑ Child ❑ Other

Cardholder Name: _____ Plan Number: _____

Group Number: _____ ID Number: _____

Prescription Benefit Manager: _____ Phone Number: _____

Cardholder Name: _____ Plan Number: _____

Group Number: _____ ID Number: _____

Lundbeck

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

TREATMENT INITIATION FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

STEP THREE: Prescriber Information

Prescriber's Name (First, Middle Initial, Last): _____ NPI #: _____

Prescriber Address: _____

City: _____ State: _____ Zip: _____

Phone Number: _____ Fax: _____

❑ I have completed the Prescriber Enrollment and Agreement Form required for prescribing Sabril.

I certify that I have reviewed the Medication Guide with the patient/parent/legal guardian, and have counseled him/her on the risks of SABRIL, including vision loss. I commit to ordering and reviewing visual testing at the appropriate intervals in accordance with the SABRIL full prescribing information.

I authorize TheraCom, LLC. in its capacity on behalf of Lundbeck Inc. to be my designated agent and to act as my business associate (as defined in 45 CFR 160.103) to use and disclose any information in this form to the insurer of the above-named patient and to obtain any information about the patient, including any protected health information (as defined in 45 CFR 160.103), from the insurer, including eligibility and other benefit coverage information, for my payment and/or health care operation purposes. As my business associate, TheraCom is required to comply with, and by its signature hereto, agrees that it will comply with, the applicable requirements of 45 CFR 164.504(e) regarding business associates, and that it will safeguard any protected health information that it obtains on my behalf, and will use and disclose this information only for the purposes specified herein or as otherwise required by law.

Prescriber Signature: _____ Date: _____
No Stamped Signature month/day/year

TheraCom Signature: _____ Date: _____
month/day/year

STEP FOUR: Prescription Information

Prescription: Sabril ❑ 500 mg tablets ❑ 500 mg powder for oral solution*† Quantity: _____ (_____) Tablets/Packets
(Digits and written words)

*Child Weight (kg): _____ Date: _____ Refills: _____ (_____)
month/day/year *(Digits and written words)*

SIG: _____

Primary ICD-9 Code: _____ Secondary ICD-9 Code: _____

Instructions: Ship to: ❑ Patient home (address in Step One) ❑ Other (address below) †*Add ancillary supplies as needed*

Patient Name: _____ Address: _____

City: _____ State: _____ Zip: _____ Phone: _____

Consultant ophthalmic professional: _____ Scheduled date of baseline visual assessment _____
month/day/year

Prescriber Signature: _____ Date: _____
month/day/year

Lundbeck

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

TREATMENT INITIATION FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

STEP FIVE: Patient History

Name (First, Middle, Last):_____ DOB:_____ (month/day/year) Today's Date: _____ (month/day/year)

Race *(Check only one)*: ❑ American Indian or Alaska Native ❑ Asian ❑ Black or African American ❑ Native Hawaiian or Other Pacific Islander ❑ Caucasian ❑ Hispanic ❑ Other

History of Sabril Use:

Is the patient currently taking Sabril? ❑ Yes ❑ No

Has the patient previously taken Sabril? ❑ Yes ❑ No

If the patient has taken or is taking Sabril, how long were they on drug?

_____day(s) (Number) _____week(s) (Number) _____month(s) (Number) _____year(s) (Number)

Reason for Use: ❑ CPS ❑ IS ❑ Other, Specify:_____

If IS, what is the etiology: ❑ Cryptogenic ❑ Symptomatic - TS ❑ Symptomatic, Other

Please check all agents previously or currently utilized by the patient:

Previously Taken	Currently Taking	
❑	❑	Phenytoin
❑	❑	Lamotrigine
❑	❑	Felbamate
❑	❑	Depakote/Valproic acid
❑	❑	Topiramate
❑	❑	Tiagabine
❑	❑	Zonisamide
❑	❑	Levetiracetam
❑	❑	Carbamazepine
❑	❑	Oxcarbazepine
❑	❑	Benzodiazepine(s)
❑	❑	ACTH
❑	❑	Other steroids, specify:_____
❑	❑	OTHER, specify: _____

Please check the # of monotherapy trials by the patient:

❑ 0
❑ 1
❑ 2
❑ >2

Please check the # of trials with 2 agents by the patient:

❑ 0
❑ 1
❑ 2
❑ >2

Please check the # of trials with 3 or more agents by the patient:

❑ 0
❑ 1
❑ 2
❑ >2

www.LundbeckSHARE.com
Fax to 1-877-742-1002

Lundbeck Inc., Four Parkway North, Deerfield, IL 60015.

Lundbeck

Sabril®
vigabatrin
500 mg tablet
500 mg powder for oral solution

S·H·A·R·E®
Support, Help And Resources for Epilepsy

TREATMENT MAINTENANCE FORM

Because the risk of vision loss increases over time with continued use, it is essential to assess a patient's response to Sabril early and determine that the benefit in treating the patient's seizures with Sabril is clinically meaningful and outweighs the risk of continued therapy with it.

You are therefore asked to attest to the following:

- That you have assessed your patient's response to Sabril
- That you have discussed the benefits and risks of continued Sabril therapy with the patient, parent, and/or legal guardian
- That you have determined in your professional judgment that the benefit of controlling seizures exceeds the risk of vision loss
- That continued Sabril therapy is appropriate and warranted

❑ I have evaluated my patient's clinical response to the recent initiation of Sabril treatment and have verified a clinically meaningful improvement in seizure control. I have determined that the benefit of Sabril treatment outweighs the risk of vision loss at this time. I recommend that my patient continue maintenance therapy with Sabril.

Patient name (First, Middle, Last): _____

Patient DOB: _____
month/day/year

Prescriber name: _____ Prescriber NPI #: _____

Signature: _____ Date: _____
month/day/year

www.LundbeckSHARE.com

Lundbeck

Fax to 1-877-742-1002

Lundbeck Inc., Four Parkway North, Deerfield, IL 60015.

Sabril® vigabatrin
500 mg tablet
500 mg powder for oral solution

OPHTHALMOLOGIC ASSESSMENT FORM

S·H·A·R·E®
Support, Help And Resources for Epilepsy

To be completed by the prescribing neurologist with each ophthalmologic assessment.

STEP ONE: Patient Profile

Name (First, Middle, Last) _____ Sex: ❒ Male ❒ Female DOB _____
month/day/year

Address _____ City _____ State _____ ZIP _____

Patient currently on Sabril: ❒ Yes ❒ No

STEP TWO: Consultant Ophthalmic Professional

Ophthalmic Professional Name (First, Middle Initial, Last) _____ NPI #_____

Ophthalmic Professional Address _____

City _____ State_____ ZIP_____

Phone _____

STEP THREE: Ophthalmologic Assessment

Taking into account benefit-risk considerations, the performance of ophthalmologic assessment will be enforced for all patients, and the drug will not continue to be dispensed unless this required documentation is completed and faxed to the SHARE Call Center at 1-877-742-1002.

Section 1

1. Was an ophthalmologic assessment conducted? ❒ Yes _____
month/day/year ❒ No *(If no, go to Section 2 on next page)*

2. If yes, was a visual acuity evaluation conducted? ❒ Yes ❒ No

What were the results? Left eye _____/_____ Right eye _____/_____

3. Was kinetic perimetry conducted? ❒ Yes ❒ No

What were the results? Degree of retained visual field to V4e target (each eye):

- ❒ >160° retained
- ❒ 120° to 160° retained
- ❒ 60° to <120° retained
- ❒ 40° to <60° retained
- ❒ 20° to <40° retained
- ❒ 10° to <20° retained
- ❒ <10° retained

4. Was static perimetry conducted? ❒ Yes ❒ No

Specify test program used:_____

What were the results? Concentric/partly concentric pattern of decreased sensitivity occurring within:

- ❒ 60°
- ❒ 40°
- ❒ 20°
- ❒ 10°

Assessment form continues on page 2

Assessment form continued from page 1

5. Was OCT conducted? ❒ Yes ❒ No

What were the results? ❒ Normal
❒ Abnormal

6. Was ERG conducted? ❒ Yes ❒ No

What were the results? ❒ Normal
❒ Abnormal

7. Other testing

Specify test:_____

What were the results? ❒ Normal
❒ Abnormal

Section 2

❒ An ophthalmologic assessment was not conducted on the patient for the following reason(s):

❒ Patient is blind

❒ Patient's general neurological condition precludes the need for visual assessment

❒ Patient's medical condition prevents visual assessment being performed safely *(please explain)*_____

_____

❒ Other *(please explain)* _____

Section 3

If the assessment occurred more than 1 month after the due date, please indicate the reason:

❒ Patient's financial/reimbursement situation

❒ Transportation issues

❒ Scheduling conflicts

❒ Other *(please explain)* _____

Prescriber's Name _____ *Prescriber's NPI #* _____

Signature _____ *Date* _____
month/day/year

If formal perimetry was conducted, please attach a copy of the visual field recordings.

www.LundbeckSHARE.com ***Fax to 1-877-742-1002***

Lundbeck Inc., Four Parkway North, Deerfield, IL 60015.

COMPLEX PARTIAL SEIZURES (CPS)

Patient/Parent/Legal Guardian–Physician Agreement for Sabril® (vigabatrin) Use

Completed forms must be faxed to the SHARE Call Center (1-877-742-1002) at treatment initiation. Place the original signed document in the patient's medical record and provide a copy to the patient, parent, or legal guardian.

Identification of Signer:

Patient—I, _____, am the patient. I am able to read and understand this document and will sign for myself.

Parent/Legal Guardian—I am not the patient. I am the parent/legal guardian of _____, who is the patient. I am able to read and understand this document and will sign on behalf of the patient.

To use Sabril appropriately, the patient/parent/legal guardian should:

- **Be aware that Sabril causes a serious vision problem in some people.**
- **Read the *Medication Guide* to understand the risks of Sabril therapy.**
- **Talk with your doctor about the information you receive before signing the *Patient/Parent/Legal Guardian-Physician Agreement*.**
- **Report any problems you might experience when using Sabril to your doctor as soon as they happen.**
- **Visit the doctor regularly to make sure that Sabril continues to be right for you to take.**

This agreement is to be completed and signed by the patient/parent/legal guardian and the doctor. The person who signs is to read each item below and initial in the space provided if the item is understood. After initialing each item, the signature goes at the end of this agreement. The signer is not to sign this agreement or take Sabril if there are any unanswered questions.

1. I, _____, have read the *Sabril Medication Guide*. My doctor has explained the risks.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

2. I understand that Sabril is a medicine used to treat complex partial seizures that have not responded to several other treatments. The doctor and I have talked about my treatment choices and have decided that treatment with Sabril is right for me.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

3. I understand that about 1 in 3 adult patients taking Sabril have damage to their vision. I understand that if any vision loss occurs, it will not improve even if Sabril is stopped.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

4. I understand that there is no way to tell if I will develop vision loss.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

5. I understand that vision tests required by the doctor when starting Sabril treatment must be obtained. This testing will continue as long as Sabril is taken and after stopping therapy. I understand that these tests will not prevent vision loss. However, by stopping the treatment as a result of these tests, the amount of vision loss may be limited. I understand that it is important to see the doctor on a regular basis to make sure that Sabril continues to be right for me to take.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

6. The doctor and I have talked about my epilepsy. We have also talked about the potential benefits and risks of taking Sabril. We have agreed that Sabril therapy will be started, and that the initial treatment with Sabril will consist of an Evaluation Phase of about 3 months.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

7. If the seizures are not better during the Evaluation Phase, Sabril® (vigabatrin) therapy must be stopped. If seizure control has improved, I will discuss with the doctor the potential benefits and risks of continuing Sabril therapy (the Maintenance Phase). I understand that the risk of vision loss will continue as long as I continue to take Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

8. I understand that Sabril will be prescribed for myself, my son or daughter, or my legal ward only. I will not share Sabril with other people.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

9. The doctor has discussed with me other treatments for my epilepsy. We have decided that Sabril is the right treatment for me. I understand that Sabril can be discontinued at any time. I also know that I cannot stop taking Sabril without my doctor telling me to do so. I agree to tell the doctor if I decide to stop taking Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

10. All my questions were answered to my satisfaction. I now authorize the doctor, _____, to begin treatment with Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

I have read and understood all of the information presented above and agree to use Sabril therapy.

Patient/Parent/Legal Guardian Agreement

Evaluation Phase

To be signed by patient/parent/legal guardian upon initiation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Maintenance Phase

To be signed by patient/parent/legal guardian upon continuation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Physician Agreement

I, _____, have fully explained to the patient/parent/legal guardian the potential benefits and risks of Sabril treatment. I have provided the patient/parent/legal guardian with the brochure entitled *Sabril Medication Guide*, and have answered all questions regarding therapy with Sabril.

Evaluation Phase

To be signed by physician upon initiation of Sabril therapy.

Signature:_____ Date_____ (month/day/year)

Maintenance Phase

To be signed by physician upon continuation of Sabril maintenance therapy.

Signature:_____ Date_____ (month/day/year)

Fax to the SHARE Call Center (1-877-742-1002)

INFANTILE SPASMS (IS)

Parent/Legal Guardian–Physician Agreement for Sabril® (vigabatrin) Use

Completed forms must be faxed to the SHARE Call Center (1-877-742-1002) at treatment initiation. Place the original signed document in the patient's medical record and provide a copy to the patient, parent, or legal guardian.

To use Sabril appropriately, you should:

- **Be aware that Sabril causes a serious vision problem in some people.**
- **Be aware that there have been reports of changes in the brain images of some patients with infantile spasms on Sabril. The importance of these changes is not known.**
- **Read the *Medication Guide* to understand the risks of Sabril therapy.**
- **Talk with your doctor about the information you receive before signing the *Parent/Legal Guardian-Physician Agreement*.**
- **Report any problems your infant might experience when using Sabril to your infant's doctor as soon as they happen.**
- **Visit your infant's doctor regularly to make sure that Sabril continues to be right for your infant to take.**

This agreement is to be completed and signed by the parent/legal guardian and the doctor. Read each item below and initial in the space provided if you understand the item. After you have initialed each item, sign your name at the end of this agreement. Do not sign this agreement or have your infant take Sabril if you have any unanswered questions.

1. I, _____, have read the *Sabril Medication Guide*. My infant's doctor has explained the risks.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

2. I understand that Sabril is a medicine used to treat infantile spasms. My infant's doctor and I have talked about my infant's treatment. We both think that Sabril should be used to treat my infant.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

3. I understand that about 1 in 3 infants taking Sabril will have damage to their vision. I understand that if any vision loss occurs, it will not improve even if my infant stops taking Sabril.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

4. I understand that there is no way to tell if my infant will develop vision loss.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

5. I understand that vision tests required by my infant's doctor when starting Sabril treatment must be obtained for my infant. This testing will continue as long as Sabril is taken and after stopping therapy. I understand that these tests will not prevent vision loss. However, by stopping the treatment as a result of these tests, the amount of vision loss may be limited. I understand that it is important to take my infant to see his or her doctor on a regular basis to make sure that Sabril continues to be right for them to take.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

6. I understand that there have been reports of a change in the brain pictures of infants taking Sabril. The change may reverse by itself or when the Sabril dose is lowered or is stopped. It is not known if this change has any effect on the infant.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

7. I understand that my infant's doctor may want to take an MRI or picture of my infant's brain before starting or during Sabril treatment.

   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

8. My infant's doctor and I have talked about my infant's epilepsy. We have talked about Sabril® (vigabatrin) as a treatment option for my infant. We have agreed that Sabril therapy will be started, and that the initial treatment with Sabril will consist of an Evaluation Phase of about 1 month.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

9. If my infant's seizures are not better during the Evaluation Phase, Sabril therapy must be stopped. If my infant's seizure control has improved, I will discuss with his or her doctor the potential benefits and risks of continuing Sabril therapy (the Maintenance Phase). I understand that the risk of developing vision loss will continue as long as my infant takes Sabril. I also understand that there may be some chance of an MRI change seen in the brain; however, we do not know if this change has any medical significance.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

10. Sabril will be prescribed only for my infant. I will not share his or her Sabril with other people.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

11. We have decided that Sabril is the most appropriate treatment for my infant. I understand that my infant can stop taking Sabril at any time. However, I will not have my infant abruptly stop using Sabril unless instructed to do so by his or her doctor. If treatment is abruptly stopped, my infant's seizures might increase or return. I agree to tell my doctor if I decide to stop giving Sabril to my infant.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

12. All my questions were answered to my satisfaction. I now authorize my doctor, _____, to begin my infant's treatment with Sabril.

Evaluation Phase Initials: _____
Maintenance Phase Initials: _____

I have read and understood all of the information presented above and agree to use Sabril therapy.

Parent/Legal Guardian Agreement

Evaluation Phase

To be signed by parent/legal guardian upon initiation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Maintenance Phase

To be signed by parent/legal guardian upon continuation of Sabril therapy.

Signature: _____ Date_____ (month/day/year)

Patient Name: _____

Patient Address: _____ (Street)

_____ (City / State / ZIP)

Telephone: _____ (Area Code / Telephone Number)

Physician Agreement

I, _____, have fully explained to the parent/legal guardian the potential benefits and risks of Sabril treatment. I have provided the parent/legal guardian with the brochure entitled *Sabril Medication Guide*, and have answered all questions regarding therapy with Sabril.

Evaluation Phase

To be signed by physician upon initiation of Sabril therapy.

Signature:_____ Date_____ (month/day/year)

Maintenance Phase

To be signed by physician upon continuation of Sabril maintenance therapy.

Signature:_____ Date_____ (month/day/year)

Fax to the SHARE Call Center (1-877-742-1002)