

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

 **SABRIL®**

vigabatrin

Tablets, 500 mg

Sachets, 500 mg

Antiepileptic

® Trademark of Lundbeck

Manufactured by:
Lundbeck
Six Parkway North
Deerfield, IL 60015
U.S.A.

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SABRIL®

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	tablet / 500 mg	Hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, titanium dioxide
Oral	sachet / 500 mg	Povidone

INDICATIONS AND CLINICAL USE

Sabril (vigabatrin) is indicated for:

- Treatment of epilepsy only in those patients who respond inadequately to alternative treatment combinations or in whom other drug combinations have not been tolerated and in whom the potential benefits conferred by its use outweigh the risk of ophthalmologic abnormalities (see WARNINGS and PRECAUTIONS, Serious Warnings and Precautions and Ophthalmologic).

Sabril is not indicated as a first line antiepileptic treatment.

If these criteria are met and the patient and caregiver have been fully apprised of the risk, Sabril can be considered for the adjunctive management of partial epilepsies, with or without secondary generalization, which are not satisfactorily controlled by other antiepilepsy drug combinations.

- Management of infantile spasms (IS or West syndrome), as monotherapy, although the benefits of its use and the risks of ophthalmologic abnormalities must be taken into account. While Sabril may be effective initially as monotherapy, clinical experience indicates that at least 50% of patients may require the addition of other antiepileptic drugs owing to relapse or emergence of other seizure types following an initial response to the treatment of infantile spasms with Sabril.

Sabril should be used under close monitoring by a neurologist and an ophthalmologist.

Geriatrics (≥65 years of age):

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see WARNINGS AND PRECAUTIONS, Geriatrics). Caution should be exercised in elderly patients, particularly those with known decreased renal function. Elderly patients should be monitored closely for adverse events such as sedation and confusion.

Pediatrics (2 months - 2 years of age):

Sabril has been studied in pediatric patients with Infantile Spasms (aged 2 months – 2 years; see CLINICAL TRIALS). In clinical trials, infection-related events were reported at higher frequencies when compared to adult studies (see ADVERSE REACTIONS). In a retrospective epidemiologic study, abnormal MRI signal changes were observed in some infants receiving vigabatrin. The specific pattern of signal changes was not observed in older children and adult patients (see WARNINGS AND PRECAUTIONS, Magnetic Resonance Imaging (MRI) Abnormalities).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Sabril is contraindicated in pregnancy and lactation.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions: VISION LOSS

- A number of ophthalmological abnormalities, including visual field defects, rare cases of bilateral optic disc pallor, subtle peripheral retinal atrophy, optic atrophy, and rare cases of optic neuritis have been reported in patients receiving Sabril (see WARNINGS AND PRECAUTIONS, Ophthalmologic).
- Visual field defects have been reported in about 1/3 of patients receiving Sabril, although the actual prevalence may be higher.
- Based on available data, the usual pattern is a concentric constriction of the visual field of both eyes, which is generally more marked nasally than temporally. In the central visual field (within 30 degrees of eccentricity), a nasal annular defect is frequently seen.
- To detect visual field defects, appropriate visual field testing (perimetry) by a standardized static perimetry (such as Humphrey or Octopus) or kinetic perimetry (such as Goldmann) must be performed before treatment initiation and at three month intervals.
- Available data suggests that visual field defects may be permanent even after discontinuation of vigabatrin treatment. It is possible that vision loss can worsen despite discontinuation of Sabril therapy.
- Symptoms of vision loss from Sabril are unlikely to be recognized by patients or caregivers before vision loss is severe.
- In patients who have any pre-existing visual field defects, either detected on perimetry or through clinical symptoms, vigabatrin use should be considered only if the benefits outweigh the risks.
- If visual field defects are exhibited in any patients using Sabril, consideration should be given to the gradual discontinuation of Sabril.
- Sabril should only be used when the potential benefits outweigh the risk for developing a visual field defect. If clinically meaningful seizure improvement is not observed within 3 months of therapy initiation in adults, and 4 weeks in infants, Sabril therapy should be discontinued.
- Sabril should not be used concomitantly with other retinotoxic drugs.

General

Information for Patients: Patients receiving Sabril should be given the following instructions by the physician:

1. Patients should be warned that Sabril treatment can damage the vision. Sabril can result in a loss of peripheral vision (narrowing of the field of vision) which may lead to permanent impairment of eyesight. About 1/3 of patients who take Sabril are affected.
2. Symptoms of vision loss from Sabril are unlikely to be recognized by patients or caregivers before vision loss is severe. Patients should have their eyes examined before

beginning Sabril treatment and at regular intervals (approximately every 3 months) thereafter.

3. Patients should be advised to tell their doctor immediately of any change in their eyesight such as narrowing of the field of vision, blurred vision or any other visual symptoms, if they start to trip, bump into things, or are more clumsy than usual; are surprised by people or things coming in front of them that seem to come out of nowhere.
4. Women of childbearing potential should be advised to inform their doctor if they are pregnant or intend to become pregnant while on Sabril therapy. Sabril is contraindicated in pregnancy and lactation.
5. Mothers should discuss with their doctor whether to take Sabril or breastfeed their baby, they should not do both.
6. Patients should be advised not to drive a car or operate other complex machinery, and refrain from other activities requiring mental alertness or physical coordination until they are familiar with the effects of Sabril on their ability to perform such activities.

Withdrawal of Antiepileptic Drugs (AEDs): As with other antiepileptic drugs, abrupt discontinuation may lead to rebound seizures. If a patient is to be withdrawn from Sabril treatment, it is recommended that this be done gradually by reducing dose over a 2-4 week period if possible. In controlled clinical studies in adults with complex partial seizures (CPS) and pediatric patients with IS, Sabril was discontinued by gradual reduction of the daily dose of 1 g/day once a week in adults, and of 25-50 mg/kg/day every 3-4 days in infants.

Somnolence and Fatigue: Sabril causes somnolence and fatigue.

Patients should be advised not to drive a car or operate other complex machinery, and refrain from other activities requiring mental alertness or physical coordination 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.

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.

Dependence/Tolerance

The abuse and dependence potential of Sabril has not been evaluated in human studies. 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 Sabril (e.g., incrementation of dose, drug-seeking behaviour). Sabril did not produce adverse

events or overt behaviours associated with abuse when administered to humans or animals. Following chronic administration of vigabatrin to animals, there were no apparent withdrawal signs upon drug discontinuation. However, as with all AEDs, Sabril should be withdrawn gradually to minimize increased seizure frequency (see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs)).

Endocrine and Metabolism

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 $\geq 7\%$ 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.

Hematologic

Anemia: In North American controlled trials in adults, 6% of patients (16/280) receiving Sabril and 2% of patients (3/188) receiving placebo had adverse events of anemia and/or met criteria for potentially clinically important hematology changes involving hemoglobin, hematocrit, and/or RBC indices. Across U.S. controlled trials, there were mean decreases in hemoglobin of about 3% and 0% in Sabril and placebo-treated patients, respectively, and a mean decrease in hematocrit of about 1% in Sabril treated patients compared to a mean gain of about 1% in patients treated with placebo.

In controlled and open label epilepsy trials in adults and pediatric patients, 3 Sabril patients (0.06%, 3/4855) discontinued for anemia and 2 Sabril (0.04%, 2/4855) patients experienced unexplained declines in hemoglobin to below 8 g/dL and/or hematocrit below 24%.

Neurologic

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. In a retrospective epidemiologic study in infants with infantile spasms (N=205), the prevalence of these changes was 22% in Sabril treated patients versus 4% 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 motor abnormalities. Movement disorders including dystonia, dyskinesia and hypertonia, have been reported in patients treated for infantile spasms. The benefit/risk of Sabril should be evaluated on an individual patient basis. If new movement disorders occur during treatment with Sabril,

consideration should be given to dose reduction or a gradual discontinuation of treatment (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

In a blinded review of MRI images obtained in prospective clinical trials in patients with refractory CPS 3 years and older (N=656), the specific pattern of signal changes observed in IS patients was not observed in older children and adult patients treated with Sabril for refractory complex partial seizures (CPS). In the post marketing setting, MRI changes have also been reported in patients 6 years of age and younger treated with Sabril.

Studies of the effects of Sabril on MRI and Evoked Potentials (EP) in adult epilepsy patients have demonstrated no clear-cut abnormalities. For adults treated with Sabril, routine MRI surveillance is unnecessary.

Neurotoxicity – Intramyelinic edema: Intramyelinic edema – characterized by spongiosis (vacuolation and fluid accumulation) and separation of the outer myelin layers in the brain – has been reported in postmortem examination of vigabatrin-treated pediatric patients and in animal models at human therapeutic doses. It is recommended that patients treated with vigabatrin be closely observed for adverse effects on neurological function.

In the dog, studies indicate that intramyelinic edema is associated with increased latencies in somatosensory and visual evoked potentials. Magnetic resonance imaging (MRI) changes also correlated with intramyelinic edema in the fornix, thalamus and hypothalamus.

Neurotoxicity (brain histopathology and neurobehavioural abnormalities) was observed in rats exposed to vigabatrin during late gestation and the neonatal and juvenile periods of development and brain histopathological changes were observed in dogs exposed to vigabatrin during 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, Magnetic Resonance Imaging (MRI) Abnormalities; Nursing Women and TOXICOLOGY, Chronic Toxicity, Vacuolization).

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

Use in Patients with Myoclonic Seizures: As with other antiepileptic drugs, some patients who take Sabril may experience an increase in seizure frequency, including status epilepticus and the onset of new seizure types. Patients with myoclonic seizures may be particularly liable to this effect. These phenomena may also be the consequence of an overdose, a decrease in plasma concentrations of concomitant antiepileptic treatment, or a paradoxical effect. New onset myoclonus and exacerbation of existing myoclonus may occur in rare cases.

Ophthalmologic

Visual field defects have been reported in about 1/3 of patients receiving Sabril, although the actual prevalence may be higher. Males may be at greater risk than females. The onset of vision loss from Sabril is unpredictable and can occur at any time during treatment but usually occurs after months to years of Sabril therapy. There is no dose or exposure known to be free of risk of vision loss. Data from systemic screening of participants in clinical studies indicate that the risk of developing visual field defects shows an increasing trend, with the greatest risk after 0.75 kg cumulative dose. The prevalence of these defects reaches a plateau after 3 kg cumulative dose. An average dose of 2 g/day translates to a greatest risk during the first year of treatment.

Based on available data, the usual pattern is a concentric constriction of the visual field of both eyes, which is generally more marked nasally than temporally. In the central visual field (within 30 degrees of eccentricity), a nasal annular defect is frequently seen. In some cases, Sabril can also damage the central retina and may decrease visual acuity. The visual field defect may result from increased levels of GABA in the retina.

This undesirable effect can only be reliably detected by systematic perimetry which is usually possible only in patients with a developmental age of more than 9 years. The degree of visual field restriction may be severe and this may have practical consequences for the patient and result in disability. To detect visual field defects, appropriate visual field testing (perimetry) by a standardized static perimetry (such as Humphrey or Octopus) or kinetic perimetry (such as Goldmann) must be performed before treatment initiation and at three month intervals. Static perimetry is the preferred method for detecting vigabatrin associated visual field defect.

Symptoms of vision loss from Sabril are unlikely to be recognized by patients or caregivers before vision loss is severe. Most patients with perimetry-confirmed defects had not previously spontaneously noticed any symptoms (were asymptomatic), even in cases where a severe defect was observed in perimetry.

In patients who have any pre-existing visual field defects, either detected on perimetry or through clinical symptoms, Sabril use should be considered only if the benefits outweigh the risks. In cases of any other eye disorders especially, but not limited to, retinal, optic nerve, glaucoma and cataracts the benefit/risk profile should be considered before prescribing Sabril.

Although data suggesting any association of Sabril to these eye disorders (except visual field defects) is inconclusive, the benefits of Sabril use and the risks of ophthalmologic abnormalities must be taken into account (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Patients should be instructed to report to their physicians any new visual problems and symptoms which may be associated with visual field constriction. If visual symptoms develop, the patient should be referred to an ophthalmologist.

If visual field defects are exhibited in any patients using Sabril, consideration should be given to the gradual discontinuation of Sabril. If the decision to continue treatment is made, consideration should be given to frequent benefit-risk assessments.

Sabril should only be used when the potential benefits outweigh the risk for developing a visual field defect. If clinically meaningful seizure improvement is not observed within 3 months of therapy initiation in adults, and 4 weeks in infants, Sabril therapy should be discontinued. If clinically meaningful seizure improvement is observed, the benefits and risks should periodically be assessed for the duration of therapy (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Psychiatric

Sabril should be used with caution in patients with a history of psychosis, depression or behavioural problems. Psychiatric events (agitation, aggression, depression, abnormal thinking, paranoid reactions and psychotic events) have been reported during Sabril treatment. These events occurred in patients with or without a psychiatric history, and were usually reversible when Sabril doses were reduced or gradually discontinued. Treatment in such patients should be initiated cautiously at low doses and with frequent monitoring.

Rare reports of encephalopathic symptoms such as marked sedation, stupor and confusion in association with non-specific slow wave activity on electroencephalogram have been described soon after the initiation of Sabril treatment. Risk factors for the development of these reactions include higher than recommended starting dose, faster dose escalation at higher steps than recommended and renal failure. These events have been reversible following dose reduction or discontinuation of Sabril (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Suicidal Ideation and Behaviour: Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known.

There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for

indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Renal

Sabril should be used with caution 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 due to decreased clearance of vigabatrin. In these patients, Sabril should be initiated at a lower dose and patients should be monitored for any dose-related side effects, including sedation and confusion (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment and ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

Special Populations

Pregnant Women: Sabril 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 is contraindicated in pregnancy and lactation. When taking into account epilepsy and the use of antiepileptic medications, the overall malformation rate in children of women with epilepsy has been shown to be 2-3 fold higher than in the overall population (approximately 3-4%).

There is no information on the possible occurrence of visual field defect in children who have been exposed to Sabril *in utero*.

If a patient becomes pregnant, treatment should be reviewed. Sudden interruption of effective antiepileptic treatment may lead to aggravation of the condition in the mother that is detrimental to the fetus.

Patients should be encouraged to enroll in the North American Antiepileptic Drug (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. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

Nursing Women: Vigabatrin is excreted into breast milk in low concentrations. Because of the potential for serious adverse reactions from vigabatrin in nursing infants (see WARNINGS AND PRECAUTIONS, Magnetic Resonance Imaging (MRI) Abnormalities and Neurotoxicity), 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 (see TOXICOLOGY, Chronic Toxicity).

Pediatrics (2 month - 2 years of age): Sabril may be used as monotherapy for the management of pediatric patients with Infantile Spasms (West syndrome) although the benefits of its use and the risks of ophthalmologic abnormalities must be taken into account (see CLINICAL TRIALS).

Geriatrics (≥ 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

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 1.5g 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 DOSAGE AND ADMINISTRATION, Elderly and Renally Impaired Patients). Caution should be exercised in elderly patients. Elderly patients should be monitored closely for adverse events such as sedation and confusion.

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

Monitoring and Laboratory Tests

Most patients who develop visual field defects do not report visual symptoms. Therefore, patients are required to have regular ophthalmologic examinations (every 3 months) through the entire course of therapy due to the relationship between development of visual field defects and cumulative dose of Sabril. A visual field defect detected during ophthalmologic testing should be promptly confirmed by additional testing. If confirmed, and the patient and physician decide to continue therapy, there is a need for ongoing benefit/risk assessments.

Monitoring of Patients with a Developmental Age of More than 9 Years: Appropriate visual field testing (perimetry) should be performed prior to initiation of treatment and periodically thereafter (approximately every 3 months).

If possible, these visual field examinations should consist of appropriate visual field testing (perimetry) by using standardised static perimetry (Humphrey or Octopus) or kinetic perimetry (Goldmann). Static perimetry is the preferred method for detecting vigabatrin associated visual field defect.

Several electroretinographic parameters appear to be correlated with vigabatrin associated visual field defect; therefore, electroretinography may be useful only in adults who are unable to cooperate with perimetry or in children less than 3 years of age. Based on the available data, the first oscillatory potential and 30 Hz flicker responses of the electroretinogram appear to be correlated with a vigabatrin associated visual field defect. These responses are delayed and reduced beyond the normal limits. Such changes have not been seen in vigabatrin treated patients without a visual field defect.

Monitoring in Pediatric Patients: In view of the difficulties of assessing visual fields in infants and young pediatric patients, Sabril should be used in these patient groups only if clearly indicated.

The need for continued use of Sabril should be reviewed at regular periodic assessments (approximately every 3 months). Frequent examinations by an ophthalmologist, if possible with pediatric subspecialization, are recommended for all infants and young children receiving Sabril.

Perimetry is seldom possible in children less than 9 years of developmental age. Currently, there is no established method to diagnose or exclude visual field defects in children in whom a standardised perimetry cannot be performed. To test the presence of peripheral vision in children aged 3 years and above, Visual Evoked Potentials (VEP) may be used. If the method reveals normal central visual field response but an absent peripheral response, benefit-risk of Sabril must be reviewed and consideration given to gradual discontinuation. The presence of peripheral vision does not exclude the possibility of a developing visual field defect.

Expert mydriatic peripheral fundus examination should also be performed at the same time points.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Pooled data from prevalence surveys suggest that about 1/3 of patients receiving Sabril therapy develop visual field defects.

Rare cases of bilateral optic disc pallor, subtle peripheral retinal atrophy, optic atrophy, and rare cases of optic neuritis have been reported in patients receiving Sabril (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions and Ophthalmologic).

In clinical studies in 4,079 Sabril patients with complex partial seizures, which includes the 438 Sabril treated patients in primary clinical studies described below, the most commonly observed reactions associated with the use of Sabril in combination with other AEDs were headache, somnolence, fatigue, dizziness, convulsion, nasopharyngitis, weight increased, upper respiratory tract infection, visual field defect, depression, tremor, nystagmus, nausea, diarrhea, memory impairment, insomnia, irritability, coordination abnormal, vision blurred, diplopia, vomiting, pyrexia, rash and constipation. The adverse events most commonly associated with discontinuation of Sabril treatment were convulsion and depression.

Sabril is generally well-tolerated in epileptic patients. Adverse events are mainly CNS-related and probably a secondary consequence of increased GABA levels caused by vigabatrin. The incidence of central nervous system related undesirable effects in controlled clinical studies in adults is generally higher at the beginning of treatment and decreases with time. The sedative effect of Sabril decreased with continuing treatment. The safety of Sabril was evaluated in 438 epileptic patients treated in double-blind, placebo-controlled clinical trials. The relationship of adverse events to Sabril therapy was not clearly established as such patients were taking other antiepileptic drugs concomitantly.

Most frequent adverse events (incidence higher than placebo): Fatigue, headache, drowsiness, dizziness, depression, weight increase, agitation, tremor, abnormal vision, amnesia including memory disturbance or forgetfulness.

Safety data is available in 299 children, aged 2 months to 16 years (1 patient was 18 years of age), participating in clinical trials with Sabril. Relationship of adverse events to Sabril therapy was not clearly established as children were taking other antiepileptic drugs concomitantly.

The most frequent adverse event observed in children was “hyperactivity” (reported as hyperkinesia 7.7%, agitation 2.3%, excitation 0.3% or restlessness 0.7%), which was observed in 11.0% of children, an incidence higher than that seen in adults. There have been post-marketing reports of visual field defects, optic disc pallor, optic atrophy, and optic neuritis in pediatric patients receiving Sabril treatment (see WARNINGS AND PRECAUTIONS). Other commonly reported adverse events were somnolence (8.0%) and weight gain (3.0%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of Sabril was evaluated in 438 adult epileptic patients, 299 children aged 2 months to 16 years (1 patient was 18 years of age), and 261 patients with infantile spasms, in clinical trials.

The following table provides a listing of all treatment emergent adverse events that were reported with an incidence of $\geq 2\%$ in double-blind, placebo-controlled trials of Sabril as add-on therapy

for the treatment of epilepsy in adults.

Table 1. Treatment Emergent Adverse Event Incidence (≥ 2%) of Adult Patients in Double-Blind, Placebo-Controlled, Add-On Clinical Trials

Body System Adverse Event	Placebo*		Sabril *	
	N = 320		N = 438	
	n	%	n	%
Body as a Whole				
weight increase	12	3.8	54	12.3
pain	21	6.6	33	7.5
asthenia	15	4.7	19	4.3
appetite increase	6	1.9	15	3.4
fever	7	2.2	14	3.2
chest pain	8	2.5	12	2.7
accident injury	14	4.4	12	2.7
Cardiovascular				
edema, dependent	2	0.6	13	3.0
Dermatologic				
rash	15	4.7	20	4.6
skin disorder	11	3.4	18	4.1
Gastrointestinal				
nausea	25	7.8	39	8.9
diarrhea	17	5.3	31	7.1
dyspepsia	22	6.9	27	6.2
abdominal pain	12	3.8	25	5.7
constipation	10	3.1	24	5.5
vomiting	15	4.7	24	5.5
tooth disorder	4	1.2	12	2.7
Hematologic				
Purpura	11	3.4	20	4.6
Musculoskeletal				
arthralgia	13	4.1	32	7.3
back pain	13	4.1	23	5.3
arthrosis	7	2.2	11	2.5
Nervous System				
fatigue	44	13.8	118	26.9
headache	79	24.7	113	25.8
drowsiness	46	14.4	97	22.1
dizziness	41	12.8	82	18.7
tremor	22	6.9	48	11.0
vision abnormal	18	5.6	47	10.7

Table 1. Treatment Emergent Adverse Event Incidence ($\geq 2\%$) of Adult Patients in Double-Blind, Placebo-Controlled, Add-On Clinical Trials

Body System Adverse Event	Placebo*		Sabril *	
	N = 320		N = 438	
	n	%	n	%
amnesia	12	3.8	45	10.3
nystagmus	15	4.7	42	9.6
diplopia	17	5.3	39	8.9
ataxia	14	4.4	35	8.0
confusion	7	2.2	30	6.8
paresthesia	6	1.9	25	5.7
coordination abnormal	7	2.2	22	5.0
seizures (not specified)	7	2.2	22	5.0
gait abnormal	10	3.1	20	4.6
concentration impaired	3	0.9	16	3.7
speech disorder	3	0.9	15	3.4
hypoesthesia	7	2.2	13	3.0
vertigo	4	1.2	13	3.0
hyporeflexia	1	0.3	12	2.7
Psychiatric				
depression	10	3.1	57	13.0
agitation	24	7.5	48	11.0
insomnia	19	5.9	29	6.6
anxiety	11	3.4	24	5.5
emotional lability	9	2.8	21	4.8
thinking abnormal	1	0.3	15	3.4
aggressive reaction	6	1.9	12	2.7
nervousness	7	2.2	12	2.7
personality disorder	3	0.9	9	2.1
Respiratory				
throat irritation	19	5.9	29	6.6
congestion	21	6.6	22	5.0
upper respiratory tract infection	10	3.1	21	4.8
sinusitis	6	1.9	10	2.3
coughing	14	4.4	9	2.1
Special Senses				
eye pain	1	0.3	11	2.5
earache	4	1.2	10	2.3
Urogenital				
dysmenorrhea	4	1.2	15	3.4
urinary tract infection	0	0	13	3.0
menstrual disorder	5	1.6	10	2.3

Table 1. Treatment Emergent Adverse Event Incidence ($\geq 2\%$) of Adult Patients in Double-Blind, Placebo-Controlled, Add-On Clinical Trials

Body System Adverse Event	Placebo*		Sabril *	
	N = 320		N = 438	
	n	%	n	%
Other				
infection viral	36	11.3	56	12.8

*Added on to patient's existing antiepilepsy drug therapy

The sedative effect of Sabril decreases with continuing treatment.

Other adverse reactions that have been reported less frequently include hypomania, mania, psychosis and suicide attempt.

Rare instances of marked sedation, stupor and confusion associated with non-specific slow wave activity on electroencephalogram have been described soon after the introduction of Sabril therapy. These reactions have been reversible following dose reduction or discontinuation of Sabril.

Rare reports of hypersensitivity reactions (including angioedema and urticaria) have been received.

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency, including status epilepticus, with Sabril treatment. Patients with myoclonic seizures may be particularly liable to this effect. New onset myoclonus and exacerbation of existing myoclonus may occur in rare cases (see WARNINGS AND PRECAUTIONS, Use in Patients with Myoclonic Seizures).

Laboratory data indicate that Sabril treatment does not lead to renal or hepatic toxicity. Decreases in ALT and AST, which are considered to be a result of inhibition of these aminotransferases by vigabatrin have been observed (see DRUG INTERACTIONS, Drug-Laboratory Interactions). Chronic treatment with Sabril may be associated with a slight decrease in hemoglobin, which rarely attains clinical significance.

Pediatric Safety:

The following adverse reactions were reported in children with a frequency greater than 1%:

Table 2. Adverse Events Reported By More Than 1% of Pediatric Patients

Body System/ Adverse Event	Number of Patients	Incidence (%) n=299
Nervous somnolence	24	8.0

Table 2. Adverse Events Reported By More Than 1% of Pediatric Patients

hyperkinesia	23	7.7
aggression	8	2.7
insomnia	8	2.7
agitation	7	2.3
ataxia	7	2.3
emotional lability	3	1.0
headache	3	1.0
increased seizures	3	1.0
Digestive		
vomiting	6	2.0
nausea	3	1.0
increased saliva	3	1.0
Body as a Whole		
weight gain	9	3.0
fatigue	8	2.7
hypotonia	3	1.0

In controlled studies of patients with Infantile Spasms (N=261), the most common adverse events in Sabril treated patients were as follows: upper respiratory tract infection, otitis media, pyrexia, viral infection, irritability, somnolence, sedation, vomiting, constipation, pneumonia, diarrhea, insomnia, ear infection, rash, nasal congestion, decreased appetite, sinusitis, bronchitis, lethargy, convulsion, status epilepticus, strabismus and conjunctivitis.

Common Clinical Trial Adverse Drug Reactions ($\geq 1\%$)

In clinical studies of Sabril, all adverse reactions were recorded by clinical investigators using terminology of their own choosing. The listing below does not include those events already listed above. The frequencies presented are the proportion of 4,079 patients who experienced an adverse event at a rate of at least 1/100 patients (considered to be “common” adverse events). Events are categorized by system organ class and listed in order of decreasing frequency.

Ear and labyrinth disorders: Vertigo, tinnitus

Gastrointestinal disorders: Abdominal pain upper, dyspepsia, stomach discomfort, abdominal pain, toothache, abdominal discomfort

General disorders and administration site conditions: Asthenia, gait disturbance, edema peripheral, chest pain

Infections and infestations: Urinary tract infection

Injury, poisoning and procedural complications: Contusion, joint sprain

Metabolism and nutrition disorders: Increased appetite

Musculoskeletal and connective tissue disorders: Back pain, arthralgia, pain in extremity, myalgia, shoulder pain, muscle spasms

Nervous system disorders: Lethargy, disturbance in attention, paraesthesia, hypohesias, dysarthria, postictal state

Psychiatric disorders: Confusional state, anxiety, abnormal behavior, expressive language disorder, nervousness

Respiratory, thoracic and mediastinal disorders: Pharyngolaryngeal pain, cough, sinus congestion

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported during post approval use of Sabril worldwide. All adverse reactions that are not listed above as adverse reactions 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. Adverse reactions are categorized by system organ class.

Congenital, familial and genetic disorders: 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 and labyrinth disorders: Deafness

Endocrine disorders: Delayed puberty

Gastrointestinal disorders: Gastrointestinal hemorrhage, esophagitis

General disorders and administration site conditions: Developmental delay, facial edema, malignant hyperthermia, multi-organ failure

Hepatobiliary disorders: Cholestasis

Nervous system disorders: Dystonia, dyskinesia, encephalopathy, hypertonia, hypotonia, intramyelinic edema, muscle spasticity, myoclonus, optic neuritis

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

Respiratory, thoracic and mediastinal disorders: Laryngeal edema, pulmonary embolism, respiratory failure, stridor

Skin and subcutaneous tissue disorders: Angioedema, maculo-papular rash, pruritus, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), alopecia

DRUG INTERACTIONS

Overview

During concurrent vigabatrin administration, a decrease in phenytoin levels has been reported in some trials but not in others. In those controlled trials in which phenytoin levels decreased, mean decreases varied between 16% and 33%.

When co-administered with vigabatrin, phenobarbital concentration (from phenobarbital or primidone) was reduced by an average of 8% to 21%, 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.

As vigabatrin is neither metabolised, nor protein bound and is not shown to be a strong inducer of hepatic cytochrome P450 drug metabolising-enzymes, interactions with other drugs are unlikely.

Drug-Drug Interactions

Table 3. Established or Potential Drug-Drug Interactions

Proper Name	Reference	Effect	Clinical Comment
Phenytoin	CT	↓ total phenytoin plasma concentrations (16%-33%) average reduction.	Likely due to induction of CYP 450 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	CT	↓ phenobarbital concentration (from phenobarbital or primidone) by average of 8% to 21%	Not clinically relevant

		<p>↓ Sodium valproate plasma concentration by average of 8%</p> <p>Carbamazepine, clonazepam, primidone, sodium valproate have no effect on plasma concentrations of vigabatrin.</p>	<p>Not clinically relevant</p> <p>Based on population PK</p>
Clonazepam	CT	<p>Clonazepam 0.5 mg had no pharmacokinetic effect on vigabatrin (1.5 g twice daily). Sabril increases the mean C_{max} of clonazepam by 29% and decreases the mean T_{max} by 44%.</p>	Neither drug influences the other
Alcohol	CT	<p>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.</p>	Neither drug influences the other
Oral Contraceptives	CT	<p>In a double-blind, placebo-controlled study using a combination oral contraceptive containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel, vigabatrin (3 g/day) did not interfere significantly with the cytochrome P450 isoenzyme (CYP3A)-mediated metabolism of the contraceptive tested. 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.</p>	Vigabatrin is unlikely to affect the efficacy of steroid oral contraceptives

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

Food did not have a significant effect on vigabatrin absorption (C_{max} decreased by 33% and AUC decreased by 8%) and therefore vigabatrin can be given without regard to meals.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Possibility of unreliable liver enzyme laboratory tests

Vigabatrin decreases alanine transaminase (ALT) and aspartate transaminase (AST) plasma activity in up to 90% of patients. The magnitude of suppression for ALT has been reported to vary between 30% and 100%, while the magnitude of AST suppression ranged from 0-60%. In some patients, these enzymes become undetectable. This suppression of ALT and AST activity may preclude the use of these markers, especially ALT, to detect early hepatic injury. The effect appears to represent a chemical interference with the assay and not a direct effect on the liver. Therefore, these liver tests may be quantitatively unreliable in patients taking vigabatrin. Gamma-glutamyl transpeptidase (GGT) activity is not affected by vigabatrin.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

- All patients should have ophthalmological consultation with visual field examination before initiation of Sabril treatment and every 3 months thereafter (see WARNINGS AND PRECAUTIONS, Ophthalmologic and Monitoring and Laboratory Tests).
- Monitoring of Sabril plasma concentrations to optimize therapy is not helpful (see ACTION AND CLINICAL PHARMACOLOGY, Excretion).
- If the control of epilepsy is not clinically significantly improved after an adequate dose titration and maintenance period, Sabril should be gradually withdrawn under close medical supervision (see WARNINGS AND PRECAUTIONS, Ophthalmologic and DOSAGE AND ADMINISTRATION, Withdrawal).
- Abrupt discontinuation should be avoided, as there is evidence suggesting occurrence of withdrawal seizures in some epileptic patients. If Sabril has to be discontinued it is recommended that this be done gradually by reducing the dose over a 2-4 week period if possible (see WARNINGS AND PRECAUTIONS, Withdrawal of Antiepileptic Drugs (AEDs)).
- If new movement disorders occur during treatment with Sabril, consideration should be given to dose reduction or a gradual discontinuation of treatment (see WARNINGS AND PRECAUTIONS, Magnetic Resonance Imaging (MRI) Abnormalities).
- Treatment in psychiatric patients should be initiated cautiously at low doses and with frequent monitoring (see WARNINGS AND PRECAUTIONS, Psychiatric).
- Risk factors for the development of encephalopathic symptoms include higher than recommended starting dose, faster dose escalation at higher steps than recommended and renal failure. These events have been reversible following dose reduction or discontinuation of Sabril (see WARNINGS AND PRECAUTIONS, Psychiatric).

- Elderly patients and patients with impaired renal function require dose adjustment (see WARNINGS AND PRECAUTIONS, Geriatrics and DOSAGE AND ADMINISTRATION, Elderly and Renally Impaired Patients).
- Dose adjustment of phenytoin or any other concomitant AED should be considered if clinically indicated (see DRUG INTERACTIONS, Overview and Drug-Drug Interactions).
- The Sabril dosing regimen depends on the indication, age group, weight, and dosage form (tablets or powder for oral solution) (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).
- A single Sabril tablet and powder sachet for oral solution contains equivalent doses. Powder for oral solution should be used for IS; tablets should not be used for IS because of difficulty in the administration of tablets to infants and young children (see ACTION AND CLINICAL PHARMACOLOGY, Distribution).
- Sabril powder for oral solution should be mixed with water, fruit juice, milk or infant formula prior to administration (see DOSAGE AND ADMINISTRATION, Reconstitution).
- If using Sabril powder for oral solution, physicians should review and discuss the instructions for mixing and giving Sabril with the patient or caregiver(s) (see DOSAGE AND ADMINISTRATION, Reconstitution).

Recommended Dose and Dosage Adjustment

Adults: Sabril 500 mg tablets should be given orally once or twice daily and may be taken with or without food. Sabril should be added to the patient’s current antiepileptic therapy. The recommended starting dose is 1 g/day, although patients with severe seizure manifestations may require a starting dose of up to 2 g/day. The daily dose may be increased or decreased in increments of 0.5 g depending on clinical response and tolerability. The optimal dose range is between 2 - 3 g/day. Increasing the dose beyond 3 g/day does not usually result in improved efficacy and may increase the occurrence of adverse reactions. The highest recommended dose is 3 g/day.

Children (2-16 years of age): The recommended starting dose in children (2-16 years of age) is 40 mg/kg/day. The maximum recommended dose in each of the categories should not be exceeded. For maintenance dosing the recommended doses are specified in the following table:

Table 4. Maintenance Dosing in Children

Body Weight	Daily Dose
10-15 kg	0.5 - 1 g/day
16-30 kg	1 - 1.5 g/day
31-50 kg	1.5 - 3 g/day
> 50 kg	2 - 3 g/day

Infants (Treatment of Infantile Spasms): The recommended dose for the management of infantile spasms (West Syndrome) is between 50-100 mg/kg/day, depending on the severity of the spasms. This dose may be titrated over a period of one week if necessary. Doses of up to 150 mg/kg/day have been used with good tolerability.

Sabril should be given orally as divided doses (twice daily) with or without food. The initial dosing is 50 mg/kg/day (1 mL/kg/day) given in two divided doses and can be titrated by 25-50 mg/kg increments every 3 days up to a maximum of 150 mg/kg/day (reconstitution instructions are provided below).

Table 5 provides the volume that should be administered as individual doses in infants of various weights:

Table 5. Infant Dosing Table

Weight (kg)	Starting Dose 50 mg/kg/day	Maximum Dose 150 mg/kg/day
3	1.5 mL twice daily	4.5 mL twice daily
4	2 mL twice daily	6 mL twice daily
5	2.5 mL twice daily	7.5 mL twice daily
6	3 mL twice daily	9 mL twice daily
7	3.5 mL twice daily	10.5 mL twice daily
8	4 mL twice daily	12 mL twice daily
9	4.5 mL twice daily	13.5 mL twice daily
10	5 mL twice daily	15 mL twice daily
11	5.5 mL twice daily	16.5 mL twice daily
12	6 mL twice daily	18 mL twice daily
13	6.5 mL twice daily	19.5 mL twice daily
14	7 mL twice daily	21 mL twice daily
15	7.5 mL twice daily	22.5 mL twice daily
16	8 mL twice daily	24 mL twice daily

Elderly and Renally Impaired Patients: Vigabatrin is almost exclusively eliminated via the kidney and, therefore, caution should be exercised when administering the drug to the elderly, and more particularly to patients with creatinine clearance less than 50 mL/min. It is recommended that such patients be started on a lower dose of Sabril and observed closely for adverse events such as sedation and confusion (see WARNINGS AND PRECAUTIONS, Renal; Geriatrics and ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

The following dose adjustments are pertinent to the possible use of Sabril in pediatric patients 2 years and older and adult patients with renal impairment:

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

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

- Patients 2 to <12 years old:

$$\text{CLcr (mL/min/1.73 m}^2\text{)} = (\text{K} \times \text{Ht})/\text{Scr}$$

Height (Ht) in cm; serum creatinine (Scr) in mg/dL

K (proportionality constant): Female Child (<12 years): K=0.55; Male Child (<12 years): K=0.70

- Pediatric patients 12 years or older and adult patients:

$$\text{CLcr (mL/min)} = [140 - \text{age (years)}] \times \text{weight (kg)} / [72 \times \text{serum creatinine (mg/dL)}] (\times 0.85 \text{ for female patients})$$

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

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

Withdrawal

If a patient is to be withdrawn from Sabril treatment, it is recommended that this be done gradually by reducing dose over a 2-4 week period if possible. In controlled clinical studies in adults with CPS and pediatric patients with IS, Sabril was discontinued by gradual reduction of the daily dose of 1 g/day once a week in adults, and of 25-50 mg/kg/day every 3-4 days in infants.

Missed Dose

If a dose of Sabril is missed, it should be taken as soon as possible. However, if the next dose should be taken soon, then patients should take the next dose and skip the missed dose, then continue dosing as instructed.

Administration

Tablets: Sabril 500 mg tablets should be given orally once or twice daily and may be taken with or without food.

Oral Solution: The total daily dose should be divided and administered on a twice daily basis and may be taken with or without food.

Sabril powder for oral solution should be mixed with water, fruit juice, milk or infant formula prior to administration.

Physicians should review and discuss the instructions for mixing and giving Sabril with the patient or caregiver(s). Physicians should confirm that patients or caregiver(s) understand how to reconstitute Sabril powder and administer the correct daily dose.

Reconstitute per the instructions below. The concentration of the final solution is 50 mg/mL.

Administer the resulting solution using the oral syringe supplied with the medication. Discard the resulting solution if it is not clear (or free of particles) and colorless. Each individual dose should be prepared and used immediately. Discard any unused portion of the solution after administering the correct dose.

Reconstitution

Oral Solution: The entire contents of the appropriate number of sachets (500 mg/sachet) of powder should be emptied into an empty glass, and should be dissolved in 10 mL of cold or room temperature water, fruit juice, milk or infant formula *per sachet* using the 10 mL oral syringe supplied with the medication. The concentration of the final solution is 50 mg/mL. Table 6 below describes how many sachets and how many mL of liquid will be needed to prepare each individual dose.

Table 6. Number of Sachets and mL of Liquid used for Each Individual Dose

Each Individual Dose (Prepared and Given Twice Daily)	Number of Sachets	Number of mL of Liquid for Dissolving
0 to 500 mg	1 sachet	10 mL
501 to 1000 mg	2 sachets	20 mL
1001 to 1500 mg	3 sachets	30 mL

Each individual dose should be prepared immediately before use and administered cold or at room temperature. Discard any unused portion of the solution after administration.

Instructions to the patient on the use of Sabril are provided in the PATIENT MEDICATION INFORMATION section.

OVERDOSAGE

Confirmed and/or suspected Sabril overdoses have been reported during clinical trials and in post marketing surveillance. No reported Sabril overdoses resulted in death. When reported, the Sabril dose ingested ranged from 3 g to 90 g, but most were between 7.5 g and 30 g. Nearly half of 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 Sabril overdose. Less frequently reported symptoms included vertigo, headache, psychosis, respiratory

depression or apnea, bradycardia, hypotension, agitation, irritability, confusion, abnormal behaviour, speech disorder, increased seizure activity, and status epilepticus. These symptoms resolved with supportive care.

There is no specific antidote for vigabatrin 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 patient.

Activated charcoal has not been shown to significantly adsorb vigabatrin in an *in vitro* study. The effectiveness of hemodialysis in the treatment of vigabatrin 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%.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is believed to be the result of its potent action as a selective and irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the catabolism of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the brain. 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 effect of vigabatrin is thought to be dependent on the rate of GABA-T re-synthesis rather than on the rate of elimination of the drug from the systemic circulation.

Pharmacodynamics

Concentration Associated with Therapeutic and/or Toxic Effects: Time to maximum concentration (T_{max}) was approximately 1 hour and maximum plasma concentration (C_{max}) ranged from 28.8 to 46.3 mcg/mL for a single 1 g dose. During multiple dosing of 2 g twice daily, steady-state C_{max} and T_{max} were 74.8 mcg/mL and 1 hour respectively. There was little accumulation with multiple dosing. Oral administration of vigabatrin resulted in a linear increase in the suboccipital CSF concentration of vigabatrin at 1.5 g to 4.5 g doses.

Pharmacokinetics

Absorption: Vigabatrin is rapidly absorbed following oral administration and peak plasma concentrations are reached within two hours. Administration of vigabatrin with food slightly reduces the rate, but not the extent of absorption. 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% while AUC remained unchanged under fed conditions.

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%). Cerebrospinal fluid (CSF) vigabatrin concentrations represent approximately 10% of the corresponding blood concentrations. Bioequivalence has been established between the oral solution and tablet formulations. 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 g twice daily.

Metabolism: Vigabatrin is not significantly metabolized; it is eliminated primarily through renal excretion.

Excretion: The half-life of vigabatrin is about 7.5 hours; however, serum concentrations are not correlated with clinical effect. Vigabatrin is thus excreted essentially unchanged in humans. 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.

Special Populations and Conditions

Pediatrics: Pharmacokinetics of the R(-) and S(+) enantiomers of vigabatrin in infants and children after administration of single and multiple doses of 50 mg/kg vigabatrin demonstrated little pharmacokinetic difference between infants (5 months - 2 years) and children (4 - 14 years). For the active S(+) isomer, AUC values for infants and children in this study were 90.0 hr•mcg/mL and 117.0 hr•mcg/mL, respectively; the half-life values were 5.65 hours and 5.47 hours, respectively. The pediatric population had a shorter elimination half-life and a larger apparent volume of distribution than observed in adults.

Geriatrics (≥65 years of age): The renal clearance of vigabatrin in healthy elderly patients (≥ 65 years of age) was 36% less than those in healthy young patients. This finding is confirmed by population PK analysis of patient data from a U.S. controlled clinical trial. Oral administration of a single dose of 1.5 g of vigabatrin to elderly (≥ 65 years of age) patients with reduced creatinine clearance (50mL/min) was associated with moderate to severe sedation and confusion in 4 of 5 patients, lasting up to 5 days (see DOSAGE AND ADMINISTRATION, Elderly and Renally Impaired Patients).

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

Race: A cross study comparison between 23 Caucasian and 7 Japanese patients who received

1 g, 2 g, and 4 g of vigabatrin indicated that the AUC, C_{max}, and half-life were similar for the two populations, but the mean renal clearance of Caucasian patients was 25% higher than that of Japanese patients.

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

Renal Insufficiency: Vigabatrin is eliminated via the kidney and caution should be exercised in patients with a creatinine clearance of less than or equal to 50 mL/min.

Mean AUC values increased by 30% and terminal half-life values increased by 55% (8.1 hr vs 12.5 hr) in patients with mild renal impairment (CL_{cr} 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 adult patients with moderate renal impairment (CL_{cr} 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 adult patients with severe renal impairment (CL_{cr} from >10-30 mL/min) in comparison to normal subjects.

Dosage adjustment, including starting at a lower dose, is recommended for adult patients with any degree of renal impairment (see DOSAGE AND ADMINISTRATION, Elderly and Renally Impaired Patients).

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

STORAGE AND STABILITY

Store at controlled room temperature 15°C to 30°C. Protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

None

DOSAGE FORMS, COMPOSITION AND PACKAGING

For oral use.

Available under brand name of SABRIL:

Tablets: Each Sabril 500 mg tablet is white to off-white film-coated, oval biconvex, and imprinted “SABRIL” on one side. Sabril is available in blister strips of 10 tablets in cartons containing 10 strips (100 tablets), and in HDPE bottles containing 100 tablets.

Non-medicinal ingredients: Hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate and titanium dioxide.

Sachets: Sachets containing 500 mg vigabatrin as a white to off-white granular powder. Sachets are available in cartons of 50.

Non-medicinal ingredients: povidone.

Both the tablets and the sachets are lactose free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

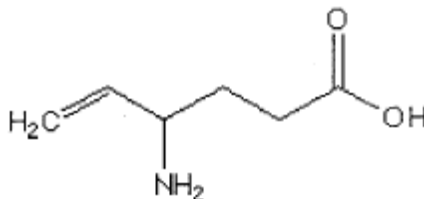
Drug Substance

Proper Name: vigabatrin

Chemical Name: (±) 4-amino-5-hexenoic acid

Molecular Formula and Molecular Mass: C₆H₁₁NO₂ and 129.16, respectively

Structural Formula:



Physicochemical Properties: White to off-white, powder which melts with decomposition in the range of 171°C-176°C. The pH of a 1% aqueous solution is 6.9. The pK value is 4 and the pK₂ value is 9.7 at room temperature (25°C). Vigabatrin is freely soluble in water, slightly soluble in methanol, very slightly soluble in ethanol and chloroform, and insoluble in hexane and toluene.

CLINICAL TRIALS

In clinical trials, including double-blind, placebo-controlled studies involving 354 patients with drug-resistant complex partial seizures, Sabril (vigabatrin) reduced seizure frequency by 50% or more in approximately half of the patients studied. The efficacy of Sabril in children with refractory partial seizures was similar to that seen in adult patients.

A multicentre, double-blind, placebo-controlled, parallel group study was performed to evaluate the safety and efficacy of Sabril versus placebo as first line monotherapy in the treatment of newly diagnosed infantile spasms. The study involved a 2-3 day baseline period, a 5 day double-blind treatment phase, and a six month open-label follow-up. Complete cessation of spasms on the final day of double-blind treatment was achieved by 45% of Sabril patients (N=20) and by 15% of placebo patients (N=20). According to the Clinical Global Impression of Improvement, 80% of Sabril patients and 15% of placebo patients were considered to be moderately or markedly improved. These differences between the treatment groups were statistically significant. In the 6 month open-label extension of this study, 51% of patients

(N=35) could be maintained on Sabril monotherapy, while 49% required the addition of other antiepileptic drugs.

In a retrospective analysis of 192 infants diagnosed with infantile spasms who had been treated with Sabril as first-line monotherapy (mean steady state dose of 99 mg/kg/day), 162 patients (84%) experienced an initial decrease in spasm frequency of at least 50% with 131 patients (68%) experiencing a complete resolution of spasms. Demographic factors which seemed to be predictive of a positive response to Sabril included an etiology of tuberous sclerosis and an age of onset of illness of less than 3 months. According to long-term (mean 9.2 months) follow-up data for this retrospective study, 42% of the 192 patients could be successfully maintained on Sabril monotherapy, while the remainder required additional antiepileptic treatments. Of the 131 patients who were considered to be complete responders, 85 (65%) experienced neither relapse of infantile spasms nor onset of other seizure types during long-term follow-up.

DETAILED PHARMACOLOGY

Pharmacodynamics

Effects on Electrocardiogram: There was no indication of a QT/QTc prolonging effect of vigabatrin in a single dose study up to 6 g. In a randomized, placebo-controlled, cross-over study, 58 healthy subjects were administered a single oral dose of vigabatrin (3 g and 6 g) and placebo. Peak concentrations for 6 g vigabatrin were approximately 2-fold higher than the peak concentrations following the 3 g single oral dose.

Pharmacokinetics

Vigabatrin displayed linear pharmacokinetics after administration of single doses ranging from 0.5 g to 4 g, and after administration of repeated doses of 0.5 g to 2 g twice daily.

TOXICOLOGY

Acute Toxicity

The acute toxicity of vigabatrin has been investigated in the rat and mouse. The LD₅₀ values are:

Species	Route	LD ₅₀ (mg/kg)
mouse	Oral	2830
	i.p.	1098
rat	Oral	3100
	i.p.	1473

Chronic Toxicity

Vacuolization: Safety studies carried out in the rat, mouse and dog at doses of 30 to 50 mg/kg/day and higher, caused dose- and time-dependent vacuolation within certain white matter tracts of the brain (the cerebellum, reticular formation and thalamus in rodents and the columns of the fornix and optic tracts in dogs were most affected). The vacuolation was caused by the separation of the outer lamellar sheath of myelinated fibres, a change characteristic of non-inflammatory intramyelinic edema (IME). The lesion was seen in animals at doses within the human therapeutic range. A no-effect dose was not established in rodents or dogs. In both the rat and dog (mouse was not tested), the intramyelinic edema was reversible after stopping the administration of vigabatrin; however, in the rat, residual changes consisting of swollen axons and mineralised microbodies were observed. Vacuolization in adult animals was correlated with alterations in MRI and changes in visual and somatosensory evoked potentials.

In the dog, studies indicate that intramyelinic edema is associated with increased latencies in somatosensory and visual evoked potentials. Magnetic resonance imaging (MRI) changes also correlated with intramyelinic edema in the fornix, thalamus and hypothalamus.

In animal reproductive studies, neurohistopathology was not performed on the fetuses; therefore, it is not known whether vacuolation occurred *in utero*. The possibility that vacuolation or other neurotoxicity may occur in human fetuses cannot be disregarded. The relevance of these data for humans is unknown.

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, and evidence of oligodendrocyte injury were additional findings in the brains of vigabatrin-treated rats. An increase in apoptosis was seen in some brain regions following vigabatrin exposure during the early postnatal period. Long-term retinal dysplasia, and neurobehavioural 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.

Administration of vigabatrin to dogs during juvenile periods of development caused vacuolar changes in the neuropil of the septal nuclei, hippocampus, hypothalamus, thalamus, cerebellum and globus pallidus. Neurobehavioural abnormalities were not assessed in this study.

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.

In monkeys, the oral administration of 300 mg/kg/day for 16 months produced minimal vacuolation with equivocal differences between treated and control animals. Low oral absorption

of vigabatrin in the monkey resulted in an actual absorbed dose of 75 mg/kg/day. In spite of the poor absorption, cerebrospinal fluid (CSF) levels of vigabatrin in the monkeys were comparable to those seen in rats treated with 300 mg/kg/day; however, GABA levels in the CSF and the brain cortex in treated monkeys were not significantly different from untreated monkeys. This finding may explain the reason for the equivocal effects, since the intramyelinic edema associated with vigabatrin treatment appears to be related to increased brain GABA levels.

Residual Histologic Effects in the Brain: Residual effects, namely swollen axons and microscopic mineralized bodies, were observed in the brains of rats at doses of 50 mg/kg/day and above, and in mice at doses of 100 mg/kg/day and above. No residual effects were observed in dogs, despite the fact that the severity of the intramyelinic edema was greater in this species and that the concentration of vigabatrin in the CSF was much higher.

Convulsions: Convulsions were observed only in rats and mice at doses of ≥ 50 mg/kg/day and ≥ 100 mg/kg/day, respectively.

Other Effects: In rats, reduced body weight gain at high doses (300 mg/kg/day) and alopecia were also observed. Retinal changes characterized by focal, multifocal and occasionally diffuse disorganisation of the outer nuclear layer have been observed in albino rats treated with vigabatrin. However, similar changes have not been observed in any pigmented species, including pigmented rats. The observed lesion is similar to that seen in albino rats exposed to excessive light.

A number of investigative studies have been carried out to further characterize the toxic effects associated with vigabatrin. In one of these studies, it was shown that in the dog, after about 5-8 weeks of treatment with vigabatrin (300 mg/kg/day), there was an increase in the latency of somatosensory and visual evoked potentials, which correlated with the presence of intramyelinic edema in the dog brain. As with the pathological change, the latency increase reversed when vigabatrin administration was stopped. Studies using magnetic resonance imaging (MRI) have shown that this technique can also be used to monitor the occurrence and the disappearance of intramyelinic edema. In the dog, MRI correlated with intramyelinic edema in the fornix, thalamus and hypothalamus. In the rat, high doses of vigabatrin led to changes in the nature of brain soluble proteins which could be detected in the CSF. Studies in man have indicated that there are no increases in the latency of evoked potentials and no changes in MRI or brain soluble proteins following vigabatrin administration.

Reproduction and Teratology

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.

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 embryoletality 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/m²) 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/m² 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 neurobehavioural (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/m² basis.

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

Mutagenesis

Vigabatrin was not mutagenic in the *in vitro* Ames assay in Salmonella or the CHO/HGPRT mammalian cell forward gene mutation assay. It was not clastogenic in the *in vitro* chromosomal aberration assay in rat lymphocytes or the *in vivo* mouse bone marrow micronucleus assay.

Carcinogenesis

Vigabatrin showed no carcinogenic potential when given in the diet of the CD₁ mouse at doses up to 150 mg/kg/day for 18 months or to the Long-Evans rat at doses up to 150 mg/kg/day for 2 years (approximately 1/4 and 1/2 of the maximum recommended human daily dose of 3 grams on a mg/m² basis, respectively).

Impairment of Fertility

Reproduction and fertility studies using doses up to 150 mg/kg/day, which correspond to approximately 1/2 of the maximum recommended human daily dose on a mg/m² basis, have shown no effect on male or female fertility in rats.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

SABRIL® (vigabatrin)

Read this carefully before you or your child start taking Sabril and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Sabril.

Serious Warnings and Precautions

- Sabril can damage the vision of anyone who takes it.
- Sabril can result in a loss of peripheral vision (narrowing your vision) which may lead to permanent damage to eyesight.
- Before starting treatment with Sabril, you should discuss with your healthcare professional the potential benefits of this medicine versus the risk of damage to your vision.
- You/your child should have your eyes examined before beginning treatment with Sabril and at regular intervals (approximately every 3 months) thereafter.
- Tell your healthcare professional immediately about any change in your/your child's eyesight such as narrowing of your vision, blurred vision or any other visual symptoms.

What is Sabril used for?

Sabril belongs to the family of medicines called antiepileptic drugs and is used to treat:

- Partial epilepsies in combination with other anti-epileptic drugs when other antiepilepsy drug combinations have not worked
- Infantile spasms (West Syndrome)

Sabril should be used under close monitoring by a neurologist and an ophthalmologist.

How does Sabril work?

Sabril helps to control electrical activity in the brain. This reduces the chances of having seizures.

What are the ingredients in Sabril?

Medicinal ingredients: Vigabatrin

Non-medicinal ingredients (Tablets): Hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate and titanium dioxide.

Non-medicinal ingredients (Powder for Oral Solution (sachets)): Povidone.

Both the tablets and the sachets are lactose free.

Sabril comes in the following dosage forms:

Sabril Tablets, 500 mg

Sabril Powder for Oral Solution (sachets), 500 mg

Do not use Sabril if:

- You/your child are allergic to vigabatrin or any other ingredients of Sabril.
- You are pregnant or plan to become pregnant.
- You are breast-feeding or planning to breastfeed.

If you become pregnant while taking Sabril, talk to your healthcare professional 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. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>

To help avoid side effects and ensure proper use, talk to your healthcare professional before you/your child take Sabril. Talk about any health conditions or problems you/your child may have, including if you/your child:

- Experience swelling
- Have a history of drug abuse
- Have ever had a rash or unusual reaction while taking vigabatrin or any other antiepileptic drug
- Have been told you have anemia (low red blood cell counts)
- Need Magnetic Resonance Imaging (MRI)
- Have a movement disorder. Movement disorders have been reported in patients treated with Sabril for infantile spasms
- Have symptoms of numbness or tingling or loss of feeling in the toes or feet
- Suffer from myoclonic seizures. Sabril may cause an increase in the number of seizures or cause new seizure types especially in people who have myoclonic seizures
- Have any eye or vision problems. Sabril can damage the vision of anyone who takes it
- Have had any mental illnesses in the past. Sabril may cause you to feel agitated, aggressive, depressed, paranoid or think abnormally
- Have ever tried or thought about committing suicide or if you or your child have or had depression, mood problems or suicidal thoughts or behaviour in the past
- Have, or have ever had any kidney problems
- Are 65 years of age or older

Other warnings you should know about:

- **Serious skin reactions (Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)):** Ask your healthcare professional about signs and symptoms of life threatening skin reactions such as Stevens-Johnson Syndrome (SJS; a skin reaction with rash and blisters) and Toxic Epidermal Necrolysis (TEN; a skin rash often with blisters, lesions and lifting skin) that have been reported when Sabril is taken in addition to other antiepileptic

drugs known to cause SJS and TEN. Closely monitor for skin reactions, if symptoms or signs of SJS or TEN are present, Sabril treatment should be stopped. The best results in managing SJS and TEN come from early detection and stopping the drug treatment right away (see table of **Serious Side Effects and What to do About Them**, below).

- **Driving and using machines:** Before driving, operating complex machinery or performing other activities that require mental alertness or physical coordination, wait until you know how you or your child respond to Sabril. Treatment with Sabril can cause you/your child to feel drowsy or tired and affect your ability to perform these activities.
- **Weight gain:** Treatment with Sabril causes weight gain.
- **Do not suddenly stop taking Sabril.** Always follow your healthcare professional's instructions. Stopping this drug quickly may lead to an increase in seizure activity or rebound seizures.

DURING treatment with Sabril, tell your healthcare professional if you/your child develops:

- Thoughts of suicide or self-harm
- Abnormal vision (narrowing of your vision, blurry or double vision)

Tell your healthcare professional about all the medicines you/your child take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Sabril:

- Phenytoin. When Sabril is given with phenytoin, the levels of phenytoin may decrease.

How to take Sabril:

It is important that you take Sabril exactly as your healthcare professional has instructed. Your healthcare professional will start with a low dose and slowly increase the dose to the lowest amount needed to control your/your child's epilepsy.

Sabril tablets and powder for oral solution (sachets) may be taken with or without food.

Do not suddenly stop taking your medicine. Discontinuation of your medicine should be done gradually over a few weeks and only in consultation with your healthcare professional. Always check that you have enough medicine and do not run out.

Usual dose:

Adults: The usual maintenance dose in adults is between 2 to 3 g/day divided into 2 doses.

Children (2-16 years of age): The dose is based on weight and the maintenance dose is approximately 50 mg/kg/day.

Infants: The dose is based on weight and the recommended dose for the management of Infantile Spasms is between 50-100 mg/kg/day.

Elderly and Patients with Renal Impairment: These patients should be started on a lower dose.

It is important to follow your healthcare professional's instructions exactly. Never change the

dose yourself.

Your healthcare professional will have told you how much medicine to take or give to your child. Each dose should be made up just before it is used.

If you are using powder for oral solution (sachets):

1. Open the number of sachets your healthcare professional told you to use.
2. Empty the entire contents into an empty glass.
3. Using an oral syringe measure 10 mL of liquid for each sachet used and add it to the powder. You may use cold or room temperature water, fruit juice, milk or infant formula as the liquid. Mix the liquid and the powder until the powder has dissolved completely.

Number of Sachets	Number of mL of Liquid for Dissolving
1 sachet	10 mL
2 sachets	20 mL
3 sachets	30 mL

4. Using the oral syringe, measure the exact volume of dissolved medicine your healthcare professional told you to use.
5. Take or give to your child the measured volume of dissolved medicine immediately.
6. Throw away any unused dissolved medicine immediately; do not save this medicine for the next dose.

Overdose:

If you think you have taken too much Sabril, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you/your child forget to take a dose, take it as soon as you remember, and then go on as usual. However, if it is almost time for your next dose, skip the forgotten dose, and go on as usual.

What are possible side effects from using Sabril?

These are not all the possible side effects you may feel when taking Sabril. If you or your child experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The most common side effects associated with the use of Sabril are:

- Headache
- Sleepiness/drowsiness, fatigue, trouble sleeping
- Common cold, sore throat
- Weight gain

- Nausea/vomiting, diarrhea, constipation, indigestion
- Joint pain
- Rash

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
VERY COMMON Hyperactivity in children		√	
COMMON Vision problems (symptoms like blurred vision, double vision, narrowing your vision, any other vision changes)		√	
Breathing problems, cough	√		
Seizures		√	
Anemia (symptoms like fatigue, loss of energy, weakness, shortness of breath)		√	
Edema (symptoms like swelling of your legs, ankles and/or feet)		√	
Nervous system problems (symptoms like abnormal movements, memory problems, abnormal eye movements, confusion, dizziness, trouble walking or with coordination, tremor (shakiness), trouble talking, dizziness along with the feeling of a spinning movement)		√	
Nerve problems (symptoms like numbness and tingling in the feet and toes, loss of feeling)		√	
Psychiatric disorders (symptoms like depression, irritability, agitation, mood swings, restlessness, anxiety, aggressiveness, nervousness, delusions, changes in thinking, personality changes)		√	
Fever		√	
UNCOMMON Thoughts of suicide or self-harm			√

RARE Severe allergic reactions (symptoms like swelling of face, eyes, lips, or tongue, trouble swallowing or breathing, skin rash)			√
Brain disease, including swelling in the brain (symptoms like excessive sleepiness, unconsciousness and confusion)		√	
VERY RARE Serious Skin Reactions (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis): Any combination of itchy skin rash, redness, blistering and peeling of the skin and/or of the lips, eyes, mouth, nasal passages, or genitals. You may also get fever, sore throat, fatigue, chills, headache, cough, body aches or joint pain.			√

If you or your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p>Reporting Side Effects</p> <p>You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.</p> <p>3 ways to report:</p> <ul style="list-style-type: none"> • Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php); • By calling 1-866-234-2345 (toll-free); • By completing a Consumer Side Effect Reporting Form and sending it by: <ul style="list-style-type: none"> - Fax to 1-866-678-6789 (toll-free), or - Mail to: Canada Vigilance Program Health Canada, Postal Locator 0701E Ottawa, ON K1A 0K9 <p>Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).</p> <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>

Storage:

Leave your tablets and sachets in their original packaging and keep them in a safe place.

Store at controlled room temperature (15°C-30°C). Protect from moisture.

If your healthcare professional decides to stop your treatment, return any leftover medicine to your pharmacist. Only keep it if your healthcare professional tells you to do so.

Keep out of reach and sight of children.

If you want more information about Sabril:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the manufacturer's website www.lundbeckus.com, or by calling Lundbeck, at: 1-800-586-2325.

This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

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