PRODUCT MONOGRAPH

PrSABRIL®
(vigabatrin)

Tablets, 500 mg

Sachets, 0.5 g

Antiepileptic

AVENTIS PHARMA INC.
2150 St. Elzear Blvd. West
Laval, Quebec H7L 4A8

Version Date:
April 27, 2001

Control No. 066844

Aventis Version 2.0

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ACTION AND CLINICAL PHARMACOLOGY

SABRIL (vigabatrin) is an 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. The mechanism of action of vigabatrin is attributed to irreversible enzyme inhibition of GABA-T, and consequent increased levels of the inhibitory neurotransmitter, GABA.

Decreased serum levels of SGOT (AST) and SGPT (ALT) have been observed during treatment with vigabatrin and may be the result of inhibition of these transaminases by vigabatrin. The clinical significance of these findings is unknown.

The duration of effect of vigabatrin is thought to be dependent on the rate of GABA-T resynthesis rather than on the plasma concentration of vigabatrin.

Clinical Trials

In clinical trials, including double-blind, placebo-controlled studies involving 354 patients with drug-resistant complex partial seizures, vigabatrin reduced seizure frequency by 50% or more in approximately half of the patients studied. The efficacy of vigabatrin 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 vigabatrin 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 vigabatrin patients (N=20) and by 15% of placebo patients (N=20). According to the Clinical Global Impression of Improvement, 80% of vigabatrin 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 vigabatrin 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 vigabatrin 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 vigabatrin 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 vigabatrin 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.

Pharmacokinetics

Vigabatrin is rapidly absorbed following oral administration and peak plasma concentrations are reached within two hours. Vigabatrin is widely distributed with an apparent volume of distribution slightly greater than total body water. The primary route of elimination is via the kidney, with little metabolic transformation occurring. Following a single dose, approximately 70% is excreted in the urine as unchanged drug within the first 24 hours post-dose. The plasma elimination half-life is approximately 5-8 hours in young adults and 12-13 hours in the elderly. In renal impairment the elimination is prolonged and the rate of renal clearance is directly related to creatinine clearance (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Vigabatrin does not induce

the hepatic cytochrome P450 system nor is it extensively metabolized or plasma-protein bound. Administration of vigabatrin with food slightly reduces the rate, but not the extent of absorption.

INDICATIONS AND CLINICAL USE

Sabril is recommended for use in the 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).

Sabril (vigabatrin) 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.

Sabril may also be used as monotherapy for the management of infantile spasms (West syndrome), 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.

CONTRAINDICATIONS

SABRIL (vigabatrin) is contraindicated in pregnancy and lactation (see WARNINGS) and in patients with a known hypersensitivity to vigabatrin or to any components of the product.

WARNINGS

Ophthalmological Abnormalities

In the course of international postmarketing surveillance and in some clinical trials, a number of ophthalmological abnormalities, including visual field defects (see OCCUPATIONAL HAZARDS), 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 (vigabatrin).

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 is usually after months to years of Sabril therapy. Data to date (August 2000) 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 gms/day translates to a greatest risk during the first year of treatment. If a patient has not developed defects after 4 years of treatment the risk of developing defects with continuation of Sabril therapy is likely to be small.

Based on currently available data (August 2000), 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. Central acuity is not impaired. 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. 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.

Available data suggests that visual field defects may be permanent even after discontinuation of vigabatrin treatment.

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, vigabatrin 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 vigabatrin.

Although data suggesting any association of vigabatrin to these eye disorders (except visual field defects) is inconclusive at the current time, the benefits of vigabatrin use and the risks of ophthalmologic abnormalities must be taken into account.

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 co-operate 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 vigabatrin 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.

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.

Vigabatrin should not be used concomitantly with other retinotoxic drugs.

Neurotoxicity in Animals

Rat, Mouse and Dog: 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 microvacuolation 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 microvacuolation was caused by the separation of the outer lamellar sheath of myelinated fibres, a change characteristic of non-inflammatory intramyelinic edema.

In both the rat and dog (mouse was not tested), the intramyelinic edema was reversible after stopping the administration of vigabatrin; however, in the mouse and rat, residual changes consisting of swollen axons and mineralised microbodies were observed.

Monkey: In monkeys, the oral administration of 300 mg/kg/day for 16 months produced minimal microvacuolation 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.

Evoked Potentials

Evoked potentials in animals: 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.

Evoked potentials in man: No increased evoked potential latencies have been observed in man. Two hundred and twenty-one patients treated for 4-5 months showed no significant evoked potential latency changes at the end of treatment as compared to baseline. MRI results in man did not show the changes observed in

dogs who had intramyelinic edema.

Postmortem neuropathological changes seen in 11 patients who were treated with vigabatrin (mean duration of treatment was 28 months, and the longest treatment was 6 years) showed no myelin vacuolation in the white matter that was considered to be outside of the control range.

Although clinical trials have not revealed the type of neurotoxicity seen in animal studies, increased CSF GABA levels are observed in humans. It is recommended that patients treated with vigabatrin be closely observed for adverse effects on neurological function, with special attention to visual disturbance.

Use in Pregnancy and Lactation

No adequate and well-controlled studies with Sabril have been conducted in pregnant women. Sabril should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. 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 vigabatrin 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.

Although abnormal pregnancy outcomes have been reported in the offspring of mothers using vigabatrin during pregnancy, no increase in the incidence or types of abnormal outcomes (malformation anomalies or spontaneous abortions) has been observed compared to the general epilepsy population. No definite conclusions can be drawn as to whether vigabatrin produces an increased risk of malformation when taken during pregnancy because of limited data and the presence of concomitant anti-epileptic drugs during each reported pregnancy.

Vigabatrin is excreted into breast milk in low concentration. Therefore, a decision should be made on whether to discontinue Sabril, taking into account the importance of the drug to the mother.

In a teratology study in the rabbit a dose-related incidence, 2% and 9%, of cleft palate was observed at doses of 150 and 200 mg/kg/day, respectively.

In animal reproductive studies neurohistopathology was not performed on the fetuses, therefore it is not known whether microvacuolation occurred *in utero*. The possibility that microvacuolation or other neurotoxicity may occur in human fetuses cannot be disregarded.

The relevance of these data for humans is unknown.

PRECAUTIONS

Use in Patients with a History of Psychosis, Depression or Behavioural Problems

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 vigabatrin treatment. These events occurred in patients with or without a psychiatric history, and were usually reversible when vigabatrin 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 vigabatrin 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 vigabatrin

Use in the Elderly and in Patients with Renal Impairment

Vigabatrin is eliminated via the kidney and caution should be exercised in patients with a creatinine clearance of less than 60ml/min and in elderly patients. These patients should be monitored closely for adverse events such as sedation and confusion (see DOSAGE AND ADMINISTRATION).

Use in Patients with Myoclonic Seizures

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency including status epilepticus and the onset of new types of seizures with vigabatrin. Patients with myoclonic seizures may be particularly liable to this effect. These phenomena may also be the consequence of an overdosage, 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.

Discontinuation of Therapy

As with other antiepileptic drugs, abrupt discontinuation may lead to rebound seizures. If a patient is to be withdrawn from vigabatrin treatment, it is recommended that this be done gradually by reducing the dose over a 2 to 4 week period if possible.

Drug Interactions

During concurrent vigabatrin administration, mean decreases of 16-33% in phenytoin levels have been reported. A 9-21% reduction in phenobarbital levels has also been seen in patients receiving concomitant vigabatrin treatment. The exact nature of this interaction is presently not understood. The clinical relevance of these decreases is not known.

The plasma concentrations of carbamazepine, primidone, and sodium valproate have also been monitored during controlled clinical trials and no clinically significant interactions have been detected.
As vigabatrin is neither metabolised, nor protein bound and is not an inducer of hepatic cytochrome P450 drug metabolising-enzymes, interactions with other drugs are unlikely.

Laboratory test findings

Vigabatrin may lead to a decrease in measured plasma activity of alanine aminotransferase (ALT) and to a lesser extent, aspartate aminotransferase (AST). The magnitude of suppression for ALT has been reported to vary between 30% and 100%. Therefore, these liver tests may be quantitatively unreliable in patients taking 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 aminoadipic aciduria).

Occupational Hazards

Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials, the most common adverse reactions observed were drowsiness and fatigue. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that vigabatrin does not affect them adversely.

Visual field defects which can significantly affect the ability to drive and use machines have been frequently reported in association with Sabril. Patients should be evaluated for the presence of visual field defect (see WARNINGS). Special care should be taken by patients driving, operating machinery or performing any hazardous task.

ADVERSE REACTIONS

SABRIL (vigabatrin) 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 vigabatrin 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 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.

Post-Marketing Ophthalmological Adverse Events:

Pooled data from prevalence surveys suggest that about 1/3 of patients receiving vigabatrin therapy develop visual field defects (see WARNINGS).

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).

The following table provides a listing of all treatment emergent adverse events that were reported with an incidence of 2% or greater in double-blind, placebo-controlled clinical trials of vigabatrin as add-on therapy for the treatment of epilepsy.

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

Body System Adverse Event	Placebo* N = 320		SABRIL* 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

Treatment Emergent Adverse Event Incidence (≥ 2%) of Adult Patients in Double-Blind, Placebo-Controlled Add-On Clinical Trials				
Body System Adverse Event	**Placebo*** **N = 320**		**SABRIL*** **N = 438**	
	n	**%**	**n**	**%**
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
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
Other				
infection viral	36	11.3	56	12.8

*** Added on to patient's existing antiepilepsy drug therapy.**

The sedative effect of vigabatrin decreases with continuing treatment.

Other adverse events 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 vigabatrin therapy. These events have been reversible following dose reduction or discontinuation of vigabatrin.

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 vigabatrin 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 PRECAUTIONS).

Laboratory data indicate that vigabatrin 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. Chronic treatment with vigabatrin may be associated with a slight decrease in hemoglobin, which rarely attains clinical significance.

Pediatric Safety

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 vigabatrin. Relationship of adverse events to vigabatrin 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).

Other commonly reported adverse events were somnolence (8.0%) and weight gain (3.0%). The following adverse events were reported in children with a frequency greater than 1%:

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
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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Cases of vigabatrin overdose have been reported. The doses of vigabatrin taken were usually between 7.5 and 30 g; however, ingestions of up to 90 g have been reported. Nearly half of the cases involved multiple drug ingestions. When reported, the most common symptoms included drowsiness, loss of consciousness and coma. Other less frequently reported symptoms included vertigo, headache, psychosis, respiratory depression or apnea, bradycardia, hypotension, agitation, irritability, confusion, abnormal behaviour or speech disorder.

There is no specific antidote. The usual supportive measures should be employed. Measures to remove unabsorbed drug should be considered. Activated charcoal has been shown to not 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%

DOSAGE AND ADMINISTRATION

All patients should have ophthalmological consultation with visual field examination before initiation of SABRIL (vigabatrin) treatment.

SABRIL (vigabatrin) is intended for oral administration 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 doses may be taken as tablets or sachets. The entire contents of the sachet(s) should be dissolved in a 10 ml volume (cold or room temperature) of either water, fruit juice, milk or infant formula, immediately before oral administration. Instructions to the patient on the use of SABRIL are provided in the INFORMATION FOR THE CONSUMER section.

If the control of epilepsy is not clinically significantly improved after an adequate dose titration and maintenance period, vigabatrin treatment should not be continued. SABRIL should be gradually withdrawn under close medical supervision.

Adults

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

The recommended starting dose in children 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:

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.

The total daily dose should be divided and administered on a b.i.d. basis. The entire contents of the Sabril sachet(s) should be dissolved in a 10 ml volume (cold or room temperature) of either water, fruit juice, milk or infant formula, and the appropriate aliquot of this volume administered using an oral syringe.

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 60 mL/min. It is recommended that such patients be started on a lower dose of vigabatrin and observed closely for adverse events such as sedation and confusion.

PHARMACEUTICAL INFORMATION

Drug Substance

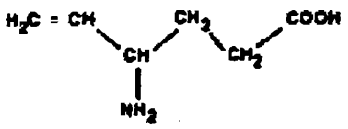
International

Non-proprietary Name: vigabatrin

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

Molecular Formula: $C_6H_{11}NO_2$

Structural Formula:



Molecular Weight: 129.16

Physical Form: White to off-white, free-flowing crystalline powder which melts with decomposition in the range 171°C-177°C. The pH of a 20% aqueous solution is 6.8. The pK value is 4.02 and the pK_2 value is 9.72.

Solubility: Freely soluble in water, sparingly soluble in methanol, slightly soluble in ethanol, and insoluble in chloroform, hexane and toluene.

Stability and Storage Recommendations

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

AVAILABILITY OF DOSAGE FORMS

Tablets

Each SABRIL (vigabatrin) 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.

Sachets

Sachets containing 0.5 g vigabatrin as a white to off-white granular powder. Sachets are available in cartons of 50.

Both the tablets and sachets are lactose free.

INFORMATION FOR THE CONSUMER OR CAREGIVER

Please read this leaflet carefully before you start to take your medicine, even if you have taken this medicine before. It contains a brief description and summary of information needed for the proper use of SABRIL. If you have any questions or are not sure about anything, ask your doctor or pharmacist. Please do not throw this leaflet away until you have finished all the medication prescribed by your doctor. You may need to read it again.

1. The Name of Your Medicine

Your medicine is called SABRIL (vigabatrin). SABRIL can only be obtained with a prescription from your doctor.

2. The Purpose of Your Medicine

SABRIL was prescribed to you to reduce the frequency of epileptic seizures.

3. How Your Medicine Works

It is thought that a shortage of a naturally occurring brain chemical may be involved in epilepsy. Treatment with SABRIL causes a rise in the levels of this chemical in the brain.

4. Important Points to Note Before Taking Your Medicine

Sabril treatment can result in a loss of peripheral vision (narrowing of the field of vision) which may lead to permanent impairment of eyesight. The proportion of patients affected has been estimated to be about 1/3 of patients. Before starting treatment with Sabril, you should discuss with your doctor the potential benefits of this medicine versus the risk of damage to your eyes. You should have your eyes examined before beginning Sabril treatment and at regular intervals (approximately every 3 months) thereafter. Advise your doctor immediately of any change in your eyesight such as narrowing of your field of vision, blurred vision or any other visual symptoms.

You should tell your doctor if you have had any nervous or mental illnesses in the past.

If you currently have, or have ever had any kidney problems, make sure your doctor knows.

In some patients, SABRIL may cause side effects. You can find more information in this leaflet (see Item 7).

5. The Use of This Medicine During Pregnancy and Breast-Feeding.

SABRIL should not be used if you are pregnant or breast-feeding. Before you use this medicine, tell your doctor if you are pregnant, are likely to become pregnant, or are planning to become pregnant.

Tell your doctor immediately if you become pregnant, or suspect that you may be pregnant, during your treatment.

Sabril is excreted in breast milk in low concentrations.

6. How to Take Your Medicine

It is important to follow your doctor's instructions exactly. Never change the dose yourself.

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

If you 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 dose you forgot, and go on as usual.

SABRIL tablets and sachets may be taken with or without food.

If you are using sachets, dissolve the entire contents of the sachet(s) in a glass of cold or room temperature water, juice or milk immediately before taking your medicine.

To give Sabril to your baby, dissolve the whole sachet in a 10 mL volume of either water, fruit juice, milk or infant formula. Use an oral syringe to measure the 10 mL volume. Give your baby the appropriate amount of this made up medicine, using an oral syringe to measure the exact volume. Your doctor will have told you how much medicine to give to your child. Each dose should be made up just before you give the medicine to your child.

7. After Taking Your Medicine

This medicine may cause side effects.

Your doctor will be monitoring your response to SABRIL on a regular basis; however, if you develop any of the following side effects tell your doctor immediately:

- vision disorders
- confusion
- drowsiness
- tiredness
- headache
- stomach upset
- dizziness

Your doctor will ensure that you receive appropriate attention and treatment.

If your epilepsy is uncontrolled, it is very important that you do not perform any hazardous tasks such as driving or operating machinery. If, however, your epilepsy is controlled by medication it is very important that you refrain from any hazardous tasks until you are sure the medication does not cause drowsiness or impair your ability to drive or operate machinery.

If you feel unwell in any other way or have any symptoms that you don't understand, tell your doctor immediately.

8. What to Do if an Overdose is Taken

If you accidentally take an overdose of your medicine, tell your doctor immediately and go to the nearest hospital.

9. Storing Your Medicine

Leave your tablets and sachets in their original packaging and keep them in a safe place out of the reach of children.

Keep your medicine in a cool dry place (15°C-30°C).

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

10. What is in Your Medicine

TABLETS:

SABRIL tablets are white to off-white oval tablets and each one contains 500 mg of vigabatrin.

SACHETS:

SABRIL sachets are available in strengths of 0.5 g of vigabatrin, as a white to off-white granular powder.

Both the tablets and sachets are lactose free.

11. The Class of Your Medicine

This medicine is one of a group of drugs called anti-epileptics.

12. Who Produces Your Medicine

Manufacturer: Aventis Pharma Inc.

Laval, Quebec H7L 4A8

13. A Reminder

REMEMBER this medicine has been prescribed only for you. Never give it to anyone else.

14. Further Information

This leaflet is a brief description and summary of information about your medicine. If you are unsure about anything, ask your doctor or pharmacist.

PHARMACOLOGY

Pharmacodynamics

Vigabatrin is an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the major enzyme responsible for the catabolism of gamma-aminobutyric acid (GABA) in the mammalian central nervous system. The ability of vigabatrin to specifically and irreversibly inhibit GABA-T was confirmed by *in vitro* biochemical experiments. Administration of vigabatrin to laboratory animals by either the oral or parenteral route produces a pronounced decrease in whole brain GABA-T activity and a marked increase in whole brain GABA concentrations.

The vigabatrin-induced increase in brain GABA concentration is dose-dependent and is proportionally greater in the synaptosomal pool than in the non-synaptosomal pool. Repeated administration of vigabatrin produces cumulative effects, and with repeated treatment, there is no loss of effectiveness in the maintenance of elevated brain GABA levels.

Pharmacokinetics

Vigabatrin is rapidly and completely absorbed in the rat and dog over the dose range used in chronic toxicity studies. In the monkey, however, absorption is dose limited, with only about 25% of a 300 mg/kg dose being absorbed. In all three species, first pass metabolism is minimal, leading to almost complete availability of the absorbed dose.

As would be expected of a highly water soluble compound, vigabatrin distributes into the total body water in all species, although in the rat the volume of distribution exceeds the total body water, suggesting even greater distribution to the tissues. Vigabatrin penetrates into the central nervous system of all three species and in both the rat and dog reaches steady state within 2 weeks of daily oral dosing, with the concentrations achieved being much higher in the dog.

Vigabatrin is mainly (70%) eliminated unchanged in the urine. The rate of renal clearance of the drug is much higher in the rat than in the other two species, but in all species renal clearance rates reflect the glomerular

filtration rate of the particular animal.

Vigabatrin does not bind to plasma proteins or induce the hepatic drug metabolising enzymes in the rat.

TOXICOLOGY

Acute Toxicity

The acute toxicity of vigabatrin has been investigated in the rat and mouse. The LD_{50} values are:

Species	Route	LD_{50} (mg/kg)
mouse	oral	2830
	i.p.	1098
rat	oral	3100
	i.p.	1473

Chronic Toxicity

Repeat dose toxicity studies of 12-18 months duration in the rat, dog, mouse and monkey have identified the following treatment-related effects:

Microvacuolization: Microvacuoles, a change indicative of non-inflammatory intramyelinic edema, have been observed in white matter tracts of rat, dog and mouse brains at doses of 30-50 mg/kg/day and higher. In the rat and the dog, this effect is clearly reversible on discontinuation of treatment; reversibility of this effect was not evaluated in the mouse. No changes have been seen in the peripheral nervous system of any species. In monkeys receiving 300 mg/kg/day for 16 months, minimal vacuolation was observed with equivocal differences between treated and control animals. Similarly, no lesions attributable to drug treatment were observed in monkeys when continued on treatment with 50 and 100 mg/kg/day vigabatrin for 6 years.

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

The effect of vigabatrin at doses up to 150 mg/kg/day on all phases of the reproductive process and on the development of offspring has been examined. Teratology studies in the rat (2 studies, morphological and behavioural) and rabbit, fertility studies in male and female rats, and a peri- and post-natal study in the rat were

conducted. In all of these studies, the only toxicologically significant effects were: (a) a dose-related incidence, 2% and 9%, of cleft palate in the rabbit teratology study, observed only at maternally toxic doses of 150 and 200 mg/kg/day respectively, and (b) decreased food consumption and reduced body weight gain in most of the rat studies, leading to secondary effects such as reduced fetal implants in the uterus, reduced pup weights etc., in the top dose groups (100 and 150 mg/kg/day).

Mutagenicity

The data from a battery of 6 mutagenicity tests, which included *in vitro* and *in vivo* systems, eukaryotic and prokaryotic cells and tests for both gene mutations and chromosome aberrations, found no evidence of potential genotoxicity of vigabatrin.

Carcinogenesis

Two carcinogenicity studies have been completed with oral doses of vigabatrin up to 150 mg/kg/day. One study was conducted in the mouse (18 months) and one in the rat (24 months). In neither study did vigabatrin exhibit any carcinogenic potential. Other findings from these studies are presented in the chronic toxicity section.

REFERENCES

1. Appleton RE. Vigabatrin in the management of generalized seizures in children. Seizure 1995; 3:45-48.

2. Ben-Menachem E et al. Long-term evaluation of once daily vigabatrin in drug-resistant partial epilepsy. Epilepsy Res 1990; 5:240-246.

3. Ben-Menachem E et al. The effect of different vigabatrin treatment regimens on CSF biochemistry and seizure control in epileptic patients. Br J Clin Pharmac 1989; 27:79S-85S.

4. Browne TR et al. Multicentre long-term safety and efficacy study of vigabatrin for refractory complex partial seizures: An Update. Neurology 1991; 41:363-364.

5. Chiron C et al. Magnetic resonance imaging in epileptic children treated with gamma-vinyl GABA (vigabatrin). (Abstract). Epilepsia 1989; 30:736.

6. Cosi V et al. Effects of vigabatrin on evoked potentials in epileptic patients. Br J Clin Pharmac 1989; 27:61S-68S.

7. Gibson JP et al. Chronic toxicity studies with vigabatrin, a GABA-transaminase inhibitor. Toxicologic Pathology 1990; 18:225-238.

8. Gram L. Vigabatrin. Comprehensive Epileptology. Ed. Mogens Dam and Lennan Gram, Raven Press, New York, 1990; 631-640.

9. Gram L, Klosterskov P, Dam M. Gamma-vinyl GABA: A double-blind, placebo-controlled trial in partial epilepsy. Ann Neurol 1985; 17:262-266.

10. Grant SM, Heel RC. Vigabatrin: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. Drugs 1991; 41(6):889-926.

11. Hammond EJ et al. Evoked potential monitoring of vigabatrin patients. Br J Clin Pract 1988; 42(61):16-23.

12. Loiseau P et al. Double-blind, placebo-controlled study of vigabatrin (Gamma-vinyl GABA) in drug-resistant epilepsy. Epilepsia 1986; 27(2):115-120.

13. Mumford JP. Vigabatrin for epilepsy in children and adults. Single Topic Supplement to Journal of Child Neurology 1991; 6(2):2S2-2S59.

14. Remy C et al. Double-blind, placebo-controlled, crossover study of vigabatrin in drug-resistant epilepsy of the adult. Boll Lega It Epil 1987; 54/55:241-243.

15. Reynolds EH et al. Open, double-blind and long-term study of vigabatrin in chronic epilepsy. Epilepsia 1991; 32(4):530-538.

16. Rimmer EM, Richens A. A double-blind study of gamma-vinyl GABA in patients with refractory epilepsy. Lancet January 28, 1984; 189-190.

17. Schmitt B, Wohlrab G, Boltshauser E. Vigabatrin in newly diagnosed infantile spasms. Neuropediatrics 1994; 25:54

18. Schroeder CE et al. Vigabatrin-induced intramyelinic edema I: Effects on visual and somatosensory evoked potentials in dogs. Neurology March 1991; 41(Suppl.1):331.

19. Shorvon SD. Medical assessment and treatment of chronic epilepsy. Br Med J 1991; 302:6773.

20. Sivenius J et al. Vigabatrin in drug-resistant partial epilepsy: A 5-year follow-up study. Neurology April 1991; 41:562-565.

21. Tartara A et al. Vigabatrin in the treatment of epilepsy. A double-blind placebo-controlled study. Epilepsia 1986; 27(6):717-723.

22. Tassinari CA et al. Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy. Arch Neurol 1987; 44:907-910.

23. Vles JSH, van der Heyden AMHG, Ghijs A, Troost J. Vigabatrin in the treatment of infantile spasms. Neuropediatrics 1993; 24:230-231.

24. Weiss KL et al. Vigabatrin-induced intramyelinic edema II: Effects on MRI in dogs. Neurology March 1991; 41(Suppl.1):331.