

Data Sheet

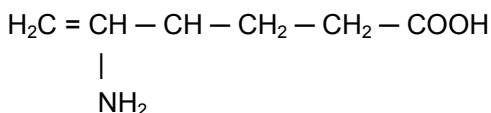
SABRIL® TABLETS 500 mg

Name of the Medicine

Non-proprietary Name

Vigabatrin

Chemical Structure



CAS Number

60643-86-9

Description

Sabril tablets contain the following inactive ingredients: povidone BP, cellulose microcrystalline EP, sodium starch glycollate USNF, magnesium stearate EP, hydroxypropyl methylcellulose EP, titanium dioxide BP and polyethylene glycol 8000.

Pharmacology

Class

Actions: Anticonvulsant

Pharmacodynamics

The mechanism of action is attributed to dose-dependent enzyme inhibition of GABA-transaminase (GABA-T) and consequent increased levels of the inhibitory neurotransmitter, GABA. In mice, decreased GABA-T levels in the brain persisted for 5 days following a single intraperitoneal dose (1500 mg/kg) and was accompanied by a marked rise in brain GABA concentration.

Animal safety studies carried out in rat, mouse, dog and monkey have indicated that vigabatrin has no significant adverse effects on the liver, kidney, lung, heart or gastrointestinal tract. In the brain, microvacuolation has been observed in white matter tracts of rat, mouse and dog at doses of 30-50 mg/kg/day. This effect is caused by a separation of the outer lamellar sheath of myelinated fibres, a change characteristic of intramyelinic oedema.

In both rat and dog (mouse, not tested), the intramyelinic oedema was reversible on stopping vigabatrin treatment. However, in rodents, residual changes consisting of swollen axons and mineralised microbodies have been observed. In the monkey, no lesions were noted after 6 years of treatment at 50 and 100 mg/kg. In monkeys receiving 300 mg/kg for 16 months, minimal microvacuolation was noted with equivocal differences between treated and control animals. In the dog, results of an electrophysiological study indicate that intramyelinic oedema is associated with increased latency of the somatosensory-evoked potential which is reversible when the drug is withdrawn.

Short and long-term controlled clinical trials have shown that vigabatrin reduces seizure frequency when given as add-on therapy in patients with epilepsy not controlled satisfactorily by conventional therapy. Efficacy is particularly marked in patients with complex partial seizures.

During long-term clinical follow up, tests done to confirm lack of significant adverse effect on neurological function include evoked potential studies, magnetic resonance imaging and, in a small number of cases, neuropathological examinations of human brain specimens. Therefore, clinical

trials have revealed no evidence in humans of the type of neurotoxicity seen in animal studies. In man, no tendency towards increased evoked potential latency was observed even on prolonged treatment.

Pharmacokinetics

Vigabatrin is a water soluble compound and is rapidly absorbed from the gastrointestinal tract; absorption is unaffected by the presence of food. The drug is widely distributed with an apparent volume of distribution slightly greater than total body water.

Plasma and CSF concentrations are linearly related to dose over the recommended dose range. There is no direct correlation between plasma concentration and efficacy. Duration of drug effect is thought to be dependent on the rate of enzyme resynthesis rather than the plasma concentration of drug.

Vigabatrin is eliminated from the plasma with a terminal half life of 5-8 hours with approximately 70% of a single oral dose being recovered in the urine as unchanged drug in the first 24 hours post-dose.

Vigabatrin does not induce the hepatic cytochrome P450 enzymes nor is it extensively metabolised or plasma-protein bound, therefore drug interactions are unlikely.

Indications

For the treatment of epilepsy which is not satisfactorily controlled by other antiepileptic medicines.

For the management of infantile spasms (West Syndrome).

Monotherapy for the treatment of partial seizures and secondarily generalised tonic-clonic seizures.

Contraindications

Contraindicated for patients who have a history of hypersensitivity to vigabatrin or any of the components.

Precautions

Animal safety studies indicate that vigabatrin causes intramyelinic oedema in the brain of some species. Currently, there is no evidence to suggest that this effect occurs in man. However, it is recommended that patients treated with vigabatrin are closely observed for adverse effects on neurological functions.

Drowsiness has been observed in clinical trials and patients should be warned of this possibility at the start of treatment.

Special care should be taken by patients driving, operating machinery or performing any hazardous task.

Vigabatrin should be used with caution in patients with a history of psychosis, depression or behavioral problems. Psychiatric events (agitation, depression, abnormal thinking, paranoid reactions) have been reported during vigabatrin therapy. These events occurred in patients with and without a psychiatric history and were usually reversible when vigabatrin doses were reduced or gradually discontinued. It is advisable that in patients who may be susceptible to such reactions (e.g., patients with a previous history), vigabatrin be introduced cautiously at low dose with frequent monitoring. In clinical trials, depression occurred in less than 10% of patients and seldom required discontinuation of vigabatrin. Less common events included psychotic symptoms.

Cases of abnormal brain magnetic resonance imaging (MRI) findings have been reported, particularly in young infants treated for infantile spasms with high doses of vigabatrin. The clinical significance of these findings is currently unknown.

Movement disorders including dystonia, dyskinesia and hypertonia have been reported in patients treated for infantile spasms. The benefit/risk of vigabatrin should be evaluated on an individual

patient basis. If new movement disorders occur during treatment with vigabatrin, consideration should be given to dose reduction or a gradual discontinuation of treatment.

As with other antiepileptic drugs, abrupt withdrawal may lead to rebound seizures; therefore, it is recommended that withdrawal from vigabatrin treatment occurs by gradual dose reduction over a 2 to 4 week period.

Vigabatrin is eliminated via the kidney and, therefore, caution should be exercised when administering the product to elderly patients and more particularly to patients with a creatinine clearance of less than 60mL/min. Reduced doses should be used and patients monitored closely for adverse events such as sedation and confusion.

Rare reports of encephalopathic symptoms such as marked sedation, stupor and confusion in association with non-specific slow wave activity on electroencephalogram (EEG) 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.

Visual field defects (VFDs) have been reported in patients receiving vigabatrin. Based on currently available data, the VFDs may result from increased levels of GABA in the retina. Males may be at greater risk than females. Asymptomatic VFDs appear to be frequent (about 30%) whereas symptomatic visual field constriction of various degrees is uncommon. Most patients were receiving other antiepilepsy drugs and baseline examinations were generally not provided. In case of symptomatic defects, where the information was available, the condition was diagnosed between 1 month and over 6 years of treatment, but most frequently during the first year. In most reported cases, VFDs persisted even after discontinuation of treatment.

Data from systematic screening of participants in clinical studies appear to indicate that the risk of developing VFDs with the continuation of vigabatrin therapy is low, if a patient has not developed defects after 3 to 4 years of treatment.

Based on currently 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. Central visual acuity is not impaired.

Vigabatrin should not be used concomitantly with retinotoxic drugs.

Most patients with perimetry confirmed defects had not previously spontaneously noticed any symptoms (i.e. were asymptomatic), even in cases where a severe defect was observed in perimetry.

Therefore, VFDs may only be reliably detected by systematic perimetry. This is only usually possible in patients with a developmental age of more than 9 years.

Severe cases of VFDs may have practical consequences for the patient. Available evidence suggests that VFDs are irreversible even after discontinuation of vigabatrin. A deterioration of VFD after the treatment is discontinued cannot be excluded.

The onset is months to years of vigabatrin therapy. A possible association between the risk of VFDs and the extent of vigabatrin exposure, both in terms of daily dose (from 1 g to more than 3 g) and in terms of duration of treatment has been shown in an open clinical study.

Vigabatrin is not recommended for use in patients with any pre-existing clinically significant VFD.

Appropriate visual field testing should be performed at baseline and during routine follow-up of the patient (initially and at about six month intervals). Static perimetry is the preferred method for detecting a vigabatrin associated VFD. The patient and/or caregiver must be given a thorough description of the frequency and implications of the development of VFDs during vigabatrin treatment. Patients should be instructed to report any new vision problems and symptoms which may be associated with visual field constriction. If visual symptoms develop, then the patient should be referred to an ophthalmologist for further evaluation.

If VFDs are identified, the decision to continue or discontinue vigabatrin should be based on an individual benefit-risk assessment. If the decision to continue treatment is made, consideration

should be given to more frequent follow-up (perimetry) in order to detect progression or sight threatening defects.

In patients where visual field testing cannot be adequately performed (e.g., commonly in young children), the decision to start vigabatrin should similarly be based on an individual benefit-risk judgement.

Suicidal Behaviour and Ideation

Antiepileptic drugs (AEDs), including vigabatrin increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. The following Table shows absolute and relative risk by indication for all evaluated AEDs.

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

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

Anyone considering prescribing vigabatrin or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Use in Pregnancy

Category D

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

The risk of congenital defects is increased from 2 to 3 fold in children born from mothers treated with an antiepileptic; those more frequently reported are cleft lip, cardiovascular defects and neural tube defects. Polytherapy with antiepileptic drugs may be associated with a higher risk of congenital malformation than monotherapy.

Based on data on a limited number of exposed pregnancies with vigabatrin, available from spontaneous reports, abnormal outcomes (congenital anomalies or spontaneous abortion) were reported in the offspring of mothers taking vigabatrin. No definite conclusion 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 antiepileptic drugs during each reported pregnancy.

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy. It is recommended that women on antiepileptic drugs receive pre-pregnancy counselling with regard to foetal abnormalities. Antiepileptic medication should be continued during pregnancy at the lowest effective dose. The need of antiepileptic treatment must be re-evaluated when a patient plans a pregnancy. Folic acid supplementation (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception. Specialist prenatal diagnosis including detailed mid-trimester ultrasound should also be offered during pregnancy.

Reproductive studies in rats have shown no evidence of embryotoxicity, fetotoxicity, or teratogenicity at doses up to 150 mg/kg/day. Studies in rabbits administered vigabatrin during the period of organogenesis at doses above 100 mg/kg/day have shown an increased incidence of cleft palate together with evidence of maternal toxicity.

There are no well controlled studies with vigabatrin in pregnant women or during lactation.

Use in Lactation

Vigabatrin is excreted into breast milk in low concentrations. Based on vigabatrin breast milk concentrations from one patient, it was estimated that 0.3% of a daily maternal dose of 2g daily would have been excreted into breast milk. Therefore, a decision should be made on whether to discontinue the drug, taking into account the importance of the drug to the mother.

Use in the Elderly

Vigabatrin is eliminated via the kidney and, therefore, caution should be exercised when administering the drug to the elderly and more particularly in patients with creatinine clearance less than 60 mL/min. It is recommended that such patients are started on a lower dose of vigabatrin and observed closely for adverse events such as sedation and confusion.

Carcinogenicity

Carcinogenicity studies indicate that vigabatrin is not a potential carcinogen nor did it adversely affect life expectancy in the two species studied (rat and mouse).

No evidence of carcinogenic potential was observed in rats during a 24 month study or in mice during an 18 month study at doses up to 150 mg/kg/day. In standard mutagenicity studies, vigabatrin did not induce gene mutations or cause chromosomal damage.

Interactions with other Medicines

As vigabatrin is neither extensively metabolised, nor plasma-protein bound, and is not an inducer of hepatic cytochrome P450, interactions with other drugs are unlikely. However, during controlled clinical studies a gradual reduction of about 20% in the plasma concentration of phenytoin has

been observed. The exact nature of this interaction is presently not understood and the therapeutic significance is not known.

The plasma concentrations of carbamazepine, phenobarbital and sodium valproate have also been monitored during controlled clinical trials and no clinically significant interactions have been detected.

Effect on Laboratory Tests

Vigabatrin may lead to a decrease in measured plasma activity of alanine transaminase (ALT) and, to a lesser extent, aspartate transaminase (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 diseases (e.g. alpha aminoadipic aciduria).

Adverse Effects

Pooled data from prevalence surveys suggest that as many as 1/3 of patients receiving vigabatrin therapy develop visual field defects.

Adverse events are mainly CNS-related, such as sedation, somnolence, fatigue and impaired concentration and probably a secondary consequence of increased GABA levels caused by vigabatrin. The most commonly reported adverse effects in children are excitation and agitation. The incidence of these undesirable effects is generally higher at the beginning of treatment and decreases with time.

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency, including status epilepticus, or the onset of new types of seizures 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.

Undesirable effects, ranked under heading of frequency, are listed below in CIOMS format.

The following CIOMS frequency rating is used:

Very common: $\geq 10\%$; Common: ≥ 1 and $< 10\%$; Uncommon: ≥ 0.1 and $< 1\%$; Rare: ≥ 0.01 and $< 1.0\%$; Very rare: $< 0.01\%$; Unknown: cannot be estimated from available data.

Investigations*

Common: weight increased

Nervous system disorders

Very common: somnolence

Common: speech disorder, headache, dizziness, paraesthesia, disturbance in attention and memory impairment, mental impairment (thought disturbance), tremor

Uncommon: coordination abnormality (ataxia); movement disorder, including dystonia, dyskinesia and hypertonia, either alone or in association with abnormalities in nuclear magnetic resonance imaging.

Rare: encephalopathy**

Very rare: optic neuritis

Not known: cases of brain MRI abnormalities, which might be indicative of cytotoxic oedema have been reported.

Eye disorders

Very common: visual field defects***

Common: blurred vision, diplopia, nystagmus

Rare: retinal disorder (such as peripheral retinal atrophy)

Very rare: optic atrophy

Gastrointestinal disorders

Common: nausea, abdominal pain

Skin and subcutaneous tissue disorders

Uncommon: rash

Rare: angioedema, urticaria

General disorders and administration site conditions

Very common: fatigue

Common: oedema, irritability

Psychiatric disorders****

Very common: excitation (children), agitation (children)

Common: agitation, aggression, nervousness, depression, paranoid reaction

Uncommon: hypomania, mania, psychotic disorder

Rare: suicide attempt

Very rare: hallucination

*Chronic treatment with vigabatrin may be associated with a slight decrease in haemoglobin which rarely attains clinical significance. Decreases in ALT and AST, which are considered to be a result of inhibition of these aminotransferases by vigabatrin, have been observed.

**Rare reports of encephalopathic symptoms such as marked sedation, stupor and confusion in association with non-specific slow wave activity on EEG have been described soon after the introduction of vigabatrin therapy. Such reactions have been fully reversible following dose reduction or discontinuation of vigabatrin.

***Visual field defects (VDFs) have been reported in patients receiving vigabatrin. Males may be at greater risk than females. Asymptomatic VDFs appear to be frequent (about 30%) whereas symptomatic visual field constriction of various degrees is uncommon.

Rare cases of retinal disorders (such as peripheral retinal atrophy) and very rare cases of optic neuritis or atrophy have also been reported.

****Psychiatric reactions have been reported during vigabatrin therapy. These reactions occurred in patients with and without a psychiatric history and were usually reversible when vigabatrin doses were reduced or gradually discontinued. Depression was a common psychiatric reaction in clinical trials but seldom required discontinuation of vigabatrin.

Dosage and Administration

Adults

Vigabatrin is intended for oral administration once or twice daily. Initiation of treatment should be as add-on therapy in epilepsy which is not satisfactorily controlled by other drugs. Thus, the starting dose of 1 g (2 tablets) should be added on to the patient's current antiepileptic drug regimen.

If necessary, the daily dose may be increased or decreased in 0.5 g or 1.0 g increments at weekly or greater intervals depending on clinical response and tolerability. Maximum efficacy usually occurs in the range of 2 to 4 g daily; slight increases in efficacy have been seen at higher doses up to 6g daily but are associated with increased incidence of adverse events.

Vigabatrin may be taken before or after meals. The tablets should be swallowed with a little water.

Children

The recommended starting dose is 40 mg/kg/day, increasing to 80 to 100 mg/kg per day, depending on response.

For maintenance dosing, the recommendations are:

Bodyweight:

| | |
|------------|---------------|
| 10 to 15kg | 0.5-1g/day |
| 15 to 30kg | 1-1.5 g/day |
| 30 to 50kg | 1.5 - 3 g/day |
| >50kg | 2-4 g/day |

Elderly

Since vigabatrin is eliminated via the kidney, caution should be exercised when administering the medicine to patients with creatinine clearance less than 60 mL/min. Because of decreased clearance in elderly patients with normal or decreased renal function, similar precautions are necessary. Adjustment of dose or frequency of administration should be considered. Such patients may respond to a lower maintenance dose.

Overdosage

Symptoms

When reported, the most common symptoms included drowsiness or coma; other less frequently reported symptoms included vertigo, headache, psychosis, respiratory depression or apnoea, bradycardia, hypotension, agitation, irritability, confusion, abnormal behaviour, or speech disorder. None of the overdoses resulted in death.

Treatment

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 absorb vigabatrin in an *in vitro* study. The effectiveness of haemodialysis in the treatment of vigabatrin overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, haemodialysis reduced vigabatrin plasma concentrations by 40 % to 60 %. Isolated cases of vigabatrin overdosage have been reported. In the first case, the patient accidentally took a dose of 14g daily for 3 days and transient vertigo and tremor were reported. In the second case, an 18 year old female took 30g of vigabatrin and 250mg of dipotassium chlorazepate in a suicide attempt. The patient was admitted to hospital in a state of coma which lasted 4 days. However, the coma was considered to be due to the dipotassium chlorazepate rather than vigabatrin. The patient recovered without sequelae.

Presentation and Storage Conditions

*Tablets 500 mg (white to off-white, biconvex oval shaped tablets with a single breakline on one face and SABRIL inscribed on the other), 100's.

Sachets containing 500 mg vigabatrin in a pack of 60.

Store below 30°C.

Name and Address of the Sponsor

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Medicine Classification

Prescription Medicine

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♦Marketed presentation