SABRIL® 500mg

Vigabatrin

Film-coated tablet

[sanofi aventis logo]

COMPOSITION
Each film-coated tablet contains : vigabatrin (active ingredient) 500mg – Other excipients : microcrystalline cellulose, povidone, sodium, starch glycolate, magnesium stearate, hypromellose, titanium dioxide, Macrogol 8000.

INDICATIONS
Treatment in combination with other anti-epileptic drugs for patients with resistant partial epilepsy with or without secondary generalization, that is where all other appropriate drug combinations have proved inadequate or have not been tolerated.

POSOLOGY AND METHOD OF ADMINISTRATION
SABRIL treatment may only be initiated by a specialist in epileptology, neurology. Follow-up should be arranged under supervision of a specialist in epileptology, neurology or paediatric neurology.
SABRIL is for oral administration once or twice daily and may be taken before or after meals. Tablets are swallowed with half a glass of water.
If the control of epilepsy is not clinically significantly improved after an adequate trial, vigabatrin treatment should be discontinued. Vigabatrin should be gradually withdrawn under close medical supervision.
The tablet form is not suitable for children aged less than 6 years due to the risk of choking.

Adults:
Maximal efficacy is usually seen in the 2 – 3g/day range.
A starting dose of 1g daily should be added to the patient's current anti-epileptic drug regimen. The daily dose should then be titrated in 0.5g increments at weekly intervals depending on clinical response and tolerability.
The highest recommended dose is 3g/day.
No direct correlation exists between the plasma concentration and the efficacy. The duration of the effect of the drug is dependent on the rate of GABA transaminase resynthesis rather than the concentration of the drug in the plasma (see also Sections Properties and Pharmacokinetic properties).

Children:
The recommended starting dose in children is 40mg/kg/day. Maintenance recommendations in relation to bodyweight are:

Bodyweight:	10-15 kg	0.5-1 g/day
	15-30 kg	1-1.5 g/day
	30-50 kg	1.5-3 g/day
> 50 kg	2-3 g/day	

The maximum recommended dose in each of the categories should not be exceeded.

Elderly and Patients with renal impairment:
Since vigabatrin is eliminated via the kidney, caution should be exercised when administering the drug to the elderly and more particularly in patients with creatinine clearance less than 60ml/min. Adjustment of dose or frequency of administration should be considered. Such patients may respond to a lower maintenance dose. Patients should be monitored for undesirable effects such as sedation or confusion (see sections Special warnings and special precautions for use and undesirable effects).

CONTRAINDICATIONS
Hypersensitivity to vigabatrin or to any excipient in the medicinal product.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

SABRIL should not be initiated as monotherapy.

Visual field defects (VFD) have been reported with a high prevalence, i.e. in about 1/3 of patients receiving vigabatrin. The incidence of visual field defects (VFD) as determined in an open label clinical study is presented in section Pharmacological properties. The onset is generally after months or even years of vigabatrin therapy. The degree of visual field narrowing may be significant. Most of the patients with confirmed visual field defects were asymptomatic. This undesirable effect can therefore only be reliably detected by systematic perimetry, which is usually only possible in patients with a developmental age of more than 9 years. In children aged 3 years and above, a specially developed method based on field specific Visual Evoked Potentials (VEP) is available from the company on request to test peripheral vision. At present, this method has not been validated for the detection of vigabatrin related visual field defects. Electroretinography may be useful but should only be used in adults who are unable to cooperate with perimetry or in very young children (see Visual Field Defects).

Available evidence suggest that visual field defects are irreversible even after discontinuation of vigabatrin. A deterioration of VFD after the treatment is discontinued cannot be excluded.

Therefore, vigabatrin should only be used after a careful assessment of the balance of benefits and risk compared with alternatives.

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

Patients should have routine screening examinations from the start of vigabatrin treatment, then at regular intervals to detect visual field defects and a reduction in visual acuity. Visual field and visual acuity testing should continue at 6-month intervals for the whole duration of treatment (see Visual Field Defects and Visual Acuity).

Visual Field Defects (VFD)

Based on the 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 degree of eccentricity), frequently an annular nasal defect is seen. Severe cases may be characterized by tunnel vision. However, the VFDs reported in patients receiving vigabatrin have ranged from mild to severe. Severe cases can be characterised by tunnel vision. Cases of blindness have also been reported in serious cases.

Most patients with perimetry-confirmed defects had not previously spontaneously noticed any symptoms, even in cases where a severe defect was observed in perimetry. Available evidence suggests that the VFD is irreversible even after discontinuation of vigabatrin. A deterioration of VFD after the treatment is discontinued cannot be excluded.

Pooled data from prevalence surveys suggest that as many as 1/3 of patients receiving vigabatrin therapy have VFDs. Males may be at greater risk than females. The incidence of VFD as determined in an open label clinical study is presented in section Pharmacological properties. The study showed a possible association between the risk of visual field defects 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 (at its highest during the first three years).

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

Appropriate visual field testing (perimetry) by using a standardized static perimetry (Humphrey or Octopus) or kinetic perimetry (Goldmann) must be performed before treatment initiation then every six months for the whole duration of treatment. Static perimetry is the preferred method for detecting vigabatrin-associated visual field defects.

Electroretinography may be useful but should be used only in adults who are unable to cooperate with perimetry. 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 VFDs. These responses are

delayed and reduced beyond the normal limits. Such changes have not been seen in vigabatrin treated patients without a VFD.

The patient and/or caregiver must be given a thorough description of the frequency and implications of the development of VFD during vigabatrin treatment. Patients should be instructed to report 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 a visual field constriction is identified during follow-up, gradual withdrawal of vigabatrin treatment should be considered. 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.

Vigabatrin should not be used concomitantly with other retinotoxic drugs.

Paediatric population
Perimetry can seldom be performed in children less than 9 years of developmental age. The possible benefit in children must be very carefully weighed against the risks of treatment. Currently, no established method is available to diagnose and establish or exclude visual field defects in children in whom standard perimetry cannot be performed. In children aged 3 years and above, a specially developed method based on field specific Visual Evoked Potentials (VEP) is available from the company on request to test peripheral vision. At present, this method has not been validated for the detection of vigabatrin related visual field defects.

If the method reveals normal central visual field response but no peripheral response, the benefit and risk of vigabatrin must be reassessed and gradual withdrawal considered. Peripheral vision does not rule out the potential onset of VFD. Electroretinography may be useful but should be used only in children under 3 years of age.

Visual acuity
The prevalence of a decrease in visual acuity in patients treated with vigabatrin is unknown.

Impairment of the retina, visual impairment, optic nerve atrophy or optic nephritis could lead to a decrease in visual acuity (see section Undesirable effects).

Visual acuity should be assessed during ophthalmological consultations before initiating vigabatrin treatment, and again every 6 months during the treatment period.

Neurological and psychiatric conditions
Considering the results of the animal safety studies (see section Preclinical safety data), it is recommended that patients treated with vigabatrin be closely monitored for neurological adverse effects.

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 and/or dose escalation using higher levels than recommended, and renal failure. These effects have been reversible following dose reduction or discontinuation of vigabatrin (see Section undesirable effects).

Cases of abnormal brain MRI findings have been reported, in particular in infants/young children treated for infantile spasms with high doses of vigabatrin. The clinical significance of these findings is currently unknown. Furthermore, cases of intramyelinic oedema (IMO) have been reported, in particular in infants/young children being treated for infantile spasms (see sections Undesirable effects and Preclinical safety data). IMO has been reported to be reversible upon treatment discontinuation; consequently, gradual withdrawal of vigabatrin is recommended if IMO is observed.

Movements disorders including dystonia, dyskinesia and hypertonia have been reported in patients treated for infantile spasms. The benefit/risk balance of vigabatrin should be evaluated. on an individual patient basis. If new movements disorders occur during treatment with vigabatrin, consideration should be given to dose reduction or a gradual discontinuation of treatment.

As with other antiepileptic drugs, some patients may experience an increase in seizures frequency or the onset of new types of seizures with vigabatrin (see Section undesirable effects). These effects may

also occur as result of an overdose, a decrease in plasma concentrations of concomitant antiepileptic treatment, or a paradoxical effect.

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

Vigabatrin must be used with caution in patients with a history of psychosis, depression or behavioural disorders. Adverse psychiatric events (e.g., agitation, depression, abnormal ideation, paranoid reactions) have been reported during vigabatrin treatment. These reactions occurred in patients with and without a psychiatric history, and were usually reversible when vigabatrin doses were reduced or gradually discontinued.

Suicide risk

Suicidal ideation and behaviour have been reported in patients receiving antiepileptic treatment in various indications. A meta-analysis of randomized, placebo-controlled studies of antiepileptic drugs also showed a slight increase in the risk of suicidal ideation and behaviour. The causes of the risk are unknown and the possibility of an increased risk with vigabatrin cannot be ruled out based on available data.

Patients must therefore be closely monitored for any signs of suicidal ideation or behaviour and appropriate treatment considered. Patients (and their care-givers) should be advised to seek medical advice if signs of suicidal ideation and behaviour occur.

Elderly and patients with renal impairment
Since vigabatrin is eliminated via the kidney, special 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 undesirable effects such as sedation and confusion (see Section Posology and method of administration).

Interactions to be taken into account:
The concomitant use of vigabatrin and clonazepam may exacerbate the sedative effect (see section Interaction with other medicinal products and other forms of interaction). Need for concomitant use must be carefully assessed.

Sabril 500 mg film coated tablets contain sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
As vigabatrin is neither metabolized nor protein bound and is not an inducer of hepatic cytochrome P450 drug-metabolising enzymes, interactions with other drugs are unlikely. However, during controlled clinical studies a gradual reduction of 16% - 33% in the plasma concentration of phenytoin has been observed. The exact nature of this interaction is presently not understood, however, in the majority of cases it is unlikely to be of therapeutic significance.

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

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 test may be quantitatively unreliable in patients taking vigabatrin (see Section Undesirable effects).

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).

The concomitant use of vigabatrin and clonazepam may exacerbate the sedative effect or lead to coma

PREGNANCY AND LACTATION

Vigabatrin should only be used during pregnancy if absolutely necessary.

Data on a limited number (n=192) of exposed pregnancies are available. Congenital anomalies were reported in 14.5% of exposed pregnancies. Of these, 64.3% were major malformations. Spontaneous abortion was reported in 10.9% of exposed pregnancies.

No definite conclusion can be drawn as to whether vigabatrin produces an increased risk of malformation when taken during pregnancy because of limited data, epilepsy itself, and the presence of concomitant anti-epilepsy medicinal products during each reported pregnancy.

Women of child bearing potential – contraception

Appropriate advice should be given to all women wishing to become pregnant or of child-bearing age. The need for antiepileptic treatment must be re-evaluated when a patient is considering pregnancy.

Pregnancy

Risks related to epilepsy and antiepileptic drugs in general

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. Monotherapy should therefore be used whenever possible.

Medical advice should be given to women starting a pregnancy or of child bearing age. The need for antiepileptic treatment must be re evaluated when a woman plans a pregnancy. If a patient treated for epilepsy is already pregnant, antiepileptic therapy should not be suddenly interrupted due to the hazard of epileptic attack relapse that might have serious outcomes both for the mother and the child.

Risks related to vigabatrin

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.

Animal studies have shown that vigabatrin has reproductive toxicity (see section Preclinical safety data).

Sabril should only be used during pregnancy if absolutely necessary.

There is very little available data on the possibility of a visual field defect occurring in children exposed to vigabatrin *in utero*.

Breast feeding

Vigabatrin is excreted in human milk. There is insufficient information on the effects of vigabatrin on newborns/infants. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from Sabril therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility studies in rats have shown no effect on male or female fertility (see section Preclinical safety data).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As a general rule, patients with uncontrolled epilepsy are not allowed to drive or handle potentially dangerous machinery. Drowsiness has been observed in clinical trials and patients should be cautioned of this possibility at the start of Sabril treatment.

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 also Section Special warnings and special precautions for use). Special care should be taken by patients driving, operating machinery or performing any hazardous task.

UNDESIRABLE EFFECTS

Summary of safety data

Mild to severe visual field defects have frequently been reported in patients receiving vigabatrin therapy. Severe cases are potentially disabling. These reactions usually occur months to years after starting vigabatrin therapy. Pooled data from prevalence surveys suggest that as many as 1/3 of patients receiving vigabatrin therapy develop visual field defects (see section 4.4).

Approximately 50% of patients in controlled clinical studies experienced undesirable effects during vigabatrin treatment. In adults, these were mostly central nervous system related, such as sedation, drowsiness, fatigue and impaired concentration. However, in children, excitation or agitation is frequent. 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 treated with vigabatrin may experience an increase in seizure frequency, including status epilepticus. Patients with myoclonic seizures may be particularly liable to this effect. New onset myoclonus and exacerbation of existing myoclonus may occur in rare cases.

Summary table of undesirable effects
Undesirable effects are ranked in order of incidence as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); frequency not known (cannot be estimated from the available data).

	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Frequency not known**
Blood and lymphatic system disorders		*anaemia*				
Psychiatric disorders*		*agitation, aggressiveness, nervousness, depression, paranoid reaction, insomnia*	*hypomania, mania, psychotic disorders*	*suicide attempt*	*hallucinations*	
Nervous system disorders	*somnolence*	*speech disorders, headache, dizziness, paraesthesia, attention and memory disorders, mental impairment (thought disturbance), tremor*	*coordination disorders (ataxia)*	*encephalopathy***	*optic neuritis*	*abnormal brain MRI findings and intramyelinic oedema (in particular in infants/young children) have been reported (see sections Special warnings and precautions for use and Preclinical safety data).* *Abnormal movements, including dystonia, dyskinesia and hypertonia have been reported, either alone or in association with abnormal MRI findings (see section Special warnings and precautions for use).*
Eye disorders	*visual field disorders*	*blurred vision, double vision, nystagmus*		*retinal disorders (mainly*	*optic nerve atrophy*	*reduced visual acuity*

	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
				peripheral)		
Gastrointestinal disorders		*nausea, vomiting, abdominal pain*				
Hepatobiliary disorders					*hepatitis*	
Skin and subcutaneous tissue disorders		*alopecia*	*rash*	*angioedema, urticaria*		
Musculoskeletal and connective tissue disorders	*arthralgia*					
General disorders and administration site conditions	*fatigue*	*oedema, irritability*				
Investigations* **		*weight gain*				

* 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 (see Section Special warnings and special precautions for use). Depression was a common psychiatric reaction in clinical trials but seldom required discontinuation of vigabatrin.
** 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. Such reactions have been fully reversible following dose reduction or discontinuation of vigabatrin (see Section Special warnings and special precautions for use).
*** Laboratory data indicate that vigabatrin treatment does not cause renal toxicity. Decreases in ALT and AST, possibly caused by inhibition by vigabatrin, have been observed.

Paediatric population
Psychiatric disorders
- Very common: excitation, agitation.

OVERDOSE
Symptoms
Vigabatrin overdose has been reported. When provided, the most common doses were between 7.5 to 30 g; however, overdoses up to 90 g have also been reported. Nearly half of the cases involved multiple drug ingestions. The most common symptoms include drowsiness or coma.

Other symptoms that were less frequently reported included dizziness, headache, psychosis, respiratory depression or apnea, bradycardia, hypotension, agitation, irritability, confusion, bahavioural disorders, and speech disorders. None of the overdoses resulted in death.

Management
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 plasma concentration by 40% to 60%.

PHARMACOLOGICAL PROPERTIES
ANTIEPILEPTIC
(N : central nervous system)
Vigabatrin is an antiepileptic drug with a clearly defined mechanism of action. Treatment with vigabatrin leads to an increase in the concentration of GABA (gamma aminobutyric acid), the major inhibitory neurotransmitter in the brain. This is because vigabatrin was designed rationally as a selective irreversible inhibitor of GABA-transaminase, the enzyme responsible for the breakdown of GABA.
Controlled and long term clinical trials have shown that vigabatrin is an effective anticonvulsant agent when given as add-on therapy in patients with epilepsy not controlled satisfactorily by conventional therapy. This efficacy is particularly marked in patients with seizures of partial origin.

Pharmacokinetic properties
Vigabatrin is a water soluble compound and it is rapidly and completely absorbed form the gastrointestinal tract. Food administration does not alter the extent of vigabatrin absorption. The drug is widely distributed with an apparent volume of distribution slightly greater than total body water. Plasma and cerebrospinal fluid concentration are linearly related to dose over the recommended dose range. There is no direct correlation between plasma concentration and efficacy. The duration of effect of the drug is dependent on the GABA transaminase resynthesis rate. 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 as unchanged drug in the urine in the first 24 hours post-dose. No metabolites have been identified.
Vigabatrin does not induce the hepatic cytochrome P450 enzymes nor is it metabolized or protein bound. Therefore drug interactions are unlikely.

Preclinical safety data
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. In the monkey these lesions are minimal or equivocal. This effect is caused by a separation of the outer lamellar sheath of myelinated fibres, a change characteristic of intramyelinic oedema was reversible on stopping vigabatrin treatment and even with continued treatment histologic regression was observed. However, in rodents, minor residual changes consisting of swollen axons (eosinophilic spheroids) and mineralized microbodies have been observed. In the dog, the result of an electrophysiological study indicate that intramyelinic oedema is associated with an increase in the latency of the somatosensory evoked potential which is reversible when the drug is withdrawn.

Vigabatrin-associated retinotoxicity has only been observed in albino rats, but not in pigmented rats, dogs or monkeys. The retinal changes in albino rats were characterized as focal or multifocal disorganisation of the outer nuclear layer with displacement of nuclei into the rod and cone area. The outer layers of retina were not affected. These lesions were observed in 80-100% of animals at the dose of 300 mg/kg/day orally. The histologic appearance of these lesions was similar to that found in albino rats following excessive exposure to light. However, the retinal changes may also represent a direct drug-induced effect.

Animal experiments have shown that vigabatrin has no negative influence on fertility or pup development. No teratogenicity was seen in rats in doses up to 150 mg/kg (3 times the human dose) or in rabbits in doses up to 100 mg/kg. However, in rabbits, a slight increase in the incidence of cleft palate at doses of 150-200 mg/kg was seen.

Studies with vigabatrin revealed no evidence of mutagenic or carcinogenic effects.

SHELF LIFE AND SPECIAL STORAGE CONDITIONS
3 years – Store below 30°C
Do not use later than the expiry date indicated on the carton

PRESENTATION
Box of 100 tablets in blister pack (PVC/Aluminium).

PRESCRIPTION
Initial prescription restricted to neurologist, paediatricians or neuro-psychiatrists.

MANUFACTURER
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