Sabril 500mg Tablet- Draft Package Insert

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vigabatrin..... 500 mg
For one film-coated tablet

PHARMACEUTICAL FORM

Film-coated tablets.
White to off-white, oval, biconvex tablets with a score line on one side and "SABRIL" engraved on the other side. The score line makes it possible to take half a tablet at a time if the whole tablet is difficult to swallow, but is not to be used to divide into two equal doses.

CLINICAL PARTICULARS

Therapeutic indications

Treatment in combination with other anti-epileptic drugs for patients with resistant partial epilepsy with or without secondary generalization when 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 or pediatric neurology. Follow-up should be carried out under the supervision of a specialist in epileptology, neurology or pediatric neurology.

Sabril is intended for oral administration once or twice daily and can be taken before or after meals. The tablets should be swallowed with half a glass of water.

If there is no clinically significant improvement in epileptic symptoms following well-conducted initial treatment, vigabatrin must not be continued. Vigabatrin should gradually be withdrawn under close medical supervision.

Tablets are not suitable for children under the age of 6 years, because of the risk of choking.

Adults

Maximum efficacy is usually obtained with a daily dose of 2 to 3 g. A starting dose of 1 g daily should be added to the patient's current anti-epileptic drug regimen. The daily dose must then be increased in 0.5 g increments at weekly intervals depending on clinical response and tolerability. The maximum recommended dose is 3 g/day.

There is no correlation between the plasma concentrations and efficacy. The duration of action of the drug is dependent on the rate of GABA-T resynthesis rather than plasma drug concentrations (see *Pharmacodynamic and Pharmacokinetic properties*).

Children

The recommended starting dose in children is 40 mg/kg/day. Recommendations in relation to bodyweight for maintenance treatment are as follows:

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

The maximum recommended dose in each of these bodyweight categories must not be exceeded.

Elderly subjects and patients with renal insufficiency

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 60 ml/min. Adjustment of dose or frequency of administration must be considered. These patients may respond to a lower maintenance dose. Patients must be closely monitored for possible undesirable effects such as sedation or confusion (see *Special warnings and special precautions for use* and *Undesirable effects*).

Contraindications
Hypersensitivity to vigabatrin or to any excipients of the medicinal product.

Special warnings and precautions for use
Except for the treatment of infantile spasms, Sabril must not be instituted 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 Pharmacodynamic 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 treatment discontinuation cannot be excluded.

Therefore, vigabatrin should only be used after careful assessment of the benefits and risk compared with available therapeutic 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*).

<u>Visual Field Defects (VFD)</u>
Based on currently available data, the usual pattern of visual field defects 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), frequently a nasal annular defect is seen. However, the VFDs reported in patients receiving vigabatrin have ranged from mild to severe. Serious 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 spontaneously noticed any symptoms, even in cases where a severe defect was observed in perimetry. Available evidence suggests that visual field defects are irreversible even after discontinuation of vigabatrin. A deterioration of the VFD after treatment discontinuation 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 *Pharmacodynamic 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 term 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 standardised 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 only be used 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 vigabatrin-related VFDs. These responses are delayed and reduced beyond the normal limits. Such changes have not been seen in vigabatrin treated patients without VFDs.

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 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 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 must 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 from 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 associated 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 (see *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.

Movement 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 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 some patients may experience an increase in seizure frequency or the onset of new types of seizures with vigabatrin (see *Undesirable effects*). These effects may also occur as a 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 should be used with caution in patients with a history of psychosis, depression or behavioral disorders. Adverse psychiatric reactions (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 behavior have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo-controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behavior. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for vigabatrin.

Therefore, patients should be monitored for signs of suicidal ideation and behavior, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice immediately should signs of suicidal ideation or behavior emerge.

Elderly and patients with renal impairment

Since vigabatrin is eliminated via the kidney, special caution should be exercised in patients with creatinine clearance of less than 60 ml/min and in elderly patients. These patients should be monitored closely for undesirable effects such as sedation and confusion (see *Posology and method of administration*).

Interactions to be taken into account:

The concomitant use of vigabatrin and clonazepam may exacerbate the sedative effect (see *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 metabolism, interactions with other drugs are unlikely. However, during controlled clinical trials, a gradual reduction of 16 to 33% in phenytoin plasma concentrations was reported. The exact nature of this interaction is not understood; however, in the majority of cases, the interaction did not appear to be clinically relevant.

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.

Vigabatrin may lead to decreased plasma alanine aminotransferase (ALT) and to a lesser extent, to decreased aspartate aminotransferase (AST) levels. The decrease in ALT levels was between 30% and 100%. Therefore, these liver tests may be quantitatively unreliable in patients taking vigabatrin (see *Undesirable effects*).

Vigabatrin may increase in amino acid levels in the urine possibly leading to false positive results when testing for certain rare genetic metabolic disorders (e.g., alpha aminoadipic aciduria).

Concomitant use of vigabatrin and clonazepam may exacerbate the sedative effect (see *Special warnings and precautions for use*)

Fertility and pregnancy and lactation
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 reevaluated 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 with Sabril. Patients should be evaluated for the presence of visual field defects (see *Special warnings and 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 *Special warnings and precautions for use*).

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,*	*coordination disorders (ataxia)*	*encephalopathy***	*optic neuritis*	*abnormal brain MRI findings and intramyelinic oedema (in*

	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		paraesthesia, attention and memory disorders, mental impairment (thought disturbance), tremor				*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 peripheral)*	*optic nerve atrophy*	*reduced visual acuity*
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 precautions for use*). Depression was a common psychiatric reaction in clinical trials but seldom required discontinuation of vigabatrin.

** Rare cases of encephalopathic symptoms, such as marked sedation, stupor and confusion associated 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 precautions for use*).

*** Laboratory data indicate that vigabatrin treatment does not cause renal toxicity. A decrease in ALT and AST levels, possibly caused by inhibition by vigabatrin, has 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 and 30 g; however, overdoses up to 90 g have been reported. Nearly half of the cases involved multiple-drug overdose. The most commonly reported symptoms include drowsiness or coma.

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

Management
There is no specific antidote. The usual symptomatic measures should be employed. Measures to remove unabsorbed drug must be considered. Activated charcoal has been shown to not significantly adsorb vigabatrin in an *in vitro* study. The effectiveness of haemodialysis in the treatment of vigabatrin overdose is unknown. In isolated cases in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced plasma vigabatrin concentrations by 40% to 60%.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Antiepileptics, ATC code: N03AG04 (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. Vigabatrin is a selective irreversible inhibitor of GABA-transaminase, the enzyme responsible for the catabolism of GABA.

Controlled and long-term clinical trials have shown that vigabatrin is an effective anticonvulsant agent when given as supportive therapy in patients with epilepsy not controlled satisfactorily by conventional therapy. This efficacy is particularly marked in patients with partial seizures.

The epidemiology of VFD in patients with refractory partial epilepsy was examined in an observational, open-label, multicenter, comparative, parallel group, Phase IV study, including 734 patients, at least 8 years old, with refractory partial epilepsy for at least one year.

Patients were split in three treatment groups: patients currently treated with vigabatrin (group I), patients previously exposed to vigabatrin (group II) and patients never exposed to vigabatrin (group III).

The following table presents the main findings at inclusion and at the first and last evaluations in the evaluable population (n=524):

	Children (aged 8 to 12)	**Adults (aged >12 years)**

	Group I[1] N = 38	Group II[2] N = 47	Group III N = 41	Group I[3] N = 150	Group II[4] N = 151	Group III N = 97
Visual field defect with no identified etiology						
Observed at inclusion	1 (4.4%)	3 (8.8%)	2 (7.1%)	31 (34.1%)	20 (19.2%)	1 (1.4%)
Observed at first conclusive evaluation	4 (10.5%)	6 (12.8%)	2 (4.9%)	59 (39.3%)	39 (25.8%)	4(4.1%)
Observed at last conclusive evaluation	10 (26.3%)	7 (14.9%)	3 (7.3%)	70 (46.7%)	47 (31.1%)	5 (5.2%)

[1] Median treatment duration: 44.4 months; mean daily dose: 1.48 g
[2] Median treatment duration: 20.6 months; mean daily dose: 1.39 g
[3] Median treatment duration: 48.8 months; mean daily dose: 2.10 g
[4] Median treatment duration: 23.0 months; mean daily dose: 2.18 g

Pharmacokinetic properties
Vigabatrin is a water-soluble compound and it is rapidly and completely absorbed from the gastrointestinal tract.

Food intake does not alter vigabatrin absorption. The drug is widely distributed with an apparent volume of distribution slightly greater than total body water. Plasma and cerebrospinal fluid concentrations are dose-proportional over the recommended dose range.

There is no direct correlation between plasma concentrations and efficacy. The duration of action of the drug is dependent on the GABA-T resynthesis rate.

Vigabatrin is eliminated from the plasma with a terminal elimination half-life of 5 to 8 hours with approximately 70% of a single oral dose excreted unchanged in the urine 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 the 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 the white matter of rats, mice and dogs at doses of 30 to 50 mg/kg/day. In the monkey, these lesions are minimal or debatable. This effect is caused by detachment of the outer lamellar layer of myelinated fibers, a change characteristic of intramyelinic edema. In both the rat and the dog, the intramyelinic edema 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 results of an electrophysiological study indicate that intramyelinic edema is associated with an increase in the latency of the sensory evoked potential which is reversible when the drug is discontinued.

Vigabatrin-associated retinotoxicity has been observed in albino rats, but not in pigmented rats, dogs or monkeys. The retinal changes in albino rats were characterized by focal or multifocal disorganization of the outer nuclear layer with displacement of nuclei into the layer of rods and

cones. The other layers of retina were not affected. These lesions were observed in 80 to 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 be a direct drug-induced effect.

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

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

PHARMACEUTICAL PARTICULARS

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

SHELF LIFE AND STORAGE
3 years – Store below 30°C.
Do not use later than the expiry date indicated on the carton.
Keep out of reach of children.

MANUFACTURER
PATHEON FRANCE S.A.
40, Boulevard de Champaret
38300 Bourgoin-Jallieu, France.

DATE OF REVISION
May 2021
CCDS 14 based on French SmPC Jan 2021