SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sabril Tablets 500mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains
Vigabatrin 500mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Monotherapy in the treatment of infantile spasms (West's syndrome).

4.2 Posology and method of administration

Sabril treatment may only be initiated by a specialist in epileptology, neurology or paediatric 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.

If the control of epilepsy is not clinically significantly improved after an adequate trial, vigabatrin treatment should not be continued. Vigabatrin should be gradually withdrawn under close medical supervision.

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 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties).

Children

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

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

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

Infants - Monotherapy for infantile spasms (West's Syndrome). The recommended starting dose is 50mg/kg/day. This may be titrated over a period of one week if necessary. Doses of up to 150mg/kg/day have been used with good tolerability.

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 4.4 Special warnings and special precautions for use, and 4.8 Undesirable effects).

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

Except for the treatment of infantile spasms, Sabril should not be initiated as monotherapy.

Visual field defects have been reported in patients receiving vigabatrin with a high prevalence (about 1/3 of patients). The onset is usually after months to years of vigabatrin therapy. The degree of visual field restriction may be severe and this may have practical consequences for the patient. Most of the patients with perimetry-confirmed defects have been asymptomatic. Hence, 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. A specifically developed method based on field specific Visual Evoked Potentials (VEP) is available from the company on request to test the presence of peripheral vision in children aged 3 years and above. At present this method has not been validated in the detection of vigabatrin attributed visual field defects. Electroretinography may be useful but should be used only in adults who are unable to cooperate with perimetry or in the very young (see Visual Field Defects).

Available data suggests that visual field defects are irreversible even after discontinuation of vigabatrin.

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.

3/10

Patients should undergo systematic screening examination when starting vigabatrin and at regular intervals for detection of visual field defects. Visual field testing should continue at 6 month intervals for the whole duration of treatment (see Visual Field Defects).

Visual Field Defects (VFD)

Based on available data, the usual pattern is a concentric constriction of the visual field of both eyes, which is generally more marked nasally than temporally. In the central visual field (within 30 degree of eccentricity), frequently an annular nasal defect is seen. Central visual acuity is not impaired. However, the VFDs reported in patients receiving vigabatrin have ranged from mild to severe. Severe cases are potentially disabling.

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.

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.

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

Appropriate visual field testing (perimetry) by using a standardised static perimetry (Humphrey or Octopus) or kinetic perimetry (Goldmann) must be performed before treatment initiation and at six-month intervals for the whole duration of treatment. Static perimetry is the preferred method for detecting vigabatrin associated visual field defect.

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 a vigabatrin associated VFD. 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 observed during follow-up, consideration should be given to gradual discontinuation of vigabatrin. 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.

Children

Perimetry is seldom possible in children less than 9 years of developmental age. The risks of treatment must be very carefully weighed against possible benefit in children. Currently, there is no established method to diagnose or exclude visual field defects in children in whom a standardised perimetry cannot be performed. A specifically developed method based on field specific Visual Evoked Potentials (VEP) is available from the company on request to test the presence of peripheral vision in children aged 3 years and above. At present this method has not been validated in the detection of vigabatrin attributed visual field defects. If the method reveals normal central visual field response but an absent peripheral response, benefit-risk of vigabatrin must be reviewed and

4/10

consideration given to gradual discontinuation. The presence of peripheral vision does not exclude the possibility of developing VFD. Electroretinography may be useful but should be used only in children less than 3 years of age.

Neurological and psychiatric conditions

In view of the results of the animal safety studies (see Section 5.3 Preclinical safety data), it is recommended that patients treated with vigabatrin are closely observed for adverse effects on neurological function.

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. (See Section 4.8 Undesirable effects).

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 Section 4.8 Undesirable effects). These phenomena may also be the consequence of an overdosage, 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. If a patient is to be withdrawn from vigabatrin treatment, it is recommended that this is done 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 behavioural problems. Psychiatric events (e.g., agitation, depression, abnormal thinking, paranoid reactions) have been reported during vigabatrin treatment. These events occurred in patients with and without a psychiatric history, and were usually reversible when vigabatrin doses were reduced or gradually discontinued.

Elderly and patients with renal impairment

Since vigabatrin is eliminated via the kidney, 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 4.2 Posology and method of administration).

4.5 Interaction with other medicinal products and other forms of interaction

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. 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 tests may be quantitatively unreliable in patients taking vigabatrin. (See Section 4.8 Undesirable effects)

5/10

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

4.6 Pregnancy and lactation

Vigabatrin should only be used during pregnancy if clearly 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 antiepilepsy medicinal products during each reported pregnancy.

Women of child bearing potential/ contraception
Specialized advice should be provided to all patients who could begin a pregnancy or who are in the fertile age. The need of antiepileptic treatment must be re-evaluated when a patient plans a pregnancy.

Pregnancy
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.

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 foetus.

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

Fertility
Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data).

Lactation
Vigabatrin is excreted into breast milk. Breast feeding is not recommended during vigabatrin treatment.

4.7 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. In view of the fact that drowsiness has been observed in clinical trials with Sabril, patients should be warned of this possibility at the start of 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 4.4 Special Warnings and special precautions for use). Special care should be taken by patients driving, operating machinery or performing any hazardous task.

6/10

4.8 Undesirable effects

Visual field defects ranging from mild to severe have been reported frequently in patients receiving vigabatrin. Severe cases are potentially disabling. The onset is usually after months to years of vigabatrin therapy. Pooled data from prevalence surveys suggest that as many as 1/3 of patients receiving vigabatrin therapy develop visual field defects (see also Section 4.4 Special warnings and special precautions for use).

Approximately 50% of patients in controlled clinical studies have 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 may experience an increase in seizure frequency, including status epilepticus with vigabatrin. Patients with myoclonic seizures may be particularly liable to this effect. New onset myoclonus and exacerbation of existing myoclonus may occur in rare cases.

Very rare cases of hepatic reactions (including hepatitis) have been reported.
Cases of speech disorder have been reported.

Very common (>1/10)	*General disorders*: Somnolence, fatigue *Psychiatric disorders**: Excitation and agitation (children) *Eye disorders*: Visual field defect
Common (>1/100, <1/10)	*General disorders*: Headache, weight gain, tremor, oedema *Nervous system disorders*: Dizziness, paresthesia, disturbance of concentration and memory *Psychiatric disorders**: Agitation, aggression, nervousness, irritability, depression, thought disturbance, paranoid reaction *Gastrointestinal disorders*: Nausea, abdominal pain *Eye disorders*: Blurred vision, diplopia, nystagmus
Uncommon (>1/1,000, <1/100)	*Nervous system disorders*: Ataxia *Psychiatric disorders**: Hypomania, mania, psychosis *Skin disorders*: Rash
Rare (<1/1,000)	*General disorders*: Angioedema, urticaria *Nervous system disorders*: Encephalopathic symptoms** *Psychiatric disorders*: Suicide attempt *Eye disorders*: Retinal disorder (such as peripheral retinal atrophy)
Very rare (<1/10,000)	*Eye disorders*: Optic neuritis, optic atrophy *Psychiatric disorders*: Hallucinations

*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 4.4 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 4.4 Special warnings and special precautions for use).

Laboratory data indicate that vigabatrin treatment does not lead to renal 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 haemoglobin which rarely attains clinical significance.

4.9 Overdose

Symptoms

Vigabatrin overdose has been reported. When provided, doses most commonly were between 7.5 to 30g; however, ingestions up to 90g have been reported. Nearly half of the cases involved multiple drug ingestions. When reported, the most common symptoms included drowsiness or coma. Other less frequently reported symptoms included vertigo, headache, psychosis, respiratory depression or apnea, bradycardia, hypotension, agitation, irritability, confusion, abnormal behaviour, and speech disorder. 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 vigabatrin plasma concentrations by 40% to 60%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Antiepileptics, ATC code: N03AG04

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.

5.2 Pharmacokinetic properties

Vigabatrin is a water soluble compound and it is rapidly and completely absorbed from 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 concentrations are linearly related to dose over the recommended dose range.

8/10

There is no direct correlation between plasma concentration and efficacy. The duration of the effect of the drug is dependent on the GABA transaminase re-synthesis 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 metabolised or protein bound. Therefore drug interactions are unlikely.

5.3 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 white matter tracts of rat, mouse and dog at doses of 30-50mg/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. In both rat and dog the 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 mineralised microbodies have been observed. In the dog, the results 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.

In humans, there is no evidence of intramyelinic oedema. Tests done to confirm lack of significant adverse effect on neurological function include evoked potentials, CAT scans, magnetic resonance imaging, CSF analyses and in a small number of cases, neuropathological examinations of brain specimens.

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 characterised as focal or multifocal disorganisation of the outer nuclear layer with displacement of nuclei into the rod and cone area. The other layers of retina were not affected. These lesions were observed in 80-100% of animals at the dose of 300mg/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 150mg/kg (3 times the human dose) or in rabbits in doses up to 100mg/kg. However, in rabbits, a slight increase in the incidence of cleft palate at doses of 150-200mg/kg was seen.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
microcrystalline cellulose
sodium starch glycolate
magnesium stearate
hydroxypropyl methylcellulose

titanium dioxide
polyethylene glycol 8000
deionised water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

None Stated

6.5 Nature and contents of container

Container(s): PVC/Aluminium foil blister packs in cardboard cartons.

Pack size: 50 and 100 tablets

6.6 Instructions for use and handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma Limited
50 Kings Hill Avenue
Kings Hill
West Malling
Kent
ME19 4AH

8. MARKETING AUTHORISATION NUMBER(S)

PL 04425/0171

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26th January 2001/19th June 2006

10. DATE OF REVISION OF THE TEXT

19th June 2006