SABRIL®

VIGABATRIN

Tablets 500 mg

Sachets 0.5 g

ANTIEPILEPTIC

ACTION AND CLINICAL PHARMACOLOGY

SABRIL (vigabatrin) is an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the catabolism of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the brain. The mechanism of action of vigabatrin is attributed to irreversible enzyme inhibition of GABA-T, and consequent increased levels of the inhibitory neurotransmitter, GABA.

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

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

Clinical Trials

In clinical trials, including double-blind, placebo-controlled studies involving 354 patients with drug-resistant complex partial seizures, vigabatrin reduced seizure frequency by 50% or more in approximately half of the patients studied. *The efficacy of vigabatrin in children with refractory partial seizures* was similar to that seen in adult patients.

A multicentre, double-blind, placebo-controlled, parallel group study was performed to evaluate the safety and efficacy of vigabatrin versus placebo as first line monotherapy in the treatment of newly diagnosed infantile spasms. The study involved a 2-3 day baseline period, a 5 day double-blind treatment phase, and a six month open-label follow-up. Complete cessation of spasms on the final day of double-blind treatment was achieved by 45% of vigabatrin patients (N=20) and by 15% of placebo patients (N=20). According to the Clinical Global Impression of Improvement, 80% of vigabatrin patients and 15% of placebo patients were considered to be moderately or markedly improved. These differences between the treatment groups were statistically significant. In the 6 month open-label extension of this study, 51% of patients (N=35) could be maintained on vigabatrin monotherapy, while 49% required the addition of other antiepileptic drugs.

In a retrospective analysis of 192 infants diagnosed with infantile spasms who had been treated with vigabatrin as first-line monotherapy (mean steady state dose of 99 mg/kg/day), 162 patients (84%) experienced an initial decrease in spasm frequency of at least 50% with 131 patients (68%) experiencing a complete resolution of spasms. Demographic factors which seemed to be predictive of a positive response to vigabatrin included an etiology of tuberous sclerosis and an age of onset of illness of less than 3 months. According to long-term (mean 9.2 months) follow-up data for this retrospective study, 42% of the 192 patients could be successfully maintained on vigabatrin monotherapy, while the remainder required additional antiepileptic treatments. Of the 131 patients who were considered to be complete responders, 85 (65%) experienced neither relapse of infantile spasms nor onset of other seizure types during long-term follow-up.

Pharmacokinetics

Vigabatrin is rapidly absorbed following oral administration and peak plasma concentrations are reached within two hours. Vigabatrin is widely distributed with an apparent volume of distribution slightly greater than total body water. The primary route of elimination is via the kidney, with little metabolic transformation occurring. Following a single dose, approximately 70% is excreted in the urine as unchanged drug within the first 24 hours post-dose. The plasma elimination half-life is approximately 5-8 hours in young adults and 12-13 hours in the elderly. In renal impairment the elimination is prolonged and the rate of renal clearance is directly related to creatinine clearance (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). Vigabatrin does not induce the hepatic cytochrome P450 system nor is it extensively metabolized or plasma-protein bound. *Administration of vigabatrin with food slightly* reduces the rate, but not the extent of absorption.

INDICATIONS AND CLINICAL USE

SABRIL (vigabatrin) is indicated for the adjunctive management of epilepsy which is not satisfactorily controlled by conventional therapy.

SABRIL is indicated as initial monotherapy for the management of infantile spasms (West syndrome). Clinical experience indicates that at least 50% of patients may require the addition of other antiepileptic drugs owing to relapse or emergence of other seizure types following an initial response to the treatment of infantile spasms with SABRIL.

Vigabatrin should be used under close monitoring by a neurologist.

CONTRAINDICATIONS

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

WARNINGS

Ophthalmological Abnormalities

In the course of international post-marketing surveillance, a number of ophthalmological abnormalities, including visual field constriction, bilateral optic disc pallor, subtle peripheral retinal atrophy, optic atrophy, and optic neuritis have been reported in patients receiving SABRIL (vigabatrin) often in combination with other antiepileptic agents.

According to these reports, the time to onset of symptomatic visual field constriction, when specified, has ranged from less than one month to over six years. Preliminary data suggest that the onset of symptoms tends to be reported most frequently within the first year of treatment.

***Initial and periodic (approximately every 3 months) ophthalmological* examinations are recommended during SABRIL treatment including expert mydriatic peripheral fundus examination and visual field perimetry.**

Patients should be questioned at frequent intervals during treatment for narrowing of the field of vision or loss of visual acuity and should be advised to report any emerging visual problems promptly to their physicians.

The use of SABRIL should be discontinued in patients exhibiting any of the above ophthalmological abnormalities, unless the benefits of continued treatment in terms of seizure control are considered to outweigh the risk of visual impairment.

In view of the difficulties of assessing visual field in infants and young pediatric patients, SABRIL should be used in these patient groups only if clearly indicated. The need for continued use of SABRIL should be reassessed periodically. Frequent examination by a pediatric ophthalmologist are recommended for all infants and young children receiving SABRIL.

Neurotoxicity in Animals

Rat, Mouse and Dog: Safety studies carried out in the rat, mouse and dog at doses of 30 to 50 mg/kg/day and higher, caused dose- and time-dependent microvacuolation within certain white matter tracts of the brain (the cerebellum, reticular formation and thalamus in rodents and the columns of the fornix and optic tracts in dogs were most affected). The microvacuolation was caused by the separation of the outer lamellar sheath of myelinated fibres, a change characteristic of non-inflammatory intramyelinic edema.

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

Monkey: In monkeys, the oral administration of 300 mg/kg/day for 16 months produced minimal microvacuolation with equivocal differences between treated and control animals. Low oral absorption of vigabatrin in the monkey resulted in an actual absorbed dose of 75 mg/kg/day. In spite of the poor absorption, cerebrospinal fluid (CSF) levels of vigabatrin in the monkeys *were comparable to those seen in rats treated with 300 mg/kg/day; however,* GABA levels in the CSF and the brain cortex in treated monkeys were not significantly different from untreated monkeys. This finding may explain the reason for the equivocal effects, since the intramyelinic edema associated with vigabatrin treatment appears to be related to increased brain GABA levels.

Evoked Potentials

Evoked potentials in animals: In the dog, studies indicate that intramyelinic edema is associated with increased latencies in somatosensory and visual evoked potentials. Magnetic resonance imaging (MRI) changes also correlated with intramyelinic edema in the fornix, thalamus and hypothalamus.

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

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

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

Use in Pregnancy and Lactation

In a teratology study in the rabbit a dose-related incidence, 2% and 9%, of cleft palate was observed at doses of 150 and 200 mg/kg/day, respectively. In animal reproductive studies neurohistopathology was not performed on the fetuses, therefore it is not known whether microvacuolation occurred *in utero.* The possibility that microvacuolation or other neurotoxicity may occur in human fetuses cannot be disregarded.

PRECAUTIONS

Use in Patients with a History of Psychosis

Behavioural disturbances such as aggression and psychotic episodes have been reported following initiation of vigabatrin therapy. A history of abnormal behaviour or psychosis appears to be a predisposing factor for such reactions, therefore treatment in such patients should be initiated cautiously at low doses and with frequent monitoring.

Use in the Elderly and in Patients with Renal Impairment

Vigabatrin is eliminated via the kidney and caution should be exercised when administering the drug to elderly patients and to patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Use in Patients with Myoclonic Seizures

As with other antiepileptic drugs, some patients may experience an increase in seizure frequency with vigabatrin. Patients with myoclonic seizures may be particularly liable to this effect.

Discontinuation of Therapy

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

Drug Interactions

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

Occupational Hazards

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

ADVERSE REACTIONS

SABRIL (vigabatrin) is generally well tolerated in epileptic patients. Adverse events are mainly CNS-related and probably a secondary consequence of increased GABA levels caused by vigabatrin. The safety of SABRIL was evaluated in 438 *epileptic patients treated in double-blind, placebo-controlled* clinical trials. The relationship of adverse events to SABRIL therapy was not clearly established as patients were taking other antiepileptic drugs concomitantly.

Most Frequent Adverse Events (incidence higher than placebo): Fatigue, headache, drowsiness, dizziness, depression, weight increase, agitation, tremor, abnormal vision, amnesia.

Post-Marketing Ophthalmological Adverse Events: Cases of peripheral visual field constriction, bilateral optic disc pallor, subtle peripheral retinal atrophy, and optic atrophy have been reported. There are also rare reports of optic neuritis (see WARNINGS).

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

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

Body System Adverse Event	Placebo* N = 320 n	%	SABRIL* N = 438 n	%
Body as a Whole				
weight increase	12	3.8	54	12.3
pain	21	6.6	33	7.5
asthenia	15	4.7	19	4.3
appetite increase	6	1.9	15	3.4
fever	7	2.2	14	3.2
chest pain	8	2.5	12	2.7
accident injury	14	4.4	12	2.7
Cardiovascular				
edema, dependent	2	0.6	13	3.0
Dermatologic				
rash	15	4.7	20	4.6
skin disorder	11	3.4	18	4.1
Gastrointestinal				
nausea	25	7.8	39	8.9
diarrhea	17	5.3	31	7.1
dyspepsia	22	6.9	27	6.2
abdominal pain	12	3.8	25	5.7
constipation	10	3.1	24	5.5
vomiting	15	4.7	24	5.5
tooth disorder	4	1.2	12	2.7
Hematologic				
purpura	11	3.4	20	4.6
Musculoskeletal				
arthralgia	13	4.1	32	7.3
back pain	13	4.1	23	5.3
arthrosis	7	2.2	11	2.5
Nervous System				
fatigue	44	13.8	118	26.9
headache	79	24.7	113	25.8
drowsiness	46	14.4	97	22.1
dizziness	41	12.8	82	18.7
tremor	22	6.9	48	11.0
vision abnormal	18	5.6	47	10.7
amnesia	12	3.8	45	10.3
nystagmus	15	4.7	42	9.6
diplopia	17	5.3	39	8.9
ataxia	14	4.4	35	8.0
confusion	7	2.2	30	6.8
paresthesia	6	1.9	25	5.7
coordination abnormal	7	2.2	22	5.0
seizures (not specified)	7	2.2	22	5.0
gait abnormal	10	3.1	20	4.6
concentration impaired	3	0.9	16	3.7
speech disorder	3	0.9	15	3.4
hypoesthesia	7	2.2	13	3.0
vertigo	4	1.2	13	3.0
hyporeflexia	1	0.3	12	2.7
Psychiatric				
depression	10	3.1	57	13.0
agitation	24	7.5	48	11.0
insomnia	19	5.9	29	6.6
anxiety	11	3.4	24	5.5
emotional lability	9	2.8	21	4.8
thinking abnormal	1	0.3	15	3.4
aggressive reaction	6	1.9	12	2.7
nervousness	7	2.2	12	2.7
personality disorder	3	0.9	9	2.1
Respiratory				
throat irritation	19	5.9	29	6.6
congestion	21	6.6	22	5.0
upper respiratory tract infection	10	3.1	21	4.8
sinusitis	6	1.9	10	2.3
coughing	14	4.4	9	2.1
Special Senses				
eye pain	1	0.3	11	2.5
earache	4	1.2	10	2.3
Urogenital				
dysmenorrhea	4	1.2	15	3.4
urinary tract infection	0	0	13	3.0
menstrual disorder	5	1.6	10	2.3
Other				
infection viral	36	11.3	56	12.8

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

The sedative effect of vigabatrin decreases with continuing treatment.

Other adverse events that have been reported less frequently include hypomania, mania, psychosis and suicide attempt.

Rare instances of marked sedation, stupor and confusion associated with non-specific slow wave activity on electroencephalogram have been described soon after the introduction of vigabatrin therapy. These events have been reversible following dose reduction or discontinuation of vigabatrin.

Rare reports of hypersensitivity reactions (including angioedema and urticaria) have been received.

As with other antiepileptic drugs, some patients may experience an increase *in seizure frequency with vigabatrin treatment* (see PRECAUTIONS).

Laboratory data indicate that vigabatrin treatment does not lead to renal or hepatic toxicity. Chronic treatment with vigabatrin may be associated with a slight decrease in hemoglobin, which rarely attains clinical significance.

Pediatric Safety

Safety data is available in 299 children, aged 2 months to 16 years (1 patient was 18 years of age), participating in clinical trials with vigabatrin. Relationship of adverse events to vigabatrin therapy was not clearly established as children were taking other antiepileptic drugs concomitantly.

The most frequent adverse event observed in children was "hyperactivity" (reported as hyperkinesia 7.7%, agitation 2.3%, excitation 0.3% or restlessness 0.7%), which was observed in 11.0% of children, an incidence higher than that seen in adults. There have been post-marketing reports of visual field constriction, optic disc pallor, optic atrophy, and optic neuritis in pediatric patients receiving *SABRIL* treatment (see *WARNINGS*). Other commonly

References:

1. Grant SM and Heel RC. Vigabatrin: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. *Drugs,* 1991;41(6):889-926.
2. Arzimanoglou AA, Dumas C, Chirardi L et al. Multicentre clinical evaluation of vigabatrin (Sabril) in mild to moderate partial epilepsies. *Epilepsia,* 1995;36(S3).
3. Reynolds EH, Ring HA, Farr IN et al. Open, double-blind and long-term study of vigabatrin in chronic epilepsy. *Epilepsia,* 1991;32(4):530-538.
4. Dodrill CB, Arnett JL, Sommerville KW and Sussman NM. Effects of differing dosages of vigabatrin (Sabril) on cognitive abilities and quality of life in epilepsy. *Epilepsia,* 1995;36(2):164-173.