Vigabatrin Oral Solution USP, 500 mg

Viganer®t

Tentative

To be sold by retail on the prescription of Neurologist only

PRESCRIBING INFORMATION

WARNING: PERMANENT VISION LOSS

- **Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, Vigabatrin also can damage the central retina and may decrease visual acuity.**
- **The onset of vision loss from Vigabatrin is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years.**
- **Symptoms of vision loss from Vigabatrin are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient or caregiver, can still adversely affect function.**
- **The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.**
- **Vision assessment is recommended at baseline (no later than 4 weeks after starting Vigabatrin), at least every 3 months during therapy, and about 3 to 6 months after the discontinuation of therapy.**
- **Once detected, vision loss due to Vigabatrin appears to be irreversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.**
- **Consider drug discontinuation, balancing benefit and risk, if vision loss is documented.**
- **Risk of new or worsening vision loss continues as long as Vigabatrin is used. It is possible that vision loss can worsen despite discontinuation of Vigabatrin.**
- **Because of the risk of vision loss, Vigabatrin should be withdrawn from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation and within 2-4 weeks of initiation for patients with infantile spasms, or sooner if treatment failure becomes obvious. Patient response to and continued need for Vigabatrin should be periodically reassessed.**
- **Vigabatrin should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks.**
- **Vigabatrin should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.**
- **Use the lowest dosage and shortest exposure to Vigabatrin consistent with clinical objectives**

1. GENERIC NAME

Vigabatrin Oral Solution USP, 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pouch packet contains

Vigabatrin, USP.....500 mg

3. DOSAGE FORM AND STRENGTH

Vigabatrin Oral Solution USP, 500 mg is available as Vigabatrin powder for oral solution.

4. CLINICAL PARTICULARS

4.1. Indications

Refractory Complex Partial Seizures (CPS)

Vigabatrin is indicated for the treatment of Refractory Complex Partial Seizures in patients 2 years of age and older.

It should be used as an adjuvant therapy in patients who have responded inadequately to several alternative treatments.

Infantile Spasms

Vigabatrin is indicated as monotherapy for patients with infantile spasms 1 month to 2 years of age.

4.2. Posology and Method of Administration

Important Dosing and Administration Instructions

Dosing

Use the lowest dosage and shortest exposure to Vigabatrin consistent with clinical objectives.

The Vigabatrin dosing regimen depends on the indication, age group, weight, and dosage form (tablets or powder for oral solution). Patients with impaired renal function require dose adjustment.

Monitoring of Vigabatrin plasma concentrations to optimize therapy is not helpful.

Administration

Vigabatrin is given orally with or without food.

Vigabatrin powder for oral solution should be mixed with water prior to administration. A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

If a decision is made to discontinue Vigabatrin, the dose should be gradually reduced.

Refractory Complex Partial Seizures

Adults (Patients 17 Years of Age and Older)

Treatment should be initiated at 1000 mg/day (500 mg twice daily). Total daily dose may be increased in 500 mg increments at weekly intervals, depending on response. The recommended dose of Vigabatrin in adults is 3000 mg/day (1500 mg twice daily). A 6000 mg/day dose has not been shown to confer additional benefit compared to the 3000 mg/day dose and is associated with an increased incidence of adverse events.

Patients upto 16 Years of Age

The recommended dosage is based on body weight and administered as two divided doses as shown in below table. The dosage may be increased in weekly intervals to the total daily maintenance dosage, depending on response.

Pediatric patients weighing more than 60 kg should be dosed according to adult recommendations.

CPS Dosing Recommendations for Pediatric Patients Weighing 10 kg up to 60 kg††

Body Weight [kg]	Total Daily* Starting Dose [mg/day]	Total Daily* Maintenance Dose† [mg/day]
10 kg to 15 kg	350 mg	1050 mg
Greater than 15 kg to 20 kg	450 mg	1300 mg
Greater than 20 kg to 25 kg	500 mg	1500 mg
Greater than 25 kg to 60 kg	500 mg	2000 mg

* Administered in two divided doses

† Maintenance dose is based on 3000 mg/day adult-equivalent dose

†† Patients weighing more than 60 kg should be dosed according to adult recommendations

In patients with refractory complex partial seizures, Vigabatrin should be withdrawn if a substantial clinical benefit is not observed within 3 months of initiating treatment. If, in the clinical judgment of the prescriber, evidence of treatment failure becomes obvious earlier than 3 months, treatment should be discontinued at that time.

In order to discontinue, Vigabatrin should be tapered by decreasing the daily dose by one third every week for three weeks.

Infantile Spasms

The initial daily dosing is 50 mg/kg/day given in two divided doses (25 mg/kg twice daily); subsequent dosing can be titrated by 25 mg/kg/day to 50 mg/kg/ day increments every 3 days, up to a maximum of 150 mg/kg/day given in 2 divided doses (75 mg/kg twice daily).

Below table provides the volume of the 50 mg/mL dosing solution that should be administered as individual doses in infants of various weights.

Infant Dosing Table

Weight [kg]	Starting Dose 50 mg/kg/day	Maximum Dose 150 mg/kg/day
3	1.5 mL twice daily	4.5 mL twice daily
4	2 mL twice daily	6 mL twice daily
5	2.5 mL twice daily	7.5 mL twice daily
6	3 mL twice daily	9 mL twice daily
7	3.5 mL twice daily	10.5 mL twice daily
8	4 mL twice daily	12 mL twice daily
9	4.5 mL twice daily	13.5 mL twice daily
10	5 mL twice daily	15 mL twice daily
11	5.5 mL twice daily	16.5 mL twice daily
12	6 mL twice daily	18 mL twice daily
13	6.5 mL twice daily	19.5 mL twice daily
14	7 mL twice daily	21 mL twice daily
15	7.5 mL twice daily	22.5 mL twice daily
16	8 mL twice daily	24 mL twice daily

In patients with infantile spasms, Vigabatrin should be withdrawn if a substantial clinical benefit is not observed within 2 to 4 weeks. If, in the clinical judgment of the prescriber, evidence of treatment failure becomes obvious earlier than 2 to 4 weeks, treatment should be discontinued at that time.

To discontinue Vigabatrin in patients with infantile spasms, it should be tapered by decreasing the daily dose at a rate of 25 mg/kg to 50 mg/kg every 3 to 4 days.

Patients with Renal Impairment

Vigabatrin is primarily eliminated through the kidney.

Infants

Information about how to adjust the dose in infants with renal impairment is unavailable.

Adults and Patients with age 2 years and older

- Mild renal impairment (CLcr >50 to 80 mL/min): dose should be decreased by 25%
- Moderate renal impairment (CLcr >30 to 50 mL/min): dose should be decreased by 50%
- Severe renal impairment (CLcr >10 to 30 mL/min): dose should be decreased by 75%

CLcr in mL/min may be estimated from serum creatinine (mg/dL) using the following formulas:

- Patients of age 10 years to <12 years: CLcr (mL/min/1.73 m²) = (K × Ht) / Scr height (Ht) in cm; serum creatinine (Scr) in mg/dL K (proportionality constant): Female Child (<12 years): K=0.55; Male Child (<12 years): K=0.70
- Adult and pediatric patients 12 years or older: CLcr (mL/min) = [140-age (years)] × weight (kg) / [72 × serum creatinine (mg/dL)] (× 0.85 for female patients)

The effect of dialysis on Vigabatrin clearance has not been adequately studied.

Preparation and Administration Instructions for Vigabatrin Powder for Oral Solution

If using Vigabatrin powder for oral solution, physicians should give instructions for mixing and giving Vigabatrin with the patient or caregiver(s). Physicians should confirm that patients or caregiver(s) understand how to mix Vigabatrin powder with water and administer the correct daily dose.

Empty the entire contents of each 500 mg packet into a clean cup, and dissolve in 10 mL of cold or room temperature water per packet. Administer the resulting solution using the 3 mL or 10 mL oral syringe provided by the pharmacy. The concentration of the final solution is 50 mg/mL.

Below table describes how many packets and how many milliliters (mL) of water will be needed to prepare each individual dose. The concentration after reconstitution is 50 mg/mL.

Number of Vigabatrin Packets and mL of Water Needed for Each Individual Dose

Individual Dose [mg] [Given Twice Daily]	Total Number of Vigabatrin Packets	Total mL of Water Required for Dissolving
0 to 500	1 Packet	10 mL
501 to 1000	2 Packets	20 mL
1001 to 1500	3 Packets	30 mL

Discard the resulting solution if it is not clear (or free of particles) and colorless. Each individual dose should be prepared and used immediately. Discard any unused portion of the solution after administering the correct dose.

4.3. Contraindications

Vigabatrin is contraindicated in patients who are hypersensitivity to the active substance.

4.4. Special Warnings and Precautions for Use

Permanent Vision Loss

Vigabatrin can cause permanent vision loss. Because of this risk and because, when it is effective, Vigabatrin provides an observable symptomatic benefit, patient response and continued need for treatment should be periodically assessed.

Patients (30% or more) can be effected with bilateral concentric visual field constriction ranging in severity from mild to severe. Severe cases may be characterized by tunnel vision to within 10 degrees of visual fixation, which can result in disability. In some cases, Vigabatrin also can damage the central retina and may decrease visual acuity. Symptoms of vision loss from Vigabatrin are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient or caregiver, can still adversely affect function.

Because assessing vision may be difficult in infants and children, the frequency and extent of vision loss is poorly characterized in these patients. For this reason, the understanding of the risk is placed on the adult experience. The possibility that vision loss from Vigabatrin may be more common, more severe, or have more severe functional consequences in infants and children than in adults cannot be excluded.

The onset of vision loss from Vigabatrin is unpredictable and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years.

The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.

In patients with refractory complex partial seizures, Vigabatrin should be withdrawn if a substantial clinical benefit is not observed within 3 months of initiating treatment. If, in the clinical judgment of the prescriber, evidence of treatment failure becomes obvious earlier than 3 months, treatment should be discontinued at that time.

In patients with infantile spasms, Vigabatrin should be withdrawn if a substantial clinical benefit is not observed within 2 to 4 weeks. If, in the clinical judgment of the prescriber, evidence of treatment failure becomes obvious earlier than 2 to 4 weeks, treatment should be discontinued at that time.

Vigabatrin should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from Vigabatrin has not been well-characterized, but is likely adverse.

Vigabatrin should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.

Monitoring of Vision

Monitoring of vision by an ophthalmic professional with expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina is recommended. Because vision testing in infants is difficult, vision loss may not be detected until it is severe. For patients receiving, vision assessment is recommended at baseline (no later than 4 weeks after starting Vigabatrin), at least every 3 months while on therapy, and about 3-6 months after the discontinuation of therapy. The diagnostic approach should be individualized by the patient and clinical situation.

In adults and cooperative pediatric patients, perimetry is recommended, preferably by automated threshold visual field testing. Vigabatrin Additional testing may also include electrophysiology (e.g., electroretinography [ERG]), retinal imaging (e.g., optical coherence tomography [OCT]), and/or other methods appropriate for the patient. In patients who cannot be tested, treatment may continue according to clinical judgment, with appropriate patient counseling. Because of variability, results from ophthalmic monitoring must be interpreted with caution, and repeat assessment is recommended if results are abnormal or uninterpretable. Repeat assessment in the first few weeks of treatment is recommended to establish if, and to what degree, reproducible results can be obtained, and to guide selection of appropriate ongoing monitoring for the patient.

The onset and progression of vision loss from Vigabatrin is unpredictable, and it may occur or worsen precipitously between assessments. Once detected, vision loss due to Vigabatrin is not reversible. It is expected that even with frequent monitoring, some Vigabatrin patients will develop severe vision loss. Consider drug discontinuation, balancing benefit and risk, if vision loss is documented. It is possible that vision loss can worsen despite discontinuation of Vigabatrin.

Magnetic Resonance Imaging (MRI) Abnormalities in Infants

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated with Vigabatrin.

For adults treated with Vigabatrin, routine MRI surveillance is unnecessary as there is no evidence that vigabatrin causes MRI changes in this population.

Neurotoxicity

Intramyelinic Edema (IME) was observed in postmortem examination of infants being treated for infantile spasms with Vigabatrin.

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have also been observed in some infants treated for IS with Vigabatrin.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Vigabatrin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Anyone considering prescribing Vigabatrin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, Vigabatrin should be withdrawn gradually. However, if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered. Patients and caregivers should be told not to suddenly discontinue Vigabatrin therapy.

Anemia

Vigabatrin is known to cause anemia and/or met criteria for potentially clinically important hematology changes involving hemoglobin, hematocrit, and/ or RBC indices.

Somnolence and Fatigue

Vigabatrin causes somnolence and fatigue. Patients should be advised not to drive a car or operate other complex machinery until they are familiar with the effects of Vigabatrin on their ability to perform such activities.

Peripheral Neuropathy

Vigabatrin causes symptoms of peripheral neuropathy in adults, including symptoms of numbness or tingling in the toes or feet, signs of reduced distal lower limb vibration or position sensation, or progressive loss of reflexes, starting at the ankle. There is insufficient evidence to determine if development of these signs and symptoms was related to duration of Vigabatrin treatment, cumulative dose, or if the findings of peripheral neuropathy were completely reversible upon discontinuation of Vigabatrin.

Weight Gain

Vigabatrin causes weight gain in adult and pediatric patients.

Edema

Vigabatrin causes edema in adults.

4.5. Drug Interactions

Antiepileptic Drugs

Phenytoin

Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated, since Vigabatrin may cause a moderate reduction in total phenytoin plasma levels.

Clonazepam

Vigabatrin may moderately increase the C_{max} of clonazepam resulting in an increase of clonazepam-associated adverse reactions.

Other AEDs

There are no clinically significant pharmacokinetic interactions between Vigabatrin and either phenobarbital or sodium valproate. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of Vigabatrin.

Oral Contraceptives

Vigabatrin is unlikely to affect the efficacy of steroid oral contraceptives.

Drug-Laboratory Test Interactions

Vigabatrin decreases alanine transaminase (ALT) and aspartate transaminase (AST) plasma activity in up to 90% of patients. In some patients, these enzymes become undetectable. The suppression of ALT and AST activity by Vigabatrin may preclude the use of these markers, especially ALT, to detect early hepatic injury.

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

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

There are no adequate data on the developmental risk associated with the use of Vigabatrin in pregnant women. However, based on animal data, Vigabatrin use in pregnant women may result in fetal harm.

When administered to pregnant animals, Vigabatrin produced developmental toxicity, including an increase in fetal malformations and offspring neurobehavioral and neurohistopathological effects, at clinically relevant doses. In addition, developmental neurotoxicity was observed in rats treated with Vigabatrin during a period of postnatal development corresponding to the third trimester of human pregnancy.

Lactation

Vigabatrin is excreted in human milk. The effects of Vigabatrin on the breastfed infant and on milk production are unknown. Because of the potential for serious adverse reactions from vigabatrin in nursing infants, breastfeeding is not recommended. If exposing a breastfed infant to Vigabatrin, observe for any potential adverse effects.

Pediatric Use

Safety and effectiveness as adjunctive treatment of refractory complex partial seizures in pediatric patients below the age of 2 and as monotherapy for the treatment of infantile spasms in pediatric patients below the age of 1 month have not been established. Abnormal MRI signal changes and Intramyelinic Edema (IME) in infants and young children being treated with Vigabatrin have been observed.

Geriatric Use

Vigabatrin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Oral administration of a single dose of 1.5 g of Vigabatrin to elderly (≥65 years) patients with reduced creatinine clearance (<50 mL/min) was associated with moderate to severe sedation and confusion in 4 of 5 patients, lasting up to 5 days. The renal clearance of vigabatrin was 30% lower in healthy elderly subjects (≥65 years) than in young healthy males. Adjustment of dose or frequency of administration should be considered. Such patients may respond to a lower maintenance dose.

Renal Impairment

Dose adjustment, including initiating treatment with a lower dose, is necessary in pediatric patients 2 years of age and older and adults with mild (creatinine clearance >50 to 80 mL/min), moderate (creatinine clearance >30 to 50 mL/min) and severe (creatinine clearance >10 to 30 mL/min) renal impairment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Vigabatrin is not a controlled substance.

Abuse

Vigabatrin did not produce adverse events or overt behaviors associated with abuse when administered to humans or animals. It is not possible to predict the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of vigabatrin (e.g., incrementation of dose, drug-seeking behavior).

Dependence

Following chronic administration of Vigabatrin to animals, there were no apparent withdrawal signs upon drug discontinuation. However, as with all AEDs, Vigabatrin should be withdrawn gradually to minimize increased seizure frequency.

4.7. Effects on Ability to Drive and Use Machines

Vigabatrin has major influence on the ability to perform hazardous activities.

In view of the fact that drowsiness observed with Vigabatrin, patients should be warned of this possibility at the start of treatment.

Visual field defects which can significantly affect the ability to perform hazardous activities have been frequently reported in association with Vigabatrin. Patients should be evaluated for the presence of visual field defects. Special care should be taken with young patients cycling, climbing or performing any other hazardous activity.

4.8. Undesirable Effects

The following serious and otherwise important adverse reactions are:

- Permanent Vision Loss
- Magnetic Resonance Imaging (MRI) Abnormalities in Infants
- Neurotoxicity
- Suicidal Behavior and Ideation
- Withdrawal of Antiepileptic Drugs (AEDs)
- Anemia
- Somnolence and Fatigue
- Peripheral Neuropathy
- Weight Gain
- Edema

In the table below, adverse reactions are listed by System Organ Class and frequency. The following convention has been used for the classification of adverse reactions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), not known (cannot be estimated from the available data).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com→Contact us→Medical Enquiry to report a side effect.

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders		anaemia				
Psychiatric disorders		agitation, aggression, nervousness, depression, paranoid reaction, insomnia	hypomania, mania, psychotic disorder	suicide attempt	hallucination	
Nervous system disorders	somnolence	speech disorder, headache, dizziness, paraesthesia, disturbance in attention and memory impairment, mental impairment (thought disturbance), tremor	coordination abnormal (ataxia)	encephalopathy	optic neuritis	brain MRI abnormalities, movement disorders, including dystonia, dyskinesia and hypertonia, either alone or in association with abnormalities in MRI
Eye disorders	visual field defect	vision blurred, diplopia, nystagmus		retinal disorder (such as peripheral retinal atrophy)	optic 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 increased				

4.9. Overdose

Coma, unconsciousness, and/or drowsiness were described in the majority of cases of Vigabatrin overdose. Other less commonly reported symptoms included vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation, irritability, confusion, headache, hypotension, abnormal behavior, increased seizure activity, status epilepticus, and speech disorder. These symptoms resolved with supportive care.

There is no specific antidote for Vigabatrin overdose. Standard measures to remove unabsorbed drug should be used, including elimination by emesis or gastric lavage. Supportive measures should be employed, including monitoring of vital signs and observation of the clinical status of the patient.

In an *in vitro* study, activated charcoal did not significantly adsorb Vigabatrin.

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

Mechanism of action

The precise mechanism of vigabatrin's anti-seizure effects is unknown, but it is believed to be the result of its action as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased levels of GABA in the central nervous system.

No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to be dependent on the rate of enzyme re-synthesis rather than on the rate of elimination of the drug from the systemic circulation.

Effects on Electrocardiogram

There is no indication of a QTc/QTc prolonging effect of Vigabatrin in single doses up to 6.0 g. In a randomized, placebo-controlled, crossover study, 58 healthy subjects were administered a single oral dose of Vigabatrin (3 g and 6 g) and placebo. Peak concentrations for 6.0 g Vigabatrin were approximately 2-fold higher than the peak concentrations following the 3.0 g single oral dose.

5.2 PHARMACOKINETIC PROPERTIES

Vigabatrin displays linear pharmacokinetics after administration of single doses ranging from 0.5 g to 4 g, and after administration of repeated doses of 0.5 g and 2.0 g twice daily. Bioequivalence has been established between the oral solution and tablet formulations. The following PK information (T_{max}, half-life, and clearance) of Vigabatrin was obtained from stand-alone PK studies and population PK analyses.

Absorption

Following oral administration, Vigabatrin is essentially completely absorbed. The time to maximum concentration (T_{max}) is approximately 1 hour for children and adolescents (3 months to 16 years of age) and adults, and approximately 2.5 hours for infants (3 months to 2 years of age). There was little accumulation with multiple dosing in adult and pediatric patients. A food effect study involving administration of vigabatrin to healthy volunteers under fasting and fed conditions indicated that the C_{max} was decreased by 33%, T_{max} was increased to 2 hours, and AUC was unchanged under fed conditions.

Distribution

Vigabatrin does not bind to plasma proteins. Vigabatrin is widely distributed throughout the body; mean steady-state volume of distribution is 1.1 L/kg (CV = 20%).

Metabolism and Elimination

Vigabatrin is not significantly metabolized; it is eliminated primarily through renal excretion. The terminal half-life of Vigabatrin is about 5.7 hours for infants (3 months to 2 years of age), 6.8 hours for children (3 to 9 years of age), 9.5 hours for children and adolescents (10 to 16 years of age), and 10.5 hours for adults. Following administration of ^{14}PC-vigabatrin to healthy male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing about 80% of this. Vigabatrin induces CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.

Specific Populations

Geriatric

The renal clearance of vigabatrin in healthy elderly patients (≥65 years of age) was 36% less than those in healthy younger patients. This finding is confirmed by an analysis of data from a controlled clinical trial [see Use in Specific Populations (8.5)].

Pediatric

The clearance of vigabatrin is 2.4 L/hr for infants (3 months to 2 years of age), 5.1 L/hr for children (3 to 9 years of age), 5.8 L/hr for children and adolescents (10 to 16 years of age) and 7 L/hr for adults.

Gender

No gender differences were observed for the pharmacokinetic parameters of Vigabatrin in patients.

Race

No specific study was conducted to investigate the effects of race on vigabatrin pharmacokinetics. A cross study comparison between 23 Caucasian and 7 Japanese patients who received 1, 2, and 4 g of vigabatrin indicated that the AUC, C_{max}, and half-life were similar for the two populations. However, the mean renal clearance of Caucasians (5.2 L/hr) was about 25% higher than the Japanese (4.0 L/hr). Inter-subject variability in renal clearance was 20% in Caucasians and was 30% in Japanese.

Renal Impairment

Mean AUC increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in adult patients with mild renal impairment (CLcr from >50 to 80 mL/min) in comparison to normal people.

Mean AUC increased by 4.5-fold and the terminal half-life increased by 3.5-fold in adult patients with severe renal impairment (CLcr from >10 to 30 mL/ min) in comparison to normal people.

Adult patients with renal impairment

Dosage adjustment, including starting at a lower dose, is recommended for adult patients with any degree of renal impairment.

Infants with renal impairment

Information about how to adjust the dose in infants with renal impairment is unavailable.

Pediatric patients 2 years and older with renal impairment

Although information is unavailable on the effects of renal impairment on Vigabatrin clearance in pediatric patients 2 years and older, dosing can be calculated based upon adult data and an established formula.

Hepatic Impairment

Vigabatrin is not significantly metabolized. The pharmacokinetics of Vigabatrin in patients with impaired liver function has not been studied.

Drug Interactions

Phenytoin

A 16% to 20% average reduction in total phenytoin plasma levels was observed. *In vitro* drug metabolism studies indicate that decreased phenytoin concentrations upon addition of vigabatrin therapy are likely to be the result of induction of cytochrome P450 2C enzymes in some patients. Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated.

Clonazepam

Clonazepam (0.5 mg) co-administration had no effect on Vigabatrin (1.5 g twice daily) concentrations. Vigabatrin increases the mean C_{max} of clonazepam by 30% and decreases the mean T_{max} by 45%.

Other AEDs

When co-administered with Vigabatrin, phenobarbital concentration (from phenobarbital or primidone) was reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of 8%. These reductions did not appear to be clinically relevant. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of Vigabatrin.

Alcohol

Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g twice daily) indicated that neither drug influences the pharmacokinetics of the other.

Oral Contraceptives

Co-administration of contraceptive containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel, Vigabatrin (3 g/day) did not interfere significantly with the cytochrome P450 isoenzyme (CYP3A)-mediated metabolism of the contraceptive tested. Based on this vigabatrin is unlikely to affect the efficacy of oral contraceptives. Additionally, no significant difference in pharmacokinetics parameters (elimination half-life, AUC, C_{max}, apparent oral clearance, time to peak, and apparent volume of distribution) of Vigabatrin were found after treatment with ethinyl estradiol and levonorgestrel.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Vigabatrin showed no carcinogenic potential in mouse or rat when given in the diet at doses up to 150 mg/kg/day for 18 months (mouse) or at doses up to 150 mg/kg/day for 2 years (rat). These doses are less than the maximum recommended human dose (MRHD) for infantile spasms (150 mg/kg/day) and for refractory complex partial seizures (3 g/day) on a mg/m² basis.

Vigabatrin was negative in *in vitro* (Ames, CHO/HGPRT mammalian cell forward gene mutation, chromosomal aberration in rat lymphocytes) and in *in vivo* (mouse bone marrow micronucleus) assays.

No adverse effects on male or female fertility were observed in rats at oral doses up to 150 mg/kg/day (approximately 1/2 the MRHD of 3 g/day on a mg/ m² basis for refractory complex partial seizures).

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities

None

7.2 Packing Information

Sachet Pack

7.3 Storage and Handling Instructions

Do not store above 30ºC.

Keep out of reach of Children.

8. PATIENT COUNSELLING INFORMATION

Advise patients to read Prescribing information.

Administration Instructions for Vigabatrin Powder for Oral Solution

Physicians should confirm that caregiver(s) understand how to mix Vigabatrin for Oral Solution and to administer the correct dose to their infants and pediatric patients.

Permanent Vision Loss

Inform patients and caregivers of the risk of permanent vision loss, particularly loss of peripheral vision, from Vigabatrin, and the need for monitoring vision. Monitoring of vision, including assessment of visual fields and visual acuity, is recommended at baseline (no later than 4 weeks after starting Vigabatrin), at least every 3 months while on therapy, and about 3-6 months after discontinuation of therapy. In patients for whom vision testing is not possible, treatment may continue without recommended testing according to clinical judgment with appropriate patient or caregiver counseling. Patients or caregivers should be informed that if baseline or subsequent vision is not normal, Vigabatrin should only be used if the benefits of Vigabatrin treatment clearly outweigh the risks of additional vision loss.

Advise patients and caregivers that vision testing may be insensitive and may not detect vision loss before it is severe. Also advise patients and caregivers that if vision loss is documented, such loss is irreversible. Ensure that both of these points are understood by patients and caregivers.

Patients and caregivers should be informed that if changes in vision are suspected, they should notify their physician immediately.

MRI Abnormalities in Infants

Inform caregiver(s) of the possibility that infants may develop an abnormal MRI signal of unknown clinical significance.

Suicidal Thinking and Behavior

Counsel patients, their caregiver(s), and families that AEDs, including Vigabatrin, may increase the risk of suicidal thoughts and behavior. Also advise patients and caregivers of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Pregnancy

Advise pregnant women and women of child-bearing potential that the use of Vigabatrin during pregnancy can cause fetal harm which may occur early in pregnancy before many women know they are pregnant. Instruct patients to notify their physician if they become pregnant or intend to become pregnant during therapy. Advise patients that there is a pregnancy exposure registry that collects information about the safety of antiepileptic drugs during pregnancy.

Nursing

Counsel patients that Vigabatrin is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from Vigabatrin, breastfeeding is not recommended. If a decision is made to breastfeed, nursing mothers should be counseled to observe their infants for signs of vision loss, sedation and poor sucking.

Withdrawal of Vigabatrin Therapy

Instruct patients and caregivers not to suddenly discontinue Vigabatrin therapy without consulting with their healthcare provider. As with all AEDs, withdrawal should normally be gradual.

9. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,
Formulation Division, Unit II,
Sy.no.1277, 1319 to 1324,
Nandigama (Village & Mandal),
Ranga Reddy District,
Telangana-509228,
India.

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

GAN/TS/2021/AFG, 29/06/2021

11. DATE OF REVISION

June-2021

P-021213-00