Sizura®

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Carbamazepine Tablets USP 200 mg

COMPOSITION:
Each film coated tablet contains
Carbamazepine USP 200 mg
Excipients q.s.
Colour: Titanium Dioxide BP

DESCRIPTION:
SIZURA®(Carbamazepine Tablets USP 200 mg) contains Carbamazepine as an active.

PHARMACODYNAMICS:
Pharmacodynamic properties
Therapeutic class: Anti-epileptic, neurotropic and psychotropic agent; (ATC Code: N03AF01).
Dibenzazepine derivative.
As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalisation; generalised tonic-clonic seizures, as well as combinations of these types of seizures.

Mechanism of Action:
The mechanism of action of carbamazepine, the active substance of SIZURA®, has only been partially elucidated. Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses.
It is conceivable that prevention of repetitive firing of sodium-dependent action potentials in depolarised neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action.
Whereas reduction of glutamate release and stabilisation of neuronal membranes may account for the antiepileptic effects, the depressant effect on dopamine and noradrenaline turnover could be responsible for the antimanic properties
of carbamazepine.

Pharmacokinetic Properties
Absorption
Carbamazepine is almost completely absorbed but the rate of absorption from the tablets is slow and may vary amongst the various formulations and between patients. Peak concentrations of active substance in the plasma are attained within 24 hours of administration of single dose of SIZURA®. The formulation shows about 15% lower bioavailability than standard preparations due mainly to the considerable reduction in peak plasma levels occasioned by of the same dosage of carbamazepine. The bioavailability of carbamazepine in various oral formulations has been shown to lie between 85-100%. Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of carbamazepine.
Distribution
Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma (20-30%). Concentrations in breast milk were found to be equivalent to 25-60% of the corresponding plasma levels. Carbamazepine crosses the placental barrier. Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.
Biotransformation
Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites. Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine 10, 11- epoxide from carbamazepine.
Elimination
The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16-24 hours (auto-induction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9-10 hours have been found.
The mean elimination half-life of the 10, 11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself. After administration of a single oral dose of 400 mg carbamazepine, 72% is excreted in the urine and 28% in the faeces. In the urine, about 2% of the dose is recovered as unchanged drug and about 1% as the pharmacologically active 10, 11-epoxide metabolite.

THERAPEUTIC INDICATIONS:
SIZURA® (Carbamazepine Tablets USP 200 mg) is indicated in treatment of:
Epilepsy – generalised tonic-clonic and partial seizures. **SIZURA®** is indicated in newly diagnosed patients with epilepsy and in those patients who are uncontrolled or unable to tolerate their current anti-convulsant therapy.
Note:
-Carbamazepine is not usually effective in absences (petit mal) and myoclonic seizures.
-The paroxysmal pain of trigeminal neuralgia.
-For the prophylaxis of manic-depressive psychoses in patients unresponsive to lithium therapy.

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
Epilepsy:
The dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Determination of plasma levels may help in establishing the optimum dosage. In the treatment of epilepsy, the dose of carbamazepine usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre) (see warnings and precautions).
Adults: It is advised that with all formulations of carbamazepine, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient.
Special population:
Elderly population (65 years or above): Due to the potential for drug interactions, the dosage of carbamazepine should be selected with caution in elderly patients (65 years of above).
Children and adolescents: It is advised that with all formulations of carbamazepine, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient.
Usual dosage 10-20mg/kg bodyweight daily in several divided doses.

Age	Upto 5 years	SIZURA® Tablets are not recommended
	5-10 years	400-600mg daily
	10-15 years	600-1000mg
	>15 years of age	800 to 1200 mg daily (Same s adult dose)

Maximum recommended dose
Upto 6 years of age: 35 mg/kg/day
6-15 years of age: 1000mg/day
>15 years of age: 1200mg/day (same as adult dose).
Wherever possible, SIZURA® should be used as the sole drug anti-epileptic agent but if used in polytherapy, the same incremental dosage pattern is advised.
Trigeminal neuralgia:
Slowly raise the initial dosage of 200-400 mg daily until freedom from pain is achieved (normally at 200 mg 3-4 times daily). In the majority of patients, a dosage of 200 mg 3 or 4 times a day is sufficient to maintain a pain free state.
Special population
Due to drug interactions and different antiepileptic drug pharmacokinetics, the dosage of carbamazepine should be selected with caution in elderly patients.
In elderly patients, an initial dose of 100 mg twice daily is recommended.
Method of Administration:
SIZURA® is given orally, generally in the same total daily dose as conventional carbamazepine dosage forms but usually in two divided doses.
The tablets should be taken during after or between a meal with a drink of water. The tablets should be swallowed whole and not chewed or crushed.

CONTRAINDICATION:
Known hypersensitivity to carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) or any other component of the formulation.
- Patients with atrioventricular block, a history of bone marrow depression or a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda).
- The use of carbamazepine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs).

SPECIAL WARNING AND PRECAUTION FOR USE:
Warnings
Agranulocytosis and aplastic anaemia have been associated with carbamazepine; however, due to the very low incidence of these conditions, meaningful risk estimates for carbamazepine are difficult to obtain. The overall risk in the general untreated population has been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 persons per million per year for aplastic anaemia.
Decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of carbamazepine. Liver function tests should also be performed before commencing treatment and periodically thereafter, particularly in patients with a history of liver disease and in elderly patients. Some liver function tests in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyl transferase.
Cutaneous reactions
Serious and sometimes fatal cutaneous reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with carbamazepine. There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions.
HLA-B*1502 allele - in Han Chinese, Thai and other Asian populations
HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine.
HLA-A*3101 allele - European descent and Japanese populations
There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese.
Other dermatologic reactions
Mild skin reactions e.g. isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous.
Hypersensitivity
Carbamazepine may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), reactivation of HHV6 associated with DRESS, a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly.
Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon).
Carbamazepine should be used with caution in patients with mixed seizures which include absences, either typical or atypical.
Dose reduction and withdrawal effects
Abrupt withdrawal of carbamazepine may precipitate seizures therefore carbamazepine withdrawal should be gradual. If treatment with carbamazepine has to be withdrawn abruptly in a patient with epilepsy, the changeover to another antiepileptic drug should if necessary be effected under the cover of a suitable drug.
Endocrinological effects
Breakthrough bleeding has been reported in women taking carbamazepine while using hormonal contraceptives.
Monitoring of plasma levels
Although correlations between dosages and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring of the plasma levels may be useful in the following conditions: dramatic increase in seizure frequency/verification of patient compliance; during pregnancy; when treating children or adolescents; in suspected absorption disorders; in suspected toxicity when more than one drug is being used.
Precautions
Carbamazepine should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with carbamazepine. Baseline and periodic complete urinalysis and BUN determinations are recommended.
Hyponatremia
Hyponatremia is known to occur with carbamazepine. In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy.
Hypothyroidism
Carbamazepine may reduce serum concentrations of thyroid hormones through enzyme induction requiring an increase in dose of thyroid replacement therapy in patients with hypothyroidism.
Psychiatric effects
The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.
Interactions
Co-administration of inhibitors of CYP3A4 or inhibitors of epoxide hydrolase with carbamazepine can induce adverse reactions (increase of carbamazepine or carbamazepine-10,11 epoxide plasma concentrations respectively). The dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored.
Falls
Carbamazepine treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, which may lead to falls and, consequently fractures or other injuries.
Interference with serological testing
Carbamazepine may result in false positive perphenazine concentrations in HPLC analysis due to interference.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
Carbamazepine interacts with many other medicinal products, and caution should always be taken when combining carbamazepine with other medicinal products.
Pharmacokinetic interactions
Cytochrome P450 3A4 (CYP 3A4) is the main enzyme catalysing formation of the active metabolite carbamazepine 10, 11-epoxide. Co-administration of inhibitors of CYP 3A4 may result in increased carbamazepine plasma concentrations which could induce adverse reactions. Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels.
Interactions resulting in a contraindication
The use of carbamazepine is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering carbamazepine MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits (see contraindications).
Agents that may raise carbamazepine plasma levels:
Since raised plasma carbamazepine levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:
Analgesics, anti-inflammatory drugs: dextropropoxyphene.
Androgens: danazol.
Antibiotics: macrolide antibiotics (e.g. erythromycin, clarithromycin), ciprofloxacine.
Antivirals: protease inhibitors for HIV treatment (e.g. ritonavir).
Carbonic anhydrase inhibitors: acetazolamide.
Cardiovascular drugs: diltiazem, verapamil.
Gastrointestinal drugs: possibly cimetidine, omeprazole.
Other interactions: grapefruit juice, nicotinamide (only in high dosage).
Agents that may raise the active metabolite carbamazepine-10,11-epoxide plasma levels:
Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below: Quetiapine, primidone, progabide, valproic acid and valpromide.
Agents that may decrease carbamazepine plasma levels:
The dose of carbamazepine may have to be adjusted when used concomitantly with the substances described below:
Antiepileptics: oxcarbazepine, phenobarbital, phenytoin.
Antineoplastics: cisplatin or doxorubicin.
Antituberculosis: rifampicin.
Bronchodilatators or anti-asthma drugs: theophylline, aminophylline.
Effect of Carbamazepine on plasma levels of concomitant agents:
Carbamazepine may lower the plasma level, diminish or even abolish the activity of certain medicinal products, due to its inducing effect on metabolising enzymes and the transport porotein P-gp. The dosage of the following drugs may have to be adjusted to clinical requirement:
Analgesics, anti-inflammatory agents: buprenorphine, methadone, paracetamol
Antibiotics: doxycycline, rifabutin.
Anticoagulants: oral anticoagulants (e.g. warfarin, acenocoumarol, rivaroxaban, dabigatran)
Antifungals: itraconazole, voriconazole. Alternative anti-convulsants may be recommended.
Bronchodilatators or anti-asthma drugs: theophylline.
Contraceptives: hormonal contraceptives
Cardiovascular medinical products: calcium channel blockers (dihydropyridine group) e.g. felodipine, digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine.
Drugs used in erectile dysfunction: tadalafil.
Thyroid agents: levothyroxine.
Other drug interactions: products containing oestrogens and/or progesterones.
Combinations that require specific consideration:
Concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity.
The Combined use of carbamazepine with metoclopramide or major tranquillisers, e.g. Haoperidol, Thioridazine may also result in an increase in neurological side effects.

PREGNANCY, BREAST-FEEDING AND FERTILITY
Women of childbearing potential/Contraception
Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of child bearing potential should be advised to use alternative contraceptive methods while on treatment with carbamazepine and for 2 weeks following the last dose.
Pregnancy
Carbamazepine should only be used during pregnancy after a careful risk/benefit evaluation (if the potential benefit to the mother justifies the potential risk to the fetus).
Clinical considerations
Taking these data into consideration:
- Pregnant women with epilepsy should be treated with special care.
- If women receiving carbamazepine become pregnant or plan to become pregnant, or if the need of initiating treatment with carbamazepine arises during pregnancy, the drug's expected.
- Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.
In the neonate
In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K1, be given to the mother during the last weeks of pregnancy as well as to the neonate.
Animal studies have shown reproductive toxicity.
Breast-feeding
Risk summary
Carbamazepine passes into the breast milk (about 25-60% of the plasma concentrations). The benefits of breast-feeding should be weighed against the risk of adverse effects in the infant. Mothers taking carbamazepine may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction).
Fertility
There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
The patient's ability to react may be impaired by the medical condition resulting in seizures and adverse reactions including dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision have been reported with carbamazepine, especially at the start of treatment or in connection with dose adjustments. Patients should therefore exercise due caution when driving a vehicle or operating machinery.

UNDESIRABLE EFFECTS:
Particularly at the start of treatment with carbamazepine, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia); gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions.
Tabulated summary of adverse drug reactions compiled from clinical trials and from Spontaneous reports

System organ class	**Adverse drug reactions**
Blood and the lymphatic system disorders	
Very common	Leucopenia
Common	Thrombocytopenia , eosinophilia
Endocrine disorders	
Common	Oedema, fluid retention, weight increase, hyponatraemia
Nervous system disorders	
Very common	Ataxia , dizziness, somnolence
Common	Diplopia , headache.
Gastrointestinal disorders	
Very common	Vomiting , nausea, Dry mouth
Skin and subcutaneous tissue disorders	
Very common	Urticarial, which may be severe dermatitus allergic,.
Common	Dermatitis exfoliative.
General disorders and administration site conditions	
Very common	Fatigue

OVERDOSE
Signs and symptoms
The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular, respiratory systems and the adverse drug reactions mentioned.
Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria.
Respiratory system: Respiratory depression, pulmonary oedema.
Cardiovascular system: Tachycardia, hypotension and at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest.
Gastro-intestinal system: Vomiting, delayed gastric emptying, reduced bowel motility.
Musculoskeletal system: There have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity.
Renal function: Retention of urine, oliguria or anuria; fluid retention, water intoxication due to ADH-like effect of carbamazepine.
Laboratory findings: Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatine phosphokinase.

SHELF LIFE:
36 Months

PACKAGING:
10 Tablets are packed in Alu-Alu Blister & such 3 Blisters are packed in printed carton along with pack insert.

STORAGE CONDITION:
Stored at a temperature not exceeding 30°C. Protect from light and moisture.
Keep the medicine out of reach of children.

Marketed by:

LINUX
Laboratories Pvt.Ltd.
Plot No. 492, Viduthalai Nagar
Extn, Kovilambakkam, Chennai,
Tamil Nadu - 600117, India.

MANUFACTURED BY:
CIAN HEALTHCARE LTD.
Khasra No. 248, Vill. Sisona, Bhagwanpur,
Roorkee, Distt. Haridwar, Uttarakhand - 247661, India.