CAZEPSIN

Instructions for the medicinal product

Trade name: Cazepsin.
International nonproprietary name: Carbamazepine.
Dosage form: Uncoated tablets.
Composition: Each uncoated tablet contains :
Carbamazepine BP 200 mg.
Pharmacotherapeutic group: Anti-epileptic, neurotropic and psychotropic agent.
ATC Code: N03AF01.
Pharmacologic property:
Pharmacodynamics:
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.
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.
Pharmacokinetics:
Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations of the unchanged substance within 12 hours (chewable tablets 6 hours; syrup 2 hours) following single oral doses. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine in the plasma is approx. 4.5µg/ml.
The bioavailability 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 Cazepsin.
Steady-state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.
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.
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. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway.
Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.
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 400mg 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.
Indications for use:
- Epilepsy - generalised tonic-clonic and partial seizures. Note: Cazepsin is not usually effective in absences (petit mal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences;
- The paroxysmal pain of trigeminal neuralgia;
- For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy.

Contraindications:
- Hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline and nortriptyline;
- Patients with a history of previous bone marrow depression;
- Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended;
- Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

Pregnancy and Nursing Mother:
The risk of birth defects, such as head and facial deformities, spina bifida, and heart defects. It may not be safe for use during pregnancy. However, if the benefits to the pregnant woman outweigh possible the risks to the child, a healthcare provider may still prescribe carbamazepine.
Carbamazepine and its epoxide metabolite are transferred to breast milk during lactation. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Dosage and directions for use:
For oral use
Epilepsy:
Adults and children over 12 years of age –

Initial: Either 200 mg b.i.d. for tablets (400 mg/day). Increase at weekly intervals by adding up to 200 mg/day using a b.i.d. regimen of Carbamazepine or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12-15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances.
Maintenance: Adjust dosage to the minimum effective level, usually 800-1200 mg daily.
Children 6-12 years of age:
Initial: Either 100 mg b.i.d. for tablets. Increase at weekly intervals by adding up to 100 mg/day using a b.i.d. regimen of Carbamazepine or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily.
Maintenance: Adjust dosage to the minimum effective level, usually 400-800 mg.
Children under 6 years of age:
Initial: 10-20 mg/kg/day b.i.d. or t.i.d. as tablets. Increase weekly to achieve optimal clinical response administered t.i.d. or q.i.d. Maintenance: Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.
Side-effects:
Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.
Skin: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), pruritic and erythematous rashes, urticaria, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.
Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy. Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.
Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis; very rare cases of hepatic failure.
Pancreatic: Pancreatitis.
Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.
Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.
Overdose:
Symptoms: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis. Respiratory depression, pulmonary oedema. Tachycardia, hypotension and at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest. Vomiting, delayed gastric emptying, reduced bowel motility.
There have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity. Retention of urine, oliguria or anuria; fluid retention, water intoxication due to ADH-like effect of carbamazepine. Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatine phosphokinase.
Treatment: There is no specific antidote.Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm carbamazepine poisoning and to ascertain the size of the overdose.
Evacuation of the stomach, gastric lavage, and administration of activated charcoal. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.
Special recommendations:
Charcoal haemoperfusion has been recommended. Hemodialysis is the effective treatment modality in the management of the carbamazepine overdose.
Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.
Drug interaction:
Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to the following:
Agents Highly Bound to Plasma Protein: Carbamazepine is not highly bound to plasma proteins; therefore, administration of Carbamazepine to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug. Agents that Inhibit Cytochrome P450 Isoenzymes and/or Epoxide Hydrolase Carbamazepine is metabolized mainly by cytochrome P450 (CYP) 3A4 to the active carbamazepine 10,11-epoxide, which is further metabolized to the trans-diol by epoxide hydrolase. Therefore, the potential exists for interaction between carbamazepine and any agent that inhibits CYP3A4 and/or epoxide hydrolase. Agents that are CYP3A4 inhibitors that have been found, or are expected, to increase plasma levels of Carbamazepine.
Cautions:
Decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Cazepsin. Nonetheless, complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline, and periodically thereafter.
Patients and their relatives should be made aware of early toxic signs and symptoms indicative of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult his physician immediately.
If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored. However, treatment with Cazepsin should be discontinued if the patient develops leucopenia which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. Cazepsin should also be discontinued if any evidence of significant bone marrow depression appears.
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. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease.
Some liver function tests in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyl transferase. This is probably due to hepatic enzyme induction. Enzyme induction may also produce modest elevations in alkaline phosphatase. These enhancements of hepatic metabolising capacity are not an indication for the

withdrawal of carbamazepine.
Severe hepatic reactions to carbamazepine occur very rarely. The development of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment with Cazepsin suspended pending the outcome of the evaluation.
Mild skin reactions e.g. isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous. They usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage. However, since it may be difficult to differentiate the early signs of more serious skin reactions from mild transient reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing the drug should the reaction worsen with continued use.
Hypersensitivity
Cazepsin 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, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon).
In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Cazepsin should be withdrawn immediately.
Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that 25-30 % of these patients may experience hypersensitivity reactions with oxacarbazepine.
Cross-hypersensitivity can occur between carbamazepine and phenytoin.
Cazepsin should be used with caution in patients with mixed seizures which include absences, either typical or atypical. In all these conditions, Cazepsin may exacerbate seizures. In case of exacerbation of seizures, Cazepsin should be discontinued.
An increase in seizure frequency may occur during switchover from an oral formulation to suppositories.
Abrupt withdrawal of Cazepsin may precipitate seizures therefore carbamazepine withdrawal should be gradual. If treatment with Cazepsin has to be withdrawn abruptly in a patient with epilepsy, the changeover to another anti-epileptic drug should if necessary be effected under the cover of a suitable drug.
The reliability of hormonal contraceptives may be adversely affected by Cazepsin and women of childbearing potential should be advised to consider using alternative forms of birth control while taking Cazepsin.
Patients taking Cazepsin and requiring hormonal contraception should receive a preparation containing not less than 50µg oestrogen or use of some alternative non-hormonal method of contraception should be considered.
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.
Cazepsin 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 Cazepsin.
Baseline and periodic complete urinalysis and BUN determinations are recommended.
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. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. If hyponatraemia is observed, water restriction is an important counter-measurement if clinically indicated.
Carbamazepine may reduce serum concentrations of thyroid hormones through enzyme induction requiring an increase in dose of thyroid replacement therapy in patients with hypothyroidism. Hence thyroid function monitoring is suggested to adjust the dosage of thyroid replacement therapy.
The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.
Female patients of childbearing potential should be warned that the concurrent use of Cazepsin with hormonal contraceptives may render this type of contraceptive ineffective
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 reported with Cazepsin, 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.
Presentation:
5x10, PVC Blister in a pack, with instruction for use.
Storage:
Keep in dry place, protected from light at a temperature below 25°C. Keep out of reach of children.
Shelf life:
Labeled. Do not use after expiry date.
Distribution Condition:
Prescribed medicine.

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