PRODUCT MONOGRAPH

Pr MAZEPINE™

Carbamazepine Tablets USP

200 mg

Anticonvulsant
For Symptomatic Relief of Trigeminal Neuralgia

Biomed 2002 Inc.
5950, Côte de Liesse, Suite100
Ville Mont-Royal
Québec H4T 1E2

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ACTION AND CLINICAL PHARMACOLOGY

Carbamazepine has anticonvulsant properties which have been found useful in the treatment of partial seizures (simple or complex) with and without secondary generalization, and generalized tonic-clonic seizures. A mild psychotropic effect has been observed in some patients, which seems related to the effect of carbamazepine in localization-related epilepsies and syndromes.

Clinical Trials

Evidence supporting the efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with simple or complex symptomatology.
2. Generalized tonic-clonic seizures.
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Carbamazepine relieves or diminishes the pain associated with trigeminal neuralgia often within 24 to 48 hours.

Like other tricyclic compounds, carbamazepine has a moderate anticholinergic action which is responsible for some of its side effects. A tolerance may develop to the action of carbamazepine after a few months of treatment and should be watched for. Carbamazepine may suppress ventricular automaticity due to its membrane-depressant effect, similar to that of quinidine and procainamide, associated with suppression of phase 4 depolarization of the heart muscle fiber

A number of investigators have reported a deterioration of EEG abnormalities with regard to focal alterations and a higher incidence of records with nil β-activity, during carbamazepine-combined treatment.

Clinical Pharmacokinetics

The absorption of carbamazepine in man is relatively slow. When taken in a single oral dose, carbamazepine tablets yields peak plasma concentrations of unchanged carbamazepine within 4-24 hours.

Ingestion of food has no significant influence on the rate and extent of absorption regardless of the dosage form of carbamazepine.

Carbamazepine becomes bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in the saliva reflects the non-protein-bound portion present in the serum (20-30%).

The elimination half-life of unchanged carbamazepine in the plasma averages approximately 36 hours following a single oral dose, whereas after repeated administration, which leads to autoinduction of hepatic enzymes, it averages only 16-24 hours, depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing antiepileptic agents, half-life values averaging 9-10 hours have been found. One study in 39 children (aged 3-10 years) and 79 adults (aged 15-65 years) has indicated that carbamazepine elimination may be slightly enhanced in children. This data suggests that children may require higher doses of carbamazepine (in mg/kg) than adults.

Only 2-3% of the dose, whether given singly or repeatedly, is excreted in the urine in unchanged form. Approximately 30% of carbamazepine is renally eliminated via the epoxide pathway. The primary metabolite is the pharmacologically active 10,11-epoxide. The mean elimination half-life of this active metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.

In man, the main urinary metabolite of carbamazepine is the trans-diol derivative originating from the 10,11-epoxide; a small portion of the epoxide is converted into 9-hydroxymethyl-10-carbamoyl-acridan. Other important biotransformation products are various monohydroxylated compounds, as well as the N-glucuronide of carbamazepine produced by UGT2B7.

In patients with epilepsy, the therapeutic range for the steady-state plasma concentration of carbamazepine generally lies between 4-10 μg/mL.

INDICATIONS AND CLINICAL USE

A. **Epilepsy:** MAZEPINE (carbamazepine) is indicated for use as an anticonvulsant drug either alone or in combination with other anticonvulsant drugs.

Carbamazepine is not effective in controlling absence, myoclonic or atonic seizures, and does not prevent the generalization of epileptic discharge. Moreover, exacerbation of seizures may occasionally occur in patients with atypical absences.

B. **Trigeminal Neuralgia**: MAZEPINE is indicated for the symptomatic relief of pain of trigeminal neuralgia only during periods of exacerbation of true or primary trigeminal neuralgia (tic douloureux). It should not be used preventively during periods of remission. In some patients, MAZEPINE has relieved glossopharyngeal neuralgia. For patients who fail to respond to MAZEPINE, or who are sensitive to the drug, recourse to other accepted measures must be considered.

Carbamazepine is not a simple analgesic and should not be used to relieve trivial facial pains or headaches.

CONTRAINDICATIONS

Carbamazepine should not be administered to patients with hepatic disease, a history of bone-marrow depression, a history of hepatic porphyria (acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda), or serious blood disorder.

Carbamazepine should not be administered immediately before, in conjunction with, or immediately after a monoamine oxidase (MAO) inhibitor (see **PRECAUTIONS, Drug Interactions**).

Co-administration of carbamazepine and voriconazole is contraindicated, until data become available from drug interactions studies. CYP3A4 is one of the enzymes thought to be involved in the metabolism of voriconazole. Therefore, co-administration of carbamazepine, a potent inducer of CYP3A4, could diminish the therapeutic effect of voriconazole (see **PRECAUTIONS, Drug Interactions**, **Effects of carbamazepine on plasma levels of concomitant agents**).

Carbamazepine should not be administered to patients presenting atrioventricular heart block (see **ACTION AND CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

Carbamazepine should not be administered to patients with known hypersensitivity to carbamazepine, to any components of the tablets **(see Pharmaceutical Information)** or to any of the tricyclic compounds, such as amitriptyline, trimipramine, imipramine, or their analogues or metabolites, because of the similarity in chemical structure.

WARNINGS

HEAMATOLOGIC: Although reported infrequently, serious adverse effects have been observed during the use of carbamazepine. Agranulocytosis and aplastic anemia, with a fatal outcome, have occurred very rarely. Leucopenia, thrombocytopenia, hepatocellular and cholestatic jaundice, and hepatitis have also been reported. However, in the majority of cases, leucopenia and thrombocytopenia were transient and did not signal the onset of either aplastic anemia or agranulocytosis. It is important that carbamazepine be used carefully and close clinical and frequent laboratory supervision should be maintained throughout treatment in order to detect as early as possible signs and symptoms of a possible blood dyscrasias.Carbamazepine should be discontinued if any evidence of significant bone marrow depression appears (see PRECAUTIONS).

DERMATOLOGIC: Steven's-Johnson Syndrome and Toxic Epidermal Necrolysis: Serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) and Steven's-Johnson Syndrome (SJS), have been reported with carbamazepine. In countries with mainly Caucasian populations, these reactions are estimated to occur in 1 to 6 per 10,000 new users, but in some Asian countries (e.g., Taiwan, Malaysia and the Philippines) the risk is estimated to be about 10 times higher.
Human Leukocyte Antigens (HLA)-A*3101 and HLA-B*1502 may be risk factors for the development of serious cutaneous adverse drug reactions. Retrospective genome wide studies in Japanese and Northern European populations reported an association between severe skin reactions

(SJS, TEN, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP) and maculopapular rash) associated with carbamazepine use and the presence of the HLA-A*3101 allele in these patients. Similarly, in studies that included small samples of patients of Han Chinese ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B*1502 allele. The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia[1]. It is therefore, recommended that physicians should consider HLA-A*3101 and HLA-B*1502 genotyping as a screening tool in genetically at-risk populations (see Warnings - Ancestry and Allelic Variations in the HLA-A Gene and Ancestry and Allelic Variations in the HLA-B Gene). Until further information is available, the use of MAZAPINE and other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who test positive for HLA-A*3101 or HLA-B*1502 alleles (see WARNINGS- Ancestry and Allelic Variation in the HLA-A Gene; WARNINGS- Ancestry and Allelic Variation in the HLA-B Gene and warnings-Important Limitations of HLA-A and HLA-B Genotyping).

Treatment recommendations for dermatologic reactions: Carbamazepine should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. The use of other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who have shown severe dermatologic reactions during carbamazepine treatment.

CARCINOGENICITY: Long-term toxicity studies in rats indicated a potential carcinogenic risk (see TOXICOLOGY). Therefore, the possible risk of the drug must be weighed against the potential benefits before prescribing carbamazepine to individual patients.

There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions.

Ancestry and Allelic Variation in the HLA-A Gene

The frequency of the HLA-A*3101 allele, an inherited allelic variant of the HLA-A gene, varies widely between ethnic populations. The frequency of this allele is estimated less than 5% in the majority of European, Australian, Asian, African and North American populations with some exceptions within 5-12%. Prevalence above 15% has been estimated in some ethnic groups in South America (Argentina and Brazil), North America (US Navajo and Sioux, and Mexico Sonora Seri) and Southern India (Tamil Nadu) and between 10%-15% in other native ethnicities in these same regions.

Testing for the presence of HLA-A*3101 allele should be considered in patients with ancestry in genetically at-risk populations (for example, patients of the Japanese and

[1] The following rates provide a rough estimate of the prevalence of HLA-B*1502 in various populations. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2 to 4%, but this may be higher in some groups. HLA-B*1502 is present in <1% of the population in Japan and Korea. HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans). The estimated prevalence rates have limitations due to the wide variability in rates that exist within ethnic groups, the difficulties in ascertaining ethnic ancestry and the likelihood of mixed ancestry.

Caucasian populations, patients who belong to the indigenous populations of the Americas, Hispanic populations, people of southern India, and people of Arabic descent), prior to initiating treatment with carbamazepine (see Warnings - Important Limitations of HLA-A and HLA-B Genotyping). The use of carbamazepine should be avoided in patients who are found to be positive for HLA-A*3101, unless the benefits clearly outweigh the risks. Screening is generally not recommended for any current carbamazepine users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of HLA-A*3101 status (see Warnings- Important Limitations of HLA-A and HLA-B Genotyping).

Ancestry and Allelic Variation in the HLA-B Gene

In studies that included small samples of patients of Han Chinese ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia. Results of these studies suggest that the presence of HLA-B*1502 allele may be one of the risk factors for carbamazepine-associated SJS/TEN in patients with Asian ancestry. Therefore, physicians should consider HLA-B*1502 genotyping as a screening tool in these patients. Until further information is available, the use of carbamazepine and other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who test positive for the HLA-B*1502 allele.

Important Limitations of HLA-A and HLA-B Genotyping

HLA-A*3101 and HLA-B*1502 genotyping as a screening tool have important limitations and must never substitute for appropriate clinical vigilance and patient management. Many patients positive for HLA-A*3101 and treated with carbamazepine will not develop SJS, TEN, DRESS, AGEP or maculopapular rash and patients negative for HLA-A*3101 of any ethnicity can still develop these severe cutaneous adverse reactions. Similarly, many HLA-B*1502-positive Asian patients treated with carbamazepine will not develop SJS/TEN, and these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, these severe cutaneous adverse reactions, such as anti-epileptic drug (AED) dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

In addition, it should be kept in mind that over 90% of carbamazepine treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration when deciding whether to screen genetically at-risk patients currently on carbamazepine.

The identification of subjects carrying the HLA-B*1502 allele and the avoidance of carbamazepine therapy in these subjects has been shown to decrease the incidence of carbamazepine-induced SJS/TEN.

Should signs and symptoms suggest a severe skin reaction such as SJS or TEN, carbamazepine should be withdrawn at once.

Hypersensitivity
Carbamazepine may trigger hypersensitivity reactions, including multi-organ hypersensitivity reactions, which can affect the skin, liver, (including intrahepatic bile ducts), hematopoietic organs and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see **ADVERSE REACTIONS**).

The HLA-A*3101 allele has been found to be associated with the occurrence of hypersensitivity syndrome, including maculopapular rash.

In general, if signs and symptoms suggestive of hypersensitivity reactions occur, carbamazepine should be withdrawn immediately, and alternative therapy should be considered.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of these patients may experience hypersensitivity reactions with oxcarbazepine (Trileptal®).

Cross-hypersensitivity can occur between carbamazepine and phenytoin.

Pregnancy and Nursing

Pregnancy
Women with epilepsy who are, or intend to become pregnant, should be treated with special care.

In women of childbearing potential, carbamazepine should, whenever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with more than one antiepileptic drug is greater than in those of women receiving a single antiepileptic.

Minimum effective doses should be given and the plasma levels monitored.

If pregnancy occurs in a woman receiving carbamazepine, or if the problem of initiating carbamazepine arises during pregnancy, the drug's potential benefits must be weighed against its hazards, particularly during the first 3 months of pregnancy. carbamazepine should not be discontinued or withheld from patients if required to prevent major seizures because of the risks posed, to both mother and fetus, by status epilepticus with attendant hypoxia.

The possibility that carbamazepine, like all major antiepileptic drugs, increases the risk of malformations has been reported. Developmental disorders and malformations, including spina bifida, and also other congenital anomalies, e.g. craniofacial defects, cardiovascular malformations, hypospadias, and anomalies involving various body systems, have been reported in association with carbamazepine.

Conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

During pregnancy, an effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate folic acid deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy.

To prevent neonatal bleeding disorders, Vitamin K_1 administration to the mother during the last weeks of pregnancy, as well as to the newborn, has been recommended.

A few cases of neonatal seizures and respiratory depression have been associated with maternal carbamazepine and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhea, and/or decreased feeding have been associated with maternal carbamazepine use. These reactions may represent a neonatal withdrawal syndrome.

Lactation
Carbamazepine passes into breast milk in concentrations of about 25-60% of the plasma level. No reports are available on the long-term effect of breast feeding. The benefits of breast feeding should be weighed against the possible risks to the infant. Should the mother taking carbamazepine nurse her infant, the infant must be observed for possible adverse reactions, e.g., somnolence, allergic skin reaction.

It should be noted that the reliability of oral contraceptives may be adversely affected by carbamazepine (see PRECAUTIONS, Drug Interactions).

Fertility
There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis.

PRECAUTIONS

Clinical Monitoring of Adverse Reactions
MAZEPINE (carbamazepine) should be prescribed only after a critical risk-benefit appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematological reactions to other drugs, or interrupted courses of therapy with carbamazepine. **Careful clinical and laboratory supervision should be maintained throughout treatment**. Should any signs or symptoms or abnormal laboratory findings be suggestive of blood dyscrasia or liver disorder, carbamazepine should be immediately discontinued until the case is carefully reassessed.

a) **Bone marrow function**: Complete blood counts, including platelets and possibly reticulocytes and serum iron, should be carried out before treatment is instituted, and periodically thereafter.

If definitely low or decreased white blood cell or platelet counts are observed during treatment, the patient and the complete blood count should be monitored closely. Non-progressive fluctuating asymptomatic leucopenia, which is encountered, does not generally call for the withdrawal of

carbamazepine. However, treatment with carbamazepine should be discontinued if the patient develops leucopenia which is progressive or accompanied by clinical manifestations, e.g., fever or sore throat, as this could indicate the onset of significant bone marrow depression.

Because the onset of potentially serious blood dyscrasias may be rapid, patients should be made aware of early toxic signs and symptoms of a potential hematological 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 hemorrhage appear, the patient should be advised to consult his/her physician immediately.

b) **Hepatic function**: Baseline and periodic evaluations of hepatic function must be performed, particularly in elderly patients and patients with a history of liver disease. Carbamazepine should be withdrawn immediately in cases of aggravated liver dysfunction or active liver disease.

c) **Kidney function**: Pre-treatment and periodic complete urinalysis and BUN determinations should be performed.

d) **Ophthalmic examinations**: Carbamazepine has been associated with pathological eye changes. Periodic eye examinations, including slit-lamp funduscopy and tonometry are recommended.

e) **Plasma levels**: Although correlations between dosage and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring plasma levels may be useful in the following situations: dramatic increase in seizure frequency/verification of patient compliance; during pregnancy; when treating children or adolescents; in suspected absorption disorders; in suspected toxicity, especially where more than one drug is being used (see **Drug Interactions**).

Increased Seizure Frequency
Carbamazepine should be used with caution in patients with mixed seizures which includes absences, either typical or atypical. In all these conditions, carbamazepine may exacerbate seizures. In the event of exacerbation of seizures, carbamazepine should be discontinued.

Dermatologic
Mild skin reactions, e.g., isolated macular or maculopapular exanthema, usually disappear within a few days or weeks, either during a continued course of treatment or following a decrease in dosage. However, the patient should be kept under close surveillance because of the rare possibility of Steven-Johnson Syndrome or Toxic Epidermal Necrolysis occurring (see **WARNINGS DERMATOLOGIC**).

In addition to being associated with severe adverse cutaneous reactions **(see WARNINGS)**, the HLA-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from carbamazepine, and may predict the risk of such reactions as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption). However, the HLA-B*1502 allele has not been found to predict the risk of these aforementioned skin reactions **(see WARNINGS - Ancestry and Allelic Variation in the HLA-A Gene)**.

Urinary Retention and Increased Intraocular Pressure
Because of its anticholinergic action, carbamazepine should be given cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Such patients should be followed closely while taking the drug.

Psychiatric
Because it is closely related to the other tricyclic drugs, there is some possibility that carbamazepine might activate a latent psychosis, or, in elderly patients, produce agitation or confusion, especially when combined with other drugs. Caution should also be exercised in patients with alcohol dependence.

Suicidal ideation and behavior:

Suicidal ideation and behavior have been reported in patients treated with antiepileptic agents in several indications.

All patients treated with antiepileptic drugs, irrespective of indication, should be monitored for signs of suicidal ideation and behavior and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which antiepileptic drugs were used for various indications, has shown a small increased risk of suicidal ideation and behavior in patients treated with these drugs. The reason for this risk is not known.

There were 43892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (antiepileptic drug or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (antiepileptic drug or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more antiepileptic drug). Therefore, the small increased risk of suicidal ideation and behavior reported from the meta-analysis (0.43% for patients on antiepileptic drugs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (antiepileptic drug or placebo) for non-epilepsy indications. The study design does not allow for an estimation of the risk of suicidal ideation and behavior for patients with epilepsy that are taking antiepileptic drugs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct antiepileptic drug treatment in both arms.

Risk of Suicide in Patients with Bipolar Disorder:

Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking medications for bipolar disorder. Patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dosage changes.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behavior or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Prescriptions for all medications, including carbamazepine, should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Cardiovascular Disorders
Carbamazepine should be used cautiously in patients with a history of coronary artery disease, organic heart disease, or congestive heart failure. If a defective conductive system is suspected, an ECG should be performed before administering carbamazepine, in order to exclude patients with atrioventricular block.

Bone disorders
Long-term use of antiepileptics such as carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine and sodium valproate is associated with a risk of decreased bone mineral density that may lead to weakened or brittle bones.

Driving and Operating Hazardous Machinery
Because dizziness and drowsiness are possible side effects of carbamazepine, patients should be warned about the possible hazards of operating machinery or driving automobiles.

Drug Interactions
Cytochrome P450 3A4 (CYP3A4) is the main enzyme responsible for metabolizing carbamazepine. Coadministration of CYP3A4 inhibitors may increase carbamazepine plasma concentrations and induce adverse reactions. Drugs that have shown, or would be expected, to increase plasma carbamazepine levels include:

cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, fluvoxamine, nefazodone, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, azoles (e.g., ketaconazole, itraconazole, fluconazole), acetazolamide, verapamil, grapefruit juice, protease inhibitors, valproate.[2]

[2] Increased levels of the active 10,11-epoxide

Co-administration of CYP3A4 inducers may increase the rate of carbamazepine metabolism leading to potential decreases in the carbamazepine serum levels and therapeutic effect. Alternatively, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels. Drugs that have been shown, or that would be expected, to decrease plasma carbamazepine levels include:

cisplatin, doxorubicin HCl, felbamate[3], rifampin, phenobarbital, phenytoin, primidone, methsuximide, theophylline.

Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism.

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. Co-adminitration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations.

Effects of carbamazepine on plasma levels of concomitant agents
Carbamazepine may lower the plasma level, or diminish or even abolish the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirements when administered with carbamazepine:

Analgesics, anti-inflamatory agents: buprenorphine, methadone, paracetamol, phenazone (antipyrine), tramadol.

Antibiotics: doxycycline.

Anticoagulants: oral anticoagulants (warfarin, phenprocoumon, dicoumarol, and acenocoumarol).

Antidepressants: bupropion, citalopram, mianserin, nefadozone, sertraline, trazodone, tricyclic antidepressant (e.g., imipramine, amitriptyline, nortriptyline, clomipramine). The use of carbamazepine is not recommended 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**).

Antiemetics: aprepitant.

Antiepileptics: oxcarbazepine, clobazam, clonazepam, ethosuximide, primidone, valproic acid, felbamate, lamotrigine, zonisamide, tiagabine, topiramate. Phenytoin plasma levels have been reported both to be raised and lowered by carbamazepine, and mephenytoin plasma levels have been reported in rare instances to increase.

Antifungals: caspofungin, itraconazole, voriconazole (see **CONTRAINDICATIONS**).

Antihelmintics: praziquantel, albendazole.

[3] Decreased levels of carbamazepine and increased levels of the 10,11-epoxide

Antineoplastics: imatinib, irinotecan, gefitinib, cyclophosphamide, lapatinib, temsirolimus.

Antipsychotics: clozapine, haloperidol and bromperidol, olanzapine, quetiapine, risperidone, zisprasidone, aripiprazole, paliperidone.

Antivirals: protease inhibitors for HIV treatment, e.g., indinavir, ritonavir, saquinavir.

Anxiolytics: alprazolam, midazolam.

Bronchodilatators or anti-asthma drugs: theophylline.

Contraceptives: hormonal contraceptives.

Cardiovascular drugs: calcium channel blockers (dihydropyridine group), e.g., felodipine, digoxin, disopyramide, quinidine, propranolol.

Corticosteroids: corticosteroids (e.g., prednisolone, dexamethasone).

Drugs used in erectile dysfunction: tadalafil.

Immunosuppressants: cyclosporin, everolimus, tacrolimus, sirolimus.

Thyroid agents: levothyroxine.

Other drug interactions: products containing estrogens and/or progesterones.

Agents that may raise carbamazepine and/or carbamazepine-10,11-epoxide plasma levels
Since an increase in carbamazepine and/or carbamazepine-10,11-epoxide plasma levels may results in adverse reactions (e.g., dizziness, drowsiness, ataxia, diplopia), the dosage of MAZEPINE should be adjusted accordingly and the blood levels monitored when used concomitantly with the substances described below:

Analgesics, anti-inflammatory drugs: dextropropoxyphene, ibuprofen.

Androgens: danazol.

Antibiotics: macrolide antibiotics (e.g., erythromycin, troleandomycin, josamycin, clarithromycin, telithromycin), ciprofloxacine.

Antidepressants: possibly desipramine, fluoxetine, fluvoxamine, nefadozone, paroxetine, trazodone, viloxazine.

Antiepileptics: stiripentol, vigabatrin.

Antifungals: azoles (itraconazole, ketoconazole, fluconazole, voriconazole).

Antihistamines: terfenadine, loratadine.

Antipsychotics: loxapine, olanzapine, quetiapine.

Antituberculosis: isoniazid.

Antivirals: protease inhibitors for HIV treatment (e.g., ritonavir).

Carbonic anhydrase inhibitors: acetazolamide.

Cardiovascular drugs: verapamil, diltiazem.

Gastrointestinal drugs: cimetidine, omeprazole.

Muscle relaxants: oxybutynin, dantrolene.

Platelet aggregation inhibitors: ticlopidine.

Other interactions: grapefruit juice, nicotinamide (raises carbamazepine plasma levels in children, but only at high dosage in adults).

Loxapine, felbamate, quetiapine, primidone, valproic acid, and valpromide were reported to increase concentration of the active metabolite carbamazepine-10,11-epoxide.

Agents that may decrease carbamazepine plasma levels
The dose of MAZEPINE may consequently have to be adjusted when used concomitantly with the substances described below.

Antiepileptics: felbamate (might decrease the carbamazepine serum concentration associated with an increase in carbamazepine epoxide levels, and might decrease the serum felbamate levels), methsuximide, oxcarbazepine, phenobarbitone, phensuximide, phenytoin and fosphenytoin, primidone, progabide, and possibly by clonazepam, valproic acid or valpromide.

Antineoplastics: cisplatin or doxorubicin.

Antituberculosis: rifampicin.

Bronchodilatators or anti-asthma drugs: theophylline, aminophylline.

Dermatological drugs: isotretinoin.

Other interactions: herbal preparations containing St John's wort (Hypericum perforatum).

Combinations that require specific consideration
Concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity (e.g., nystagmus, nausea, vomiting).

Combined use of carbamazepine with lithium, metoclopramide, or haloperidol, may increase the risk of neurotoxic side effects (even in the presence of "therapeutic plasma levels").

Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

Carbamazepine, like other anticonvulsants, may adversely affect the reliability of hormonal contraceptives; breakthrough bleeding may occur. Accordingly, patients should be advised to use some alternative, non-hormonal method of contraception while taking MAZEPINE. Due to enzyme induction MAZEPINE may cause failure of the therapeutic effect of estrogen and/or progesterone containing drugs (e.g., failure of contraception).

Concomitant medication with carbamazepine and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia.

Carbamazepine may antagonize the effects of non-depolarizing muscle relaxants (e.g., pancuronium); their dosage may need to be raised and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.

Isotretinoin has been reported to alter the bioavailability and/or clearance of carbamazepine and carbamazepine-10,11-epoxide; carbamazepine plasma levels should be monitored.

Carbamazepine, like other psycho-active drugs, may reduce the patient's alcohol tolerance; it is therefore advisable to abstain from alcohol consumption during treatment.

Carbamazepine should not be administered in conjunction with an MAO inhibitor (see **CONTRAINDICATIONS**).

ADVERSE REACTIONS

The reactions which have been most commonly reported with MAZEPINE (carbamazepine) are CNS disturbances (e.g., drowsiness, headache, unsteadiness on the feet, diplopia, dizziness), gastrointestinal disturbances (nausea, vomiting), and allergic skin reactions. These reactions usually occur only during the initial phase of therapy, if the initial dose is too high, or when treating elderly patients. They have rarely necessitated discontinuing carbamazepine therapy, and can be minimized by initiating treatment at a low dosage.

The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels.

The more serious adverse reactions observed are the hematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy.

Abrupt withdrawal of MAZEPINE (carbamazepine) may precipitate seizures. In epileptic patients, the switch to the new antiepileptic compound should be made under cover of a suitable drug (e.g., diazepam i.v. or phenytoin i.v.).

The following adverse reactions have been reported (Frequency estimate: Very common: (≥1/10); common: (≥1/100, <1/10); uncommon: (≥1/1000, <1/100); rare: (≥1/10000, <1/1000); very rare: (<1/10000); frequency unknown:

Blood and lympathic system disorders

Very common: leucopenia;

Common: eosinophilia, thrombocytopenia;

Rare: leukocytosis, lymphadenopathy, folic acid deficiency;

Very rare: agranulocytosis, aplastic anemia, pancytopenia, pure red cell aplasia, anemia, macrocytic anemia, megaloblastic anemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda, reticulocytosis, thrombocytopenic purpura and possibly hemolytic anemia. In a few instances, deaths have occurred.

Hepatobiliary disorders

Very common: increased gamma-GT (due to hepatic enzyme induction), usually not clinically relevant;

Common: increased blood alkaline phosphatase;

Uncommon: increased transaminases;

Rare: jaundice, hepatitis of a cholestatic, parenchymal (hepatocellular), or mixed type, vanishing bile duct syndrome;

Very rare: granulomatous hepatitis, hepatic failure.

Skin and subcutaneous tissue disorders

Very common: dermatitis allergic reactions and rashes, erythematous rashes, urticaria which may be severe;

Uncommon: exfoliative dermatitis and erythroderma;

Rare: systemic lupus erythematosus, pruritis;

Very rare: Stevens-Johnson Syndrome[4], toxic epidermal necrolysis (Lyell's syndrome), photosensitivity reaction, alopecia, diaphoresis, erythema multiform, and nodosum, skin pigmentation changes, purpura, acne, neurodermatitis, hirsutism.

Unknown: Acute Generalized Exanthematous Pustulosis (AGEP).

Nervous system disorders

Very common: dizziness, drowsiness, ataxia and fatigue;

Common: an increase in motor seizures (see **INDICATIONS**), headache, diplopia, accommodation disorders (e.g., blurred vision);

Uncommon: abnormal involuntary movements (e.g., tremor, asterixis, dystonia, tics), nystagmus;

Rare: orofacial dyskinesia, paresis, eye movement disturbances, speech disorders (e.g., dysarthria, slurred speech), neuropathy peripheral, paraesthesia, muscle weakness, choreoathetosis;

Very Rare: taste disturbances, neuroleptic malignant syndrome.

Cardiac disorders

Rare: cardiac conduction disorders (including second and third degree atrioventricular heart block), hypertension or hypotension;

Very rare: bradycardia, arrhythmias, Stokes-Adams in patients with atrioventricular block, circulatory collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thromboembolism (e.g., pulmonary embolism). Some of these cardiovascular complications have had fatal outcomes. Myocardial infarction and arrhythmia have been associated with other tricyclic compounds.

Psychiatric disorders

Rare: hallucinations (visual or auditory), depression with agitation, talkativeness, agitation, anorexia, restlessness, aggression, confusional state;

Very rare: activation of psychosis. Very rare cases of suicide attempt and completed suicide have been reported, however a causal relationship has not been established.

Renal and urinary disorders

Very rare: interstitial nephritis and renal failure, renal impairment (e.g., albuminuria, glycosuria, hematuria, oliguria sometimes associated with elevated blood pressure, and blood urea nitrogen increased/azotemia), urinary frequency, urinary retention.

[4] In some Asian countries also reported as rare. See WARNINGS.

Reproductive system

Very rare: sexual dysfunction/ impotence, spermatogenesis abnormal (with decreased sperm count and/or motility).

Gastrointestinal disorders

Very common: nausea, vomiting*;*

Common: dry mouth and throat;

Uncommon: diarrhea, constipation;

Rare: abdominal pain;

Very rare: glossitis, stomatitis, pancreatitis.

Eye disorders

Very rare: lenticular opacities, conjunctivitis, intraocular pressure increased, retinal changes.

Ear and labyrinth disorders

Very rare: hearing disorders (e.g. tinnitus, hyperacusis, hypoacusis), change in pitch perception.

Endocrine disorders

Common: edema, fluid retention, weight increase, hyponatremia and blood osmolarity decreased due to antidiuretic hormone (ADH)-like effect occurs, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusional state, neurological disorders;

Very rare: blood prolactin increased with or without clinical manifestations (e.g., galactorrhea), gynecomastia, abnormal thyroid function tests: decreased L-thyroxine (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-calciferol), leading to osteomalacia/osteoporosis, increased blood cholesterol, including HDL cholesterol and triglycerides.

Musculoskeletal, connective tissue and bone disorders

Very rare: arthralgia, muscle pain, muscle spasms.

Respiratory, thoracic and mediastinal system

Very rare: pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Immune system disorders

Rare: delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, oesinophilia, hepatosplenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), occurring in various combinations. Other organs may also be affected (e.g., lungs, kidneys, pancreas, myocardium, colon);

Very rare: aseptic meningitis with myoclonus and peripheral oesinophilia, anaphylactic reaction, angioneurotic edema.

Unknown: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

Investigations

Very rare: hypogammaglobulinaemia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

.

Lowest known lethal dose: estimated 3.2 g (24 year old woman).

Highest known dose survived: 80 g (34 year old man); 34 g (13 year old girl); 1.4 g (23 month old girl).

Symptoms of Overdosage
The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular and respiratory systems.

Central Nervous System: CNS depression, ataxia, somnolence, restlessness, agitation, hallucination, coma, blurred vision, slurred speech, dysarthria, disorientation, tremor, dyskinesia, psychomotor disturbances, opisthotonia, abnormal reflexes (slowed or hyperactive), convulsions, myoclonus, mydriasis, nystagmus, hypothermia/hyperthermia, flushed skin/cyanosis, EEG changes.

Respiratory System: respiratory depression, pulmonary edema.

Cardiovascular System: tachycardia, hypotension or hypertension, conduction disturbance with widening of QRS complex, syncope in association with cardiac arrest.

Gastrointestinal System: nausea, vomiting, delayed gastric emptying, reduced bowel motility.

Renal Function: urinary retention, oliguria or anuria; fluid retention, and water intoxication.

Laboratory Findings: hyponatremia, hypokalemia, leukocytosis, reduced white cell count, metabolic acidosis, hyperglycemia, glycosuria, acetonuria, increased muscle creatine phosphokinase.

Treatment of Overdosage

For up-to date information on the management of a suspected drug overdose, contact the regional Poison Control Center.

There is no known specific antidote to carbamazepine.

Evacuate the stomach, with an emetic or by gastric lavage, then administer activated charcoal. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication.

Vital signs should be watched and symptomatic treatment should be administered as required. Hyperirritability or convulsions may be controlled by administration of parenteral diazepam or barbiturates but they may induce respiratory depression, particularly in children. Paraldehyde may be used to counteract muscular hypertonus without producing respiratory depression.

When barbiturates are employed, it is advisable to have equipment available for artificial ventilation and resuscitation. Barbiturates should not be used if drugs that inhibit monoamine oxidase have been taken by the patient, either in overdosage or in recent therapy (within two weeks).

Hyponatremia should be treated by restricting fluids and a slow and careful NaCl 0.9% infusion I.V. These measures may be useful in preventing brain damage.

Shock (circulatory collapse) should be treated with supportive measures, including intravenous fluids, oxygen, and corticosteroids. For hypotension unresponsive to measures taken to increase plasma volume, dopamine or dobutamine I.V. may be administered.

It is recommended that the electrocardiogram be monitored, particularly in children, to detect any cardiac arrhythmias or conduction defects.

Charcoal hemoperfusion has been recommended. Forced diuresis, hemodialysis and peritoneal dialysis have been reported to be ineffective.

Relapse and aggravation of symptomatology on the 2nd or 3rd day after overdose, due to delayed absorption, should be anticipated.

DOSAGE AND ADMINISTRATION

Use in Epilepsy (see INDICATIONS)
MAZEPINE (carbamazepine) may be used alone or with other anticonvulsants. A low initial daily dosage of MAZEPINE with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient. MAZEPINE should be taken with meals whenever possible.

MAZEPINE should be taken in 2 to 4 divided doses daily.

Adults and Children Over 12 Years of Age
Initially, 100 to 200 mg once or twice a day depending on the severity of the case and previous therapeutic history. The initial dosage is progressively increased, in divided doses, until the best response is obtained. The usual optimal dosage is 800 to 1200 mg daily. In rare instances some adult patients have received 1600 mg. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

Children 6-12 Years of Age
Initially, 100 mg in divided doses on the first day. Increase gradually by adding 100 mg per day until the best response is obtained. Dosage should generally not exceed 1000 mg daily. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

Combination Therapy
When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except for phenytoin, which may be increased (see **PRECAUTIONS, Drug Interactions and WARNINGS, Pregnancy and Nursing**).

Use in Trigeminal Neuralgia
The initial daily dosage should be small; 200 mg taken in two doses of 100 mg each is recommended. The total daily dosage can be increased by 200 mg/day until relief of pain is obtained. This is usually achieved at a dosage between 200 and 800 mg daily, but occasionally up to 1200 mg/day may be necessary. As soon as relief of pain has been obtained and maintained, progressive reduction in dosage should be attempted until a minimum effective dosage is reached. Because trigeminal neuralgia is characterized by periods of remission, attempts should be made to reduce or discontinue the use of MAZEPINE at intervals of not more than 3 months, depending upon the individual clinical course.

Prophylactic use of the drug in trigeminal neuralgia is not recommended.

AVAILABILITY

Each white, round, compressed tablet of MAZEPINE contains 200 mg of carbamazepine, USP. MAZEPINE tablets are scored on one side and embossed “ICN M11” on the other side. MAZEPINE tablets contain as non-medicinal ingredients: lactose, povidone, eudragit, starch, microcrystalline cellulose, magnesium stearate, and sodium carboxymethyl starch.

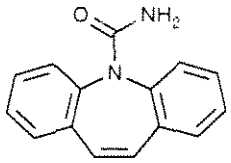
MAZEPINE tablets are available in bottles of 100’s and 500’s.

PHARMACEUTICAL INFORMATION

Chemical Substance: (1) *5H*-Dibenzo[b,*f*]azepine-5-carboxamide;

Chemical Name: Carbamazepine, USP

Structural Formula:



Molecular Formula: $C_{15}H_{12}N_2O$

Molecular Weight: 236.27

Description: Carbamazepine is a white to yellowish-white crystalline powder with a melting point from 189° to 193°C.

Solubility: Carbamazepine is practically insoluble in water and in ether; sparingly soluble in ethanol and in acetone; soluble in 1 in 10 of chloroform; soluble in propylene glycol.

PHARMACOLOGY

When administered to mice by the oral route at the dose level of 100 mg/kg, carbamazepine protected all animals against electroshock induced convulsions (50 mA for 0.2 seconds) for up to 5 hours. In rats, at 50 mg/kg orally, the convulsive threshold was increased by 88% and at the dosage of 100 mg/kg, carbamazepine increased the convulsive threshold by about 130%. On the other hand, very minimal effects were noted when carbamazepine was given to mice challenged with picrotoxin and it did not block pentylenetetrazol-induced convulsions.

Carbamazepine has slight sedative and tranquilizing effects in mice but no hypnotic effect except at almost toxic dose. Although intact and spinal animals are influenced in the same way as by muscle relaxants, carbamazepine has no clinically significant muscle relaxant action. In animals, carbamazepine has only a slight anticholinergic effect and no anti-emetic activity. Carbamazepine did not inhibit monoamine oxidase in the guinea pig liver at the drug concentration of 1×10^{-3}M.

In rabbits, carbamazepine administered intravenously could not be given in a dosage sufficient to produce a Stage IV anesthesia (Magnus and Girndt) without toxic effects. Hence, the anesthetic potential is considered nil.

In experimental animals, carbamazepine depresses certain pain reflexes that are mediated by cranial nerves, such as the lingulomandibular and infraorbital reflexes. There is no general analgesic effect and non-specific cutaneous pain is not modified by carbamazepine, except at very high doses. In humans, the effect of carbamazepine upon trigeminal or glossopharyngeal pain is probably largely due to blocking of bulbar, thalamic and higher synapses.

In experimental animals, carbamazepine is rapidly absorbed and rapidly equilibrated between the blood and tissues. It does not accumulate in tissues other than adipose tissues. In the rabbit, carbamazepine is rapidly metabolized and excreted so that blood and tissue levels are very low within 24 hours. Only about 2% is excreted unchanged in the urine.

TOXICOLOGY

Acute Toxicity

In mice, the oral LD_{50} of carbamazepine is between 1100 and 3750 mg/kg; in rats, 3850 to 4025 mg/kg; in rabbits, 1500-2680 mg/kg; in guinea pigs, about 920 mg/kg; and in dogs, more than 5620 mg/kg.

The principal toxic effects in these species were labored breathing, ataxia, clonic and tonic convulsions, and coma. In dogs, toxic doses of carbamazepine induced severe vomiting and defecation, in addition to disturbance of locomotor function.

Subacute and Chronic Toxicity

Subacute and chronic toxicity studies have been carried out on carbamazepine for up to one year at dosage levels of 50, 100, 200, and 400 mg/kg in rats and 50, 100, 150, and 200 mg/kg in the dog. In rats, at 100 and 200 mg/kg/day and above, there was evidence of hepatotoxicity including a slight increase in ALT and histological changes in the liver. At dosage of 400 mg/kg/day, 25 of 50

animals died, beginning at the 15th week. ALT and BUN levels were slightly increased. The relative organ/body weight ratios were increased for the heart, liver, and kidneys.

Carcinogenesis and Mutagenesis
Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75 and 250 mg/kg daily, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and in benign interstitial cell adenomas in the testes of males. Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these above findings relative to the use of carbamazepine in humans is as yet unknown.

Testicular atrophy and deficient spermatogenesis were observed in a four week oral study with carbamazepine in the rat at 100 mg/kg/day, but were not observed in animals dosed with 200, 500, and 1000 mg/kg/day. In a 24 week study in rats, evidence of testicular atrophy was observed in 3 of 10 animals at 50 mg/kg/day and in one of 10 at 100 mg/kg/day, but no testicular damage was observed at 200 mg/kg/day. In a one year study, inhibition of spermatogenesis and testicular atrophy were noted in 6 of 19 surviving male rats receiving 400 mg/kg/day.

In dogs, there were some macroscopic gray or brownish discolorations of urinary bladders at 100 and 200 mg/kg/day in a 3 month study and at all dose levels (50, 100, and 150 mg/kg/day) in a one year study. Histologically, the brownish pigment was found in the macrophages in the submucosa. The pigment is considered to be a non-toxic metabolite rather than melanin or argentaffin. In one dog, there was minimal hepatic damage after 12 months.

Reproductive Studies
In the course of reproductive studies with carbamazepine in rats and rabbits, approximately 1% of the offspring were listed as having some anomaly.

In the reproduction study in rats, two of the offspring showed kinked ribs bilaterally at doses of 250 mg/kg and 4 animals had cleft palates and talipes at 650 mg/kg. Two of the latter also had anophthalmos. In mice and rats, carbamazepine, when given parenterally, produced a low but nevertheless definite incidence of anomalies including anencephalia, anophthalmos, cleft palates, and rudimentary or absent tails. In one study using mice, carbamazepine (40-240 mg/kg body weight daily, orally) caused defects (mainly dilatation of cerebral ventricules) in 4.7% of exposed fetuses as compared with 1.3% in controls).

In nursing rats, toxicity was demonstrated by lack of weight gains and unthrifty appearance at the dose level of 200 mg/kg.

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PART III:

CONSUMER INFORMATION
PrMAZEPINE™
(carbamazepine Tablets USP)

This leaflet is part III of a three-part "Product Monograph" published when MAZEPINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MAZEPINE. Contact your doctor or pharmacist if you have any questions about the drug.

WARNINGS AND PRECAUTIONS

ABOUT THIS MEDICATION

What the medication is used for:
MAZEPINE has been prescribed for you by your doctor:
- to reduce your number of seizures;
- to relieve the pain of trigeminal neuralgia.

What it does:
MAZEPINE (carbamazepine) belongs to the family of medicines called anticonvulsants for treating epilepsy. MAZEPINE is also used for treating the pain of trigeminal neuralgia.

If you have any questions about how MAZEPINE works or why this medicine has been prescribed to you, ask your doctor.

When it should not be used:
You should not use MAZEPINE if YOU:
- are allergic (hypersensitive) to carbamazepine or to any of the other ingredients of MAZEPINE (See **What the non-medicinal ingredients are**). If you think you may be allergic, ask your doctor for advice. Do not take MAZEPINE if you are allergic to other trycyclic drugs such as amitriptyline, trimipramine, imipramine.
- have severe heart disease (heart block);
- have liver disease;
- have a history of bone marrow depression;
- have had serious blood illnesses in the past;
- have a disturbance in the production of porphyrin, a pigment important for liver function and blood formation (also called hepatic porphyria);
- are also taking drugs belonging to a special group of antidepressants called monoamine-oxidase inhibitors (MAOIs);
- are also taking the drug voriconazole (Vfend) for treatment of an infection.

MAZEPINE should not be used to relieve trivial pain in the face or headaches.

If any of the above applies to you, **tell your doctor before taking MAZEPINE.**

What the medicinal ingredient is:

Carbamazepine.

What the nonmedicinal ingredients are:
Eudragit, lactose, magnesium stearate, microcrystalline cellulose, povidone, sodium carboxymethyl starch, and starch.

What dosage forms it comes in:
Tablets containing 200 mg of carbamazepine.

Serious Warnings and Precautions

- **Blood: Although infrequently reported and very rarely fatal, serious adverse effects affecting blood cell counts have been observed during the use of MAZEPINE. Other side effects include: low white blood cell count, bone marrow depression, hepatitis and signs of liver failure such as jaundice (yellowing of the skin or eyes).**

Contact your doctor immediately if you are experiencing any of these symptoms. Close clinical and frequent laboratory supervision with your doctor should be maintained throughout treatment with MAZEPINE in order to detect as early as possible any possible signs of a blood disorder. Your doctor should discontinue MAZEPINE if there is significant evidence of a bone marrow depression.

- **Skin: Serious and sometimes fatal skin reactions known as toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have been reported with MAZEPINE. Other serious skin reactions such as Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP) and Maculopapular Rash have been also reported. Although very rare, serious forms of DRESS and AGEP may also lead to death. Since some cases of these skin reactions have been genetically linked, your doctor may recommend a blood test to determine whether you belong to an at-risk population.**
- **Contact your doctor immediately if you are developing a rash or any serious skin reactions such as red skin, blistering of the lips, eyes or mouth, and skin peeling accompanied by fever. Your doctor will determine if it is indeed drug related, and discontinue MAZEPINE in this case.**

- **<u>Cancer</u>: Long-term toxicity studies in rats have indicated a possible cancer risk associated with carbamazepine. Before taking MAZEPINE, discuss with your doctor the potential benefits and possible risks of this treatment for you.**

BEFORE you use MAZEPINE talk to your doctor or pharmacist:

- About your medical conditions, especially if you have or have had any liver, kidney or heart disease or blood disorders (including those caused by other drugs).
- If you have a history, or family history, of bone disease or have taken antiepileptics (such as phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrignine, sodium valproate and/or carbamezepine) for a prolonged period of time.
- Of any allergies you may have, especially if you have ever shown any unusual sensitivity (rash or other signs of allergy) to oxcarbazepine or other drugs used to treat your condition. It is important to note that if you are allergic to MAZEPINE (carbamazepine), there is an approximately 1 in 4 (25%) chance that you could also have an allergic reaction to oxcarbazepine (TRILEPTAL®).
- If you are pregnant.
- If you are planning on becoming pregnant, discuss the potential benefits against any potential hazards of MAZEPINE with your doctor. This is especially important during the first three months of pregnancy. Your doctor may recommend that you take folic acid before and during your pregnancy and vitamin K during the last weeks of pregnancy.
- If you are a women taking hormonal contraceptive (birth control medicine), MAZEPINE may render this contraceptive ineffective. Therefore, you should use a different or additional non-hormonal method of contraception while you are taking MAZEPINE. This should help to prevent an unwanted pregnancy. Tell your doctor at once if you get irregular vaginal bleeding or spotting. If you have any questions about this, ask your doctor or health professional.
- If you are breast-feeding. MAZEPINE is known to pass into breast milk. You must discuss with your doctor the benefits of breastfeeding against any possible risks to the infant.
- MAZEPINE may affect male fertility or cause abnormal sperm.
- Of any other medicines (prescription and nonprescription) you are taking.
- Of your usual alcohol consumption.
- If you have increased pressure in the eye (glaucoma).
- If you have difficulty passing urine (urinary retention).
- If you were told by your physician that you suffer from mental problems, a mental disorder called psychosis that may be accompanied by confusion or agitation, or have thoughts about suicide.

If any of these apply to you, **tell your doctor**.

- If an allergic reaction happens such as fever with lymph nodes swelling, rash or skin blistering, tell your doctor immediately or go to the emergency department at your nearest hospital. (see Side effects and what to do about them)
- If you experience an increase in the number of seizures, tell your doctor immediately.
- If you experience any side effects such as drowsiness, headache, unsteadiness on the feet, double vision, dizziness, nausea or vomiting, consult your doctor.
- If, at any time, you have thoughts of harming or killing yourself. A small number of people being treated with antiepileptic drugs have reported having such thoughts or behavior. Should this happen to you, or to those in your care if you are a caregiver or guardian, talk to your doctor immediately. Close observation by a doctor is necessary in this situation. **Do not discontinue your medication on your own.**

Periodic eye examinations are recommended while taking MAZEPINE.

Do not drive a car or operate dangerous machinery until you are sure that MAZEPINE does not cause dizziness, drowsiness or affect your alertness.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any prescription, non-prescription medicines or natural health products. It is particularly important for MAZEPINE, since many other medicines interact with it.

You may need a change in your dose or, sometimes, to stop one of these other medicines.

Irregularity of the menstrual period may occur in women taking hormonal contraceptives (birth control medicines) and MAZEPINE. The hormonal contraceptive may become less effective and you should consider using other contraceptive methods.

- Avoid alcohol consumption when taking MAZEPINE.
- Do not drink grapefruit juice or eat grapefruit since this can increase the effect of MAZEPINE. Other juices, like orange juice or apple juice, do not have this effect.

PROPER USE OF THIS MEDICATION

<u>Usual dose:</u>

Dosage should be individualised. It is very important that you take MAZEPINE exactly as your doctor instructed.

- Never increase or decrease the recommended dose of MAZEPINE you are taking unless your doctor tells you to.
- If you are taking MAZEPINE, do not suddenly stop taking it without first checking with your doctor. Your doctor will tell you if and when if and when you can stop taking this

medicine.
- MAZEPINE tablets should be taken in 2 to 4 divided doses daily, with meal whenever possible.

Adults and Children Over 12 Years of Age
Initial dose 100 to 200 mg once or twice a day. Your doctor will decide the best dosage for you. Always follow your doctor's instructions.

Children 6-12 Years of Age
Initial dose 100 mg in divided doses on the first day.
Your doctor will decide the best dosage for you.
Always follow your doctor's instructions.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take your MAZEPINE as soon as possible. However, if the time is close to the next dose, do not take the missed dose and return to your regular dosing schedule. Do not double the dose to make up for the forgotten dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

MAZEPINE, can have some side effects in some people. These are often mild and occur more often early in treatment and usually wear off after a few days of treatment.

Check with your doctor as soon as possible if any of the following side effects occur, since they may need medical attention:

More common: loss of muscle coordination, allergic skin reactions, swelling of the ankles, feet or lower legs (oedema), increase in seizures (fits), blurred vision, double vision.
Less common: trembling, uncontrolled body movements.
Rare: changes in behavior, confusion, weakness, itching with redness and swelling of the eye (conjunctivitis), feeling pressure/pain in the eye (signs of increased pressure in the eye), muscle spasms, uncontrolled eye movements, itching, swollen glands, agitation or hostility (especially in the elderly), fainting, difficulty in speaking or slurred speech, depression with restlessness, nervousness or other mood or mental changes, hallucinations (see or hear things that are not there), ringing or other unexplained sounds in the ears, decreased hearing, troubled breathing, chest pain, fast or unusually slow heartbeat, numbness, tingling in hands and feet, frequent urination, sudden decrease in amount of urine, taste disturbances, unusual secretion of breast milk, breast enlargement in men, swelling and redness along a vein which is extremely tender when touched, often experienced as painful (thrombophlebitis), increased sensitivity of the skin to sun.

Usually the following side effects do not need medical attention. However, if they last for more than a few days or cause real distress, check with your doctor.

More common: vomiting, nausea, dizziness, sleepiness, unsteadiness, weight gain, headache, dry mouth.
Less common: constipation, diarrhea.
Rare: abdominal pain, aching joints or muscles, increased sweating, loss of appetite, loss of hair, excessive body and facial hair, sexual disturbances, male infertility, red and sore tongue, mouth sores, alterations in skin pigmentation, acne.

Long-term use of antiepileptics such as carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine and sodium valproate is associated with a risk of decreased bone mineral density that may lead to weakened or brittle bones.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical treatment
		Only if severe	In all cases	
Very common	*Signs of lack of white blood cells* (fever, sore throat, rash, ulcers in the mouth, swollen glands, or easily getting infections)	√		
	Suicidal thoughts or actions (thoughts, plans and actions taken for the purpose of killing or harming yourself)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical treatment**
		Only if severe	**In all cases**	
Rare	*Signs of systemic lupus erythematosus* (Red blotchy rash mainly on the face which may be accompanied by fatigue, fever, nausea, loss of appetite)	√		
Very rare	*Signs of angioedema and severe allergic reactions* (swelling of the face, eyes, or tongue, difficulty swallowing, wheezing, hives and generalized itching, rash, fever, abdominal cramps, chest discomfort or tightness, difficulty breathing, unconsciousness)			√
	Signs of serious skin reactions (skin rash, redness of the skin, blistering of the lips, eyes or mouth, skin peeling, accompanied by fever, chills, headache, cough, body aches)			√
	Signs of hepatitis (Yellowing of the white of your eyes or your skin)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical treatment**
		Only if severe	**In all cases**	
	Signs of meningitis (fever, nausea, vomiting, headache, stiff neck and extreme sensitivity to bright light.			√
	Signs of pancreatitis (severe upper abdominal pain, vomiting, loss of appetite).	√		
	Severe decreased urine output due to kidney disorders, blood in the urine	√		
	Signs of porphyria or hepatitis (darkening of urine)		√	
	Lack of all blood cells (tiredness, headache, being short of breath when exercising, dizziness, looking pale, frequent infections leading to fever, chills, sore throat or mouth ulcers; bleeding or bruising more easily than normal, nose bleeds)	√		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical treatment
		Only if severe	In all cases	
	Signs of neuroleptic malignant syndrome (muscular stiffness, high fever, altered consciousness, high blood pressure, excessive salivation)			√
	Irregular heartbeat, chest pain.	√		
	Disturbed consciousness, fainting		√	
	Symptoms that may be linked to low sodium levels in the blood (lethargy, confusion, muscular or twitching or significant worsening of convulsions)	√		

This is not a complete list of side effects. For any unexpected effects while taking MAZEPINE, contact your doctor or pharmacist.

HOW TO STORE IT

- Store at room temperature (below 30°C).
- Protect from humidity, such as in bathrooms when you shower often.
- Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345

- **Complete a Canada Vigilance Reporting Form and:**

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at: www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This document plus the full product monograph, prepared for health professionals can be found at:
http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp
or by contacting the sponsor,
Biomed 2002 Inc.
5950, Côte de Liesse, Suite100
Ville Mont-Royal
Québec H4T 1E2

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