# PRODUCT MONOGRAPH

**[Pr]pms-CARBAMAZEPINE**

(carbamazepine)

200 mg Tablets

100 mg & 200 mg Tablets (chewable)

**[Pr]pms-CARBAMAZEPINE-CR**

(carbamazepine)

200 mg & 400 mg Controlled Release Tablets

**Anticonvulsant**

**For Symptomatic Relief of Trigeminal Neuralgia**

**Antimanic**

**PHARMASCIENCE INC.**
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## THERAPEUTIC CLASSIFICATION

Anticonvulsant

For Symptomatic Relief of Trigeminal Neuralgia

Antimanic

## ACTION AND CLINICAL PHARMACOLOGY

pms-CARBAMAZEPINE (carbamazepine) tablets have 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.

Carbamazepine given as a monotherapy or in combination with lithium or neuroleptics has been found useful in the treatment of acute mania and the prophylactic treatment of bipolar (manic-depressive) disorders.

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 and chewable tablets yield peak plasma concentrations of unchanged carbamazepine within 4-24 hours. With respect to the quantity of carbamazepine absorbed, there is no clinically relevant difference between the various dosage forms. Ingestion of food has no significant influence on the rate and extent of absorption regardless of the dosage form of carbamazepine.

When carbamazepine controlled release tablets are administered repeatedly, they yield a lower average maximal concentration of carbamazepine in the plasma, without a reduction in the average minimal concentration. This tends to result in a lower incidence of intermittent concentration-dependent adverse drug reactions. It also ensures that the plasma concentrations remain largely stable throughout the day, thereby making it possible to manage with a twice-daily dosage.

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:** pms-CARBAMAZEPINE (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:** pms-CARBAMAZEPINE 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, carbamazepine has relieved glossopharyngeal neuralgia. For patients who fail to respond to pms-CARBAMAZEPINE, 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.

**C.** **Treatment Of Acute Mania And Prophylaxis In Bipolar (Manic-Depressive) Disorders:** pms-CARBAMAZEPINE may be used as a monotherapy or as an adjunct to lithium in the treatment of acute mania or prophylaxis of bipolar (manic-depressive) disorders in patients who are resistant to or are intolerant of conventional antimanic drugs. Carbamazepine may be a useful alternative to neuroleptics in such patients. Patients with severe mania, dysphoric mania or rapid cycling who are non-responsive to lithium may show a positive response when treated with carbamazepine.

It is important to note that these recommendations are based on extensive clinical experience and some clinical trials versus active comparison agents.

## CONTRAINDICATIONS

pms-CARBAMAZEPINE (carbamazepine) tablets 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.

pms-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 pms-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 pms-CARBAMAZEPINE, a potent inducer of CYP3A4, could diminish the therapeutic effect of voriconazole (see PRECAUTIONS-Drug Interactions, Effects of pms-CARABAMAZEPINE on plasma levels of concomitant agents).

pms-CARBAMAZEPINE should not be administered to patients presenting atrioventricular heart block **(see Actions And Clinical Pharmacology and Precautions).**

pms-CARBAMAZEPINE should not be administered to patients with known hypersensitivity to carbamazepine, to any of the components of the tablets, 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

**HAEMATOLOGIC: 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 pms-CARBAMAZEPINE should 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 dyscrasia. pms-CARBAMAZEPINE should be discontinued if any evidence of significant bone marrow depression appears (see PRECAUTIONS).**

**DERMATOLOGIC: Steven's-Johnson Syndrome and Toxic Epidemal Necrolysis: Serious and sometimes fatal dermatologic reactions, including Toxic Epidermal Necrolysis (TEN) and Stevens-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.**

**HLA-B*1502: 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[1]. Results of these studies suggest that the presence of the 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 pms-CARBAMAZEPINE and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B*1502 allele (see WARNINGS-Asian Ancestry and Allelic Variation in the HLA-B gene and WARNINGS-Important Limitations of HLA-B Genotyping).**

**Treatment recommendations for dermatological reactions: pms-CARBAMAZEPINE should be discontinued at the first sign of a 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 dermatological 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 pms-CARBAMAZEPINE to individual patients.**

**Asian 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 the 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 pms-CARBAMAZEPINE and other anti-epileptic drugs associated with SJS/TEN should also be avoided in patients who test positive for the HLA-B*1502 allele.**

**Important Limitations of HLA-B Genotyping**

[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.

**HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive Asian patients treated with pms-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, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.**

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

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

**Hypersensitivity**

pms-CARBAMAZEPINE may trigger hypersensitivity reactions, including multi-organ hypersensitivity reactions, which can affect the skin, liver, hematopoietic orgrans and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see section Adverse reactions).

In general, if signs and symptoms suggestive of hypersensitivity reactions occur, pms-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 to 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, pms-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 pms-CARBAMAZEPINE, or if the problem of initiating pms-CARBAMAZEPINE arises during pregnancy, the drug's potential benefits must be weighed against its hazards, particularly during the first 3 months of pregnancy. pms-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 counselled 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 also 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 Drug Interactions section under Precautions).**

**Fertility**

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

## PRECAUTIONS

### Clinical Monitoring Of Adverse Reactions

pms-CARBAMAZEPINE (carbamazepine) tablets 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 pms-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, pms-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 pms-CARBAMAZEPINE. However, treatment with pms-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. pms-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 conditions: 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

pms-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 case of exacerbation of seizures, pms-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).**

**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 alcoholics.

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 dose 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 pms-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**
pms-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 pms-CARBAMAZEPINE, in order to exclude patients with atrioventricular block.

**Driving And Operating Hazardous Machinery**
Because dizziness and drowsiness are possible side effects of pms-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 plasma carbamazepine concentrations and induce adverse reactions. Drugs that have been 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].

Coadministration of CYP3A4 inducers may increase the rate of carbamazepine metabolism leading to a potential decrease in carbamazepine serum levels and therapeutic effect. Similarly, 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 comedications 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-administration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations.

**Effects of pms-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 pms-CARBAMAZEPINE:

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

Antibiotics: doxycycline.

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

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

Antidepressants: bupropion, citalopram, nefadozone, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortryptyline, clomipramine). The use of pms-CARBAMAZEPINE is not recommended in combination with monoamine-oxidase inhibitors (MAOIs), before administering pms-CARBAMAZAPINE MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits (see **Contraindications).**

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: casponfungin, itraconazole, voriconazole (see CONTRAINDICATIONS).

Antihelmintics: praziquantel.

Antineoplastics: imatinib, irinotecan, gefitinib.

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

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, propanolol.

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

Immunosuppressants: cyclosporin, everolimus, tacrolimus.

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 result in adverse reactions (e.g., dizziness, drowsiness, ataxia, diplopia), the dosage of pms-CARBAMAZEPINE 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, telithormycin).

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 pms-CARBAMAZEPINE 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).

**Combination that requires 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 ~~i~~soniazid has been reported to increase isoniazid-induced hepatotoxicity.

pms-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 pms-CARBAMAZEPINE. Due to enzyme induction carbamazepine may cause failure to 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-depolarising 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.

pms-CARBAMAZEPINE should not be administered in conjunction with an MAO inhibitor **(see Contraindications).**

**Information to be Provided to the Patient**
**See Information for the Consumer**

## ADVERSE REACTIONS

The reactions which have been most frequently reported with carbamazepine are CNS disturbances (e.g., drowsiness, headache, unsteadiness on the feet, diplopia, dizziness), gastrointestinal disturbances (nausea, vomiting), as well as 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 carbamazepine may precipitate seizures. In epileptic patients, the changeover 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 to <1/10); uncommon:( ≥1/1000, <1/100); rare:( ≥1/10000 ,1/1000); very rare: (<1/10000):**

**Hematologic**

*Very common*: leucopenia;

*Common*: eosinophilia, thrombocytopenia;
*Rare*: leucocytosis, 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.

**Hepatic**
*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.
*Very rare*: granulomatous hepatitis, hepatic failure.

**Dermatologic**
*Very common*: dermatitis allergic and rashes, erythematous rashes, urticaria which may be severe;
*Uncommon*: exfoliative dermatitis and erythroderma;
*Rare:* systemic lupus erythematosus, puritis;
*Very rare:* Steven Johnson syndrome[4], toxic epidermal necrolysis (Lyell's syndrome), photosensitivity reaction, erythema multiform and nodosum, skin pigmentation changes, purpura, acne, diaphoresis, alopecia and neurodermatitis, hirsutism.

**Neurologic**
*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*: neuroleptic malignant syndrome.

**Cardiovascular**
*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**
*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.

**Genitourinary**
*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 and sexual disturbances/impotence spermatogenesis abnormal (with decreased sperm count and/or motility).

**Gastrointestinal**
*Very common*: nausea, vomiting;
*Common*: dryness of the mouth and throat;
*Uncommon*: diarrhea or constipation;
*Rare*: abdominal pain;
*Very rare*: glossitis, stomatitis, pancreatitis.

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

**Sense Organs**
*Very rare*: lenticular opacities, conjunctivitis, intraocular pressure increased, retinal changes, hearing disorders (e.g. tinnitus, hyperacusis, hypoacusis), taste disturbances, change in pitch perception.
**Endocrine System And Metabolism**
*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 and 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 System**
*Very rare*: arthralgia, muscle pain, muscle spasms.

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

**Hypersensitivity Reactions**
*Rare*: delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepatosplenomegaly and abnormal liver function tests, 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 eosinophilia, anaphylactic reaction, angioneurotic edema.
**Investigations**
*Very rare*: hypogammaglobulinaemia.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Lowest known lethal dose: estimated 3.2 g (24 year old woman).
Highest known doses 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, disorientation, tremor, restlessness, somnolence, agitation, hallucination, coma, blurred vision, nystagmus, mydriasis, slurred speech, dysarthria, ataxia, dyskinesia, abnormal reflexes (slowed/hyperactive), convulsions, psychomotor disturbances, myoclonus, opisthotonia, hypothermia/ hyperthermia, flushed skin/cyanosis, EEG changes.

Respiratory System: respiratory depression, pulmonary edema.
Cardiovascular System: tachycardia, hypotension/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 creatinine phosphokinase.

**Treatment Of Overdosage**
For management of a suspected drug overdose contact your regional Poison Control Centre.

There is no known specific antidote to pms-CARBAMAZEPINE (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 the 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 the symptomatology on the 2nd or 3rd day after overdose, due to delayed absorption, should be anticipated.

## DOSAGE AND ADMINISTRATION

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

pms-CARBAMAZEPINE Tablets and Chewtabs should be taken in 2 to 4 divided doses daily.

pms-CARBAMAZEPINE Chewtabs are particularly suitable for patients who have difficulty swallowing tablets or who need initial careful adjustment of dosage.

The controlled release characteristics of pms-CARBAMAZEPINE-CR reduce the daily fluctuations of plasma carbamazepine. pms-CARBAMAZEPINE-CR tablets (either whole or, if so prescribed, only half a tablet) should be swallowed unchewed with a little liquid during or after a meal. These controlled release tablets are designed to be taken in a twice-daily dosage. If necessary, three divided doses may be prescribed. Some patients have been reported to require a dosage increase when switching from tablets to CR tablets. Dosage adjustments should be individualized based on clinical response and, if necessary, plasma carbamazepine levels.

**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 Drug Interactions section under Precautions and Pregnancy And Nursing section under Warnings).**

**Use In Trigeminal Neuralgia**
The initial daily dosage should be small; 200 mg taken in 2 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 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 minimal effective dosage is reached. Because trigeminal neuralgia is

characterized by periods of remission, attempts should be made to reduce or discontinue the use of pms-CARBAMAZEPINE 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.

**Use In Mania And Bipolar (Manic-Depressive) Disorders**

The initial daily dosage should be low, 200 to 400 mg/day, administered in divided doses, although higher starting doses of 400 to 600 mg/day may be used in acute mania. This dose may be gradually increased until patient symptomatology is controlled or a total daily dose of 1600 mg is achieved. Increments in dosage should be adjusted to provide optimal patient tolerability. The usual dose range is 400 to 1200 mg/day administered in divided doses. Doses used to achieve optimal acute responses and tolerability should be continued during maintenance treatment. When given in combination with lithium and neuroleptics, the initial dosage should be low, 100 mg to 200 mg daily, and then increased gradually. A dose higher than 800 mg/day is rarely required when given in combination with neuroleptics and lithium, or with other psychotropic drugs such as benzodiazepines. Plasma levels are probably not helpful for guiding therapy in bipolar disorders.

## PHARMACEUTICAL INFORMATION

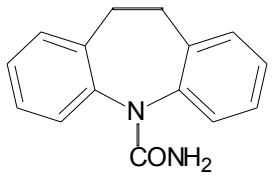
### Drug Substance

Proper Name: Carbamazepine

Chemical Name: 5-Carbamoyl-5H-dibenz(b,f)azepine

Molecular Formula: $C_{15}H_{I2}N_2O$

Structural Formula:




Molecular Weight: 236.27

Description: White to off-white powder

Solubility: Practically insoluble in water and in acetone

### Stability and Storage Recommendations

See Following Table.

Keep out of reach of children.

### Availability Of Dosage Forms

See Following Table.

| | pms-CARBAMAZEPINE Tablets 200mg | pms-CARBAMAZEPINE Tablets (Chewable) 100mg | pms-CARBAMAZEPINE Tablets (Chewable) 200mg | pms-CARBAMAZEPINE-CR Tablets (Controlled Release) 200mg | pms-CARBAMAZEPINE-CR Tablets (Controlled Release) 400mg |
|---|---|---|---|---|---|
| Colour | White | White with red specks | White with red specks | Beige-orange | Brown-orange |
| Shape | Round, flat-faced and bevel-edged | Round, flat-faced, bevel-edged | Oval, biconvex | Oval, slightly biconvex | Oval, slightly biconvex |
| Medicinal Content | 200 mg carbamazepine | 100 mg carbamazepine | 200 mg carbamazepine | 200 mg carbamazepine | 400 mg carbamazepine |
| Non-medicinal Ingredients | cellulose compounds, magnesium stearate, silicon dioxide | cherry-mint flavour, corn starch, erythrosine, gelatin, glycerin, magnesium stearate, silicon dioxide, sodium starch glycolate, stearic acid, sugar | | acrylic esters, cellulose compounds, iron oxides, magnesium stearate, silicon dioxide, talc, titanium dioxide, castor oil derivative | |
| Availability | Bottles of 100 & 500 | Bottles of 100 | Bottles of 100 | Bottles of 100 | Bottles of 100 |
| Storage Conditions | Store below 30°C, protect from humidity | Store below 30°C, protect from humidity and light | Store below 30°C, protect from humidity and light | Store below 25°C, protect from humidity | Store below 25°C, protect from humidity |

## INFORMATION FOR THE CONSUMER

Please read this information carefully before you start to take your medicine, even if you have taken this drug before. Do not throw away this leaflet until you have finished your medicine as you may need to read it again. For further information or advice, please ask your doctor or pharmacist.

### What is $^{Pr}$pms-CARBAMAZEPINE

- pms-CARBAMAZEPINE (carbamazepine) belongs to the family of medicines called anticonvulsants for treating epilepsy. pms-CARBAMAZEPINE is also used for treating the pain of trigeminal neuralgia and for treating mania.
- pms-CARBAMAZEPINE has been prescribed for you by your doctor to reduce your number of seizures; to relieve the pain of trigeminal neuralgia; or to treat your acute mania or bipolar disorder.

### Important Points you must tell your doctor before taking pms-CARBAMAZEPINE

**Tell your doctor:**

- Tell about your medical conditions, especially if you have any liver or kidney disease, heart disease or blood disorders.
- Inform your doctor 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.
- If you are Asian origin. Studies have shown that certain individuals of Asian origin may be at an increased risk of developing serious skin reactions during treatment with carbamazepine (see Preacutions When Taking pms-CARBAMAZEPINE).
- If you are pregnant or thinking about becoming pregnant.
- If you are breast-feeding.
- If you have or have ever been diagnosed with mental problems, or have thought about suicide.
- Any other medicines (prescription and nonprescription) you are taking.
- Inform your doctor of your usual alcohol consumption.

### How to take pms-CARBAMAZEPINE

- It is very important that you take pms-CARBAMAZEPINE exactly as your doctor instructed.
- Never increase or decrease the recommended amount of pms-CARBAMAZEPINE you are taking unless your doctor tells you to.
- If you are taking pms-CARBAMAZEPINE, **do not suddenly stop taking it** without first checking with your doctor. Your doctor will tell you if and when you can stop taking this medicine (**see Precautions when taking pms-CARBAMAZEPINE).**
- If you miss a dose, take your pms-CARBAMAZEPINE 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.
- If you have accidentally taken too many tablets, **talk to your doctor straight away.** You may require medical attention.
- pms-CARBAMAZEPINE Tablets and Chewtabs should be taken in 2-4 divided doses daily, with meals whenever possible. pms-CARBAMAZEPINE CR tablets should be swallowed unchewed with a little liquid during or after a meal.

**When not to use pms-CARBAMAZEPINE**
You should not use pms-CARMABAZEPINE if:

- You are allergic (hypersensitive) to carbamazepine or to any of the other ingredients of pms-CARBAMAZEPINE (See list of components at the end of this leaflet).
- you have severe heart disease
- you have had serious blood illnesses in the past
- you have a disturbance in the production of porphyrin, a pigment important for liver function and blood formation (also called hepatic porphyria);
- you are also taking drugs belonging to a special group of antidepressants called monoamine-oxidase inhibitors (MAOIs) .
- You are also taking the drug voriconazole (VFEND) for treatment of an infection.

If this applies to you, **tell your doctor before taking pms-CARBAMAZEPINE.** If you think you may be allergic, ask your doctor for advice.

**Precautions when taking pms-CARBAMAZEPINE**

- If you have blood illnesses (including those caused by other drugs).
- If you have ever shown unusual sensitivity (rash or any other signs of allergy) to oxcarbazepine or to any other medicines, especially other medicines used to treat your condition. It is important to note that if you are allergic to carbamazepine, there is an approximately 1 in 4 (25%) chance that you could also have an allergic reaction to oxcarbazepine (Trileptal®).
- If you have or have had heart, liver or kidney disease in the past.
- If you have increased pressure in the eye (glaucoma).
- If you were told by your physician that you suffer from a mental disorder called psychosis, that may be accompanied by confusion or agitation.
- Do not drive a car or operate dangerous machinery until you are sure that pms-CARBAMAZEPINE does not affect your alertness.
- If you are a women taking hormonal contraceptive (birth control medicine), pms-CARBAMAZEPINE may render this contraceptive ineffective. Therefore, you should use a different or additional non-hormonal method of contraception while you are taking pms-CARBAMAZEPINE. 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.
- Avoid alcoholic drinks when taking pms-CARBAMAZEPINE.
- Do not drink grapefruit juice or eat grapefruit since this can increase the effect of pms-CARBAMAZEPINE. Other juices, like orange juice or apple juice, do not have this effect.

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 **Possible side effects).**
- If you develop serious skin reactions such as rash, red skin, blistering of the lips, eyes or mouth, skin peeling and accompanied by fever, tell your doctor immediately. These reactions may be more frequent in patients of Asian origin. Reports of these reactions have been highest in patients from Taiwan, Malaysia and the Philippines.

- If you experience an increase in the number of seizures, tell your doctor immediately.
- If you notice symptoms suggestive of hepatitis, such as jaundice (yellowing of skin and eyes), 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.

Do not stop your treatment with pms-CARBAMAZEPINE without first checking with your doctor. To prevent sudden worsening of your seizure, do not discontinue your medicine abruptly.

**What to do in case of overdose**

- Contact your doctor or nearest hospital emergency ward, even though you may not feel sick.
- For management of a suspected drug overdose contact your regional Poison Control Centre.

**How to store pms-CARBAMAZEPINE**

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

**What does pms-CARBAMAZEPINE contain**

pms-CARBAMAZEPINE 200 mg Tablets: cellulose compounds, magnesium stearate, silicon dioxide.
pms-CARBAMAZEPINE 100 mg and 200 mg CHEWTABS: cherry-mint flavour, corn starch, erythrosine, gelatin, glycerin, magnesium stearate, silicon dioxide, sodium starch glycolate, stearic acid, sugar.
pms-CARBAMAZEPINE-CR 200 and 400 mg: acrylic esters, cellulose compounds, iron oxides, magnesium stearate, silicon dioxide, talc, titanium dioxide, castor oil derivative.

**Possible side effects**

pms-CARBAMAZEPINE, 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.

**Some effects could be serious:**
**Check with your doctor immediately or make sure that someone else can do this for you if any of the following (less common or rare) side effects occur. They may be early signs of serious damage to your blood, liver, kidneys or other organs and may urgently need medical treatment.**

- If you have fever, sore throat, rash, ulcers in the mouth, swollen glands or more easily getting infections (signs of lack of white blood cells).
- If you have 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 (lack of all blood cells).
- If you have red blotchy rash mainly on the face which may be accompanied by fatigue, fever, nausea, loss of appetite (signs of systemic lupus erythematosus).
- If you have any yellowing of the white of your eyes or your skin (signs of hepatitis).
- If you have darkening of urine (signs of porphyria or hepatitis)

- If you have severe decreased urine output due to kidney disorders, blood in the urine.
- If you have severe upper abdominal pain, vomiting, loss of appetite (signs of pancreatitis).
- If you have 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 serious skin reactions)
- If you have 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 angioedema and severe allergic reactions).
- If you have lethargy, confusion, muscular twitching or significant worsening of convulsions (symptoms that may be linked to low sodium levels in the blood).
- If you have fever, nausea, vomiting, headache, stiff neck and extreme sensitivity to bright light (signs of meningitis).
- If you have muscular stiffness, high fever, altered consciousness, high blood pressure, excessive salivation (signs of neuroleptic malignant syndrome)
- If you have irregular heartbeat, chest pain.
- If you have disturbed consciousness, fainting.

If you experience any of these, **tell your doctor straight away**.

**Other side effects:**
**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 (conjunctivis), 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, 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, softening or thinning or weakening of bones causing an increased risk of broken bones (lack of vitamin D, osteoporosis).

**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.
If any of these affects you severely, **tell your doctor.**
If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:
By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca
By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and
Effectiveness Information Division
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A OK9

*NOTE: Before contacting Canada Vigilance, you should contact your physician or pharmacist.*

**Who manufactures pms-CARBAMAZEPINE**

pms-CARBAMAZEPINE tablets and chewtabs and pms-CARBAMAZEPINE-CR are distributed by:
Pharmascience Inc.
6111 Royalmount Avenue, Suite 100
Montréal, Québec
H4P 2T4

**REMINDER:** This medicine has been prescribed only for you. Do not give it to anybody else!

**IF YOU REQUIRE ANY FURTHER INFORMATION OR ADVICE, PLEASE CONSULT YOUR DOCTOR OR PHARMACIST.**

## 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 doses. 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 antiemetic activity. Carbamazepine did not inhibit monoamine oxidase in the guinea pig liver at the drug concentration of $1 \times 10^{-3}$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 linguomandibular 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 tissue. 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, 3850-4025 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 laboured 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. ln 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 a 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 2 years in the diet at doses of 25, 75 and 250 mg/kg/day, 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 findings relative to the use of carbamazepine in humans is, at present, 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 reproductive 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 ventricles) 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.

## BIBLIOGRAPHY

Product Monograph for PrTegretol®, Novartis Pharmaceuticals Canada Inc., Date of Revision: June 5, 2008 control No. 120328.

**Clinical References - Epilepsy**

AMA DRUG EVALUATIONS: Anticonvulsants.
American Medical Assoc Chicago, Illinois 1983; 295-328

BEERMAN B, et al.
Advanced heart block aggravated by carbamazepine. Br Heart J 1975; 37: 688-691

BESSER R, et al.
Slow-Release Carbamazepine in the Treatment of Epilepsy. 2. A comparison of the 24-hour plasma levels in response to two different formulations. Akt Neurol 1985; 12: 75-77 (Translation)

BERTILSSON L.
Clinical pharmacokinetics of carbamazepine. Clin Pharmacokinet 1978; 3: 128-143

BLOMBERG J-H, et al.
Treatment of epilepsy with Tegretol. Lakartidningen 1970; 67(38): 4305-4311 (Translation)

FAIGLE JW, and FELDMANN KF.
Carbamazepine: Biotransformation.
IN: Woodbury DM et al (eds): Antiepileptic Drugs, (Raven Press, New York 1982): 2nd (ed): 483-495

GERARDIN A, et al.
HENRIKSEN O, et al. How to use Carbamazepine. In: Antiepileptic Drug Therapy in Pediatrics. Ed Morselli PL, et al. (Raven Press NY) 1983; 237-243

HÖPPENER RJ, et al.
Correlation between daily fluctuations of carbamazepine serum levels and intermittent side effects.
Epilepsia 1980; 21: 341-350

HOUBEN PFM, et al.
Anticonvulsant drugs and folic acid in young mentally retarded epileptic patients.
Epilepsia 1971; 12 (3): 235-247

HUNTER J, et al.
Altered calcium metabolism in epileptic children on anticonvulsants. Br Med J 1971; 4: 202-204

HVIDBERG EF, and DAM M.
Clinical pharmacokinetics of anticonvulsants. Clin Pharmacokinet 1976; 1: 161-188

JANZ D, and SCHMIDT D. Anti-epileptic drugs and failure of oral contraceptives. Lancet 1974; 1:1113

KRÄMER G, et al.
Slow-Release Carbamazepine in the Treatment of Epilepsy. 1. Comparisons of the 24-hour plasma levels during treatment with conventional and slow-release carbamazepine formulations. Akt Neurol 1985; 12: 70-74 (Translation)

KRÄMER G, et al.
Slow-Release Carbamazepine: Kinetic and Therapeutic Aspects. Psycho 1985; 11: 441-442 (Translation)

KRÜGER HJ. Carbamazepine in the Treatment of Epilepsy – Follow-up studies over a period of 9 years.
Med Welt 1972; 23 (24): 896 (Translation)

LAENGNER H, and DETERING K. Anti-epileptic drugs and failure of oral contraceptives. Lancet 1974; 2: 600

LEVY RH, et al. Pharmacokinetics of Carbamazepine in normal man. Clin Pharmacol Ther 1975; 17: 657-668

LIVINGSTON SI. Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence. Charles C. Thomas, Publisher, 1972

MATTSON RH, et al. Comparison of carbamazepine, phenobarbital, phenytoin and primidone in partial and secondarily generalized tonic-clonic seizures. N Engl J Med 1985; 313 (3): 145-151

MIKATI MA, and BROWNE TR.
Comparative efficacy of antiepileptic drugs. Clin Neuropharmacol (USA) 1988; 11 (2): 130-140

MIVILLE J. Le Tégrétol dans l'épilepsie. Vie Médi Can Fr 1972; 1: 1080-1083

MORSELLI PL, et al. Pharmacokinetic studies with carbamazepine in epileptic patients. IN: Birkmayer W. (ed.) "Epileptic seizures-behavior-pain", H. Huber Publisher Bern/Stuttgart/Vienna 1975; 141-150

MORSELLI PL, and FRIGERIO A. Metabolism and pharmacokinetics of carbamazepine. Drug Metab Rev 1975; 4 (1): 93-113

MORSELLI PL, et al. Bioavailability of two carbamazepine preparations during chronic administration to epileptic patients. Epilepsia (USA) 1975; 16: 759-764
MORSELLI PL, and FRANCO-MORSELLI R. Clinical pharmacokinetics of antiepileptic drugs in adults. Pharmacol Ther 1980; 10: 65-101

NAMOLI A.Prolonged Treatment with Carbamazepine (TEGRETOL) of the Convulsions and Mental Abnormalities of Epilepsy. Riv Neurol 1972; XLII fasc. 1 (Translation)

RAMSAY RE, et al. A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. N Engl J Med 1983; 33: 904-910

RODIN EA, et al. The effects of carbamazepine on Patients with Psychomotor Epilepsy: Results of a double blind study. Epilepsia 1974; 15: 547-561

SILLANPÄÄ M. Carbamazepine. Pharmacology and Clinical Uses. Acta Neurol Scand 1981; 64: (Suppl. 88): 1-202

SINGH A, and SAZENA B. Carbamazepine and Diphenylhydantoin in the Treatment of Grand Mal Epilepsy - A Comparative Clinical Trial. Sixth International Symposium on Epilepsy, Brussels, Belgium 1974

TOMSON T. Interdosage fluctuations in plasma carbamazepine concentration determine intermittent side effects.
Arch Neurol 1984; 41: 830-834

TROUPIN AS, et al. Carbamazepine as an anticonvulsant: A Pilot Study.Neurology 1974; 24: 863-869

WADA JA, et al. Pharmacokinetic comparison of tablet and suspension dosage forms of carbamazepine.
Epilepsia 1978; 19(3): 251-255

WULFSOHN M. Carbamazepine (Tegretol) in the Long-Term Treatment of Grand Mal Epilepsy. South Afr Med J 1972; 46: 1091

TEGRETOL in Epilepsy: Report of an international clinical symposium held at the Royal Garden Hotel, London 1972; CAS Wink (ed). Manchester, C. Nicholls & Co. Ltd., 1972; 140

**Clinical References - Trigeminal Neuralgia**

ARIEFF AJ, et al. Tegretol in trigeminal neuralgia. Pilot study. Trans Am Neurol Assoc 1966; 91: 186

CARNAILLE H, et al. Etude statistique de près de 700 cas de facialgies traitées par le Tégrétol. Acta Neurol Belg 1966; 66: 175-196

GRAHAM JG, et al. Treatment of trigeminal neuralgia with carbamazepine, a follow-up study. Br Med J 1966; 1: 210-211

HEATHFIELD KWG, et al. Treatment of trigeminal neuralgia with Tegretol. Br Med J 1966; 1: 481

KILLIAN JM. Tegretol in trigeminal neuralgia with special reference to hematopoietic side effects. Headache 1969; 9: 58-63

LLOYD-SMlTH DL, et al. A long-term low-dosage study of carbamazepine in trigeminal neuralgia Headache 1969; 9: 64-72

MAROTTA JT. A long-term study in trigeminal neuralgia. Headache 1969; 9: 83

MURPHY JP. Tegretol (carbamazepine): A new and effective medical treatment of trigeminal neuralgia, with a note concerning its use in the syndrome of thalamic hyperpathia.
Med Ann DC 1966; 35: 658

NICOL CF. A four year double blind study of Tegretol in Facial Pain. Headache 1969; 9: 54-57

RASKIND B. Trigeminal neuralgia. Definitive treatment of 46 patients. Int Surg 1966; 46: 5-11

RASMUSSEN P, et al. Tegretol in the treatment of trigeminal neuralgia. A controlled study of 48 patients
Proc. III Int. Cong. Neurol. Surg., Copenhagen, 1965, Excerpta Med. Int. Cong., 1965; 110 (761): 93 (224)

SACHDEV KK, and LLOYD-SMITH DL. The use and limitations of carbamazepine in trigeminal neuralgia.
Can Med Assoc J 1967; 97: 235

**Clinical References - Mania**

BALLENGER JC, and POST RM. Carbamazepine in manic-depressive illness: A new treatment. Am J Psychiatry 1980; 137: 782-790

BROWN A , et al. Carbamazepine compared to haloperidol in acute mania. Int Clin Psychopharmacol 1989; 4: 229-238

CHOU JC-Y. Recent advances in treatment of acute mania. J Clin Psychopharmacol 1991; 11: 3-21

GROSSI E, et al. Carbamazepine vs chlorpromazine in mania: A double-blind trial. IN: Emrich HM, Okuma T. and Müller A.A. (eds). Anticonvulsants in affective disorders. Excerpta medica Amsterdam 1984; 177-187
KLEIN E, et al. Carbamazepine and haloperidol v placebo and haloperidol in excited psychoses. Arch Gen Psychiatry 1984; 41: 165-170

KRAMLINGER KG, and POST RM. Adding lithium carbonate to carbamazepine: antimanic efficacy in treatment-resistant mania. Acta Psychiatr Scant 1989; 79: 378-385

LENZI A, et al. Use of Carbamazepine in acute psychosis: A controlled study. J Int Med Res 1986; 14: 78-84

LERER B, et al. Carbamazepine versus lithium in mania: A double-blind study. J Clin Psychiatry 1987; 48 (3): 89-93

LUSZNAT RM, et al. Carbamazepine vs lithium in the treatment and prophylaxis of mania. Br J Psychiatry 1988; 153: 198-204

MÖLLER HJ, et al. Double-blind evaluation of the antimanic properties of carbamazepine as comedication to haloperidol. Prog Neuropsychopharmacol Biol Psychiatry 1989; 13: 127-136

OKUMA T, et al. Comparison of the antimanic efficacy of carbamazepine and chlorpromazine: A double-blind controlled study. Psychopharmacology 1979; 66: 211-217

PLACIDI GF, et al. The comparative efficacy and safety of carbamazepine versus lithium: A randomised, double blind 3-year trial in 83 patients. J Clin Psychiatry 1986; 47: 490-494

POST RM, et al. Correlates of antimanic response to carbamazepine. Psychiatry Res 1987; 21: 71-83

POST RM. Non-lithium treatment for bipolar disorder. J Clin Psychiatry 1990; 51 (8) (Suppl 9-16)

STOLL KD, et al. Carbamazepine vs haloperidol in manic syndromes. IN: Shagass C (ed). Biological Psychiatry 1985. Elsevier Science, Amsterdam, 1986; 332-334

**Other References**

CHUNG WH et al.
Medical Genetics: a Marker for Stevens-Johnson Syndrome Nature 2004; 428 (6982): 486

HUNG SI et al.
Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenetics and Genomics 2006; 16 (4): 297-306

LONJOU C et al.
A marker for Stevens-Johnson syndrome...: ethnicity matters. The Pharmacogenomics Journal 2006; 6 (4): 265-268

MAN CB et al.
Association between HLA-B* 1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese.
Epilepsia 2007; 48 (5): 1015-1018.