PRODUCT MONOGRAPH

[Pr] APO-CARBAMAZEPINE

Carbamazepine Tablets USP

200 mg

[Pr] APO-CARBAMAZEPINE CR

Carbamazepine Controlled Release Tablets

Apotex Standard

200 mg and 400 mg

Anticonvulsant

For Symptomatic Relief of Trigeminal Neuralgia

Antimanic

APOTEX INC.
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THERAPEUTIC CLASSIFICATION

Anticonvulsant

For Symptomatic Relief of Trigeminal Neuralgia

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ACTIONS AND CLINICAL PHARMACOLOGY

APO-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.

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 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 APO-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.

Comparative Bioavailability

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 14 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of carbamazepine was measured and compared following a single oral dose (1 x 400 mg tablet) of Apo-Carbamazepine CR (carbamazepine) 400 mg tablet (Apotex Inc.) and Tegretol®CR (carbamazepine) 400 mg tablet (Novartis Pharmaceuticals Canada Inc.).

Fasting Study: Summary Table of the Comparative Bioavailability Data

Carbamazepine (A single 400 mg dose: 1 x 400 mg) From Measured Data/Fasting Conditions Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	Test[¥]	Reference[†]	Ratio of Geometric Means (%)[#]	90%Confidence Interval [#]
AUC0-72 (ng•h/mL)	132451.39 132940.56 (12.1)	143106.26 143495.88 (18.9)	92.6	84.14 – 101.81
Cmax (ng/mL)	2406.00 2418.77 (15.8)	2663.16 2660.30 (18.0)	90.3	82.20 – 99.29
Tmax[§] (h)	21.00 (31.9)	21.43 (33.4)		

¥ Apo-Carbamazepine CR (carbamazepine) 400 mg tablets (Apotex Inc.)

[†]Tegretol® CR (carbamazepine) 400 mg tablets (Novartis Pharmaceuticals Canada Inc.) was purchased in Canada.

[#] Based on Least Square Estimate

[§] Expressed as mean (CV%) only.

[€] Arithmetic Mean (CV%)

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fed conditions, was performed on healthy male volunteers. The results obtained from 15 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of carbamazepine was measured and compared following a single oral dose (1 x 400 mg tablet) of Apo-Carbamazepine CR (carbamazepine) 400 mg tablet (Apotex Inc.) and Tegretol®CR (carbamazepine) 400 mg tablet (Novartis Pharmaceuticals Canada Inc.).

Fed Study: Summary Table of the Comparative Bioavailability Data

Carbamazepine (A single 400 mg dose: 1 x 400 mg) From Measured Data/Fed Conditions Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	Test[¥]	Reference[†]	Ratio of Geometric Means (%)[#]	90%Confidence Interval [#]
AUC0-72 (ng•h/mL)	205817.32 208130.97 (14.9)	212600.62 215408.85 (15.2)	96.8	92.30 – 101.54
Cmax (ng/mL)	4024.87 4068.82 (14.2)	3897.31 3947.58 (15.0)	103.3	99.13 – 107.59
Tmax[§] (h)	11.87 (32.8)	16.67 (41.2)		

¥ Apo-Carbamazepine CR (carbamazepine) 400 mg tablets (Apotex Inc.)

[†]Tegretol® CR (carbamazepine) 400 mg tablets (Novartis Pharmaceuticals Canada Inc.) was purchased in Canada.

[#] Based on Least Square Estimate

[§] Expressed as mean (CV%) only.

[€] Arithmetic Mean (CV%)

INDICATIONS AND CLINICAL USE

Epilepsy: APO-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.

Trigeminal Neuralgia: APO-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 APO-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.

Treatment of Acute Mania and Prophylaxis in Bipolar (Manic-Depressive) Disorders: APO-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

APO-CARBAMAZEPINE (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.

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

APO-CARBAMAZEPINE should not be administered to patients presenting atrioventricular heart block (see **ACTIONS AND CLINICAL PHARMACOLOGY and PRECAUTIONS**).

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

HEMATOLOGIC: Although reported infrequently, serious adverse effects have been observed during the use of APO-CARBAMAZEPINE (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 APO-CARBAMAZEPINE (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. APO-CARBAMAZEPINE should be discontinued if any evidence of significant bone marrow depression appears (see PRECAUTIONS).

DERMATOLOGIC: <u>Stevens-Johnson Syndrome and Toxic Epidemal Necrolysis</u>: 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.

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 the HLA-B*1502 allele. The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia[†]. It is therefore, recommended that physicians 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 APO-CARBAMAZEPINE and other anti-epileptic drugs associated with SJS/TEN should be avoided in patients who test positive for the 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

[†]The following provide a rough estimate of the frequency of HLA-B* 1502 allele in various populations: from 2 to 12% in Han Chinese populations, about 8% in Thai populations, and above 15% in the Philippines and some Malaysian populations. Allele frequencies up to about 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in persons from European descent, several African populations, indigenous peoples of the Americas, Hispanic populations sampled and in Japanese (< 1%). The estimated frequencies have limitations due to the wide variation in allele frequencies that exist within ethnic groups, the difficulties in ascertaining ethnic ancestry and the likelihood of mixed ancestry.

WARNINGS - Important Limitations of HLA-A and HLA-B Genotyping).

<u>Treatment recommendations for dermatological reactions</u>: APO-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 APO-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 APO-CARBAMAZEPINE to individual patients.

Pharmacogenomics

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 and its frequency is about 2 to 5% in European populations and about 10% in the Japanese population. The frequency of this allele is estimated to be less than 5% in the majority of 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 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 APO-CARBAMAZEPINE (see WARNINGS - Important Limitations of HLA-A and HLA-B Genotyping). The use of APO-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 APO-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 carbamazepine-treated patients of Han Chinese and Thai origin, 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 APO-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-A and HLA-B Genotyping

HLA-A*3101 and HLA-B*1502 genotyping as screening tools have important limitations and must never substitute for appropriate clinical vigilance and patient management. Many patients positive for HLA-A*3101 and treated with APO-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 APO-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 antiepileptic 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 APO-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 APO-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, APO-CARBAMAZEPINE should be withdrawn at once.

Hypersensitivity

APO-CARBAMAZEPINE can trigger hypersensitivity reactions, including DRESS, a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance r of the intrahepatic bile ducts), that may occur in various combinations. One or more organs such as skin, liver, lungs, kidneys, pancreas, myocardium, bone marrow, spleen, thymus, lymph nodes and colon may be affected (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, APO-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, APO-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. The risk of malformations following exposure to carbamazepine as polytherapy may vary depending on the specific drugs used and may be higher in polytherapy combinations that include valproate.

There is evidence to suggest that the risk of malformation with carbamazepine may be dose-dependent *i.e.* at a dose <400 mg per day, the rates of malformation were lower than with higher doses of carbamazepine. The plasma concentration should be monitored and maintained in the lower end of the therapeutic range (4 to 10 μg/mL) provided seizure control is maintained.

If pregnancy occurs in a woman receiving APO-CARBAMAZEPINE, or if the problem of initiating APO-CARBAMAZEPINE arises during pregnancy, the drug's expected benefits must be weighed against its hazards, particularly during the first 3 months of pregnancy. APO-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.

Monitoring and prevention

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.

In the neonate

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.

Cholestatic hepatitis in neonates exposed to carbamazepine in the antenatal period has been reported. Infants of mothers treated with carbamazepine should be carefully observed for adverse hepatobiliary effects. A few cases of neonatal seizures and respiratory depression have been associated with maternal carbamazepine tablets and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhea, and/or decreased feeding have also been associated with maternal carbamazepine tablets use. These reactions may represent a neonatal withdrawal syndrome.

Women of child-bearing potential and contraceptive measures

Due to enzyme induction carbamazepine may result in a failure of the therapeutic effect of oral contraceptive drugs containing estrogen and/or progesterone. Women of child bearing potential should be advised to use alternative contraceptive methods while on treatment with carbamazepine.

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

Breast-feeding

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 but there have been some reports of cholestatic hepatitis in neonates exposed to carbamazepine during breast feeding. The benefits of breast feeding should be weighed against the possible risks to the infant and a decision should be made whether to discontinue nursing or to discontinue APO-CARBAMAZEPINE**, taking into account the importance of the drug to the mother. Therefore breast-fed infants of mothers treated with carbamazepine should be carefully observed for adverse reactions such as somnolence, allergic skin reactions and adverse hepatobiliary effects.**

Fertility

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

PRECAUTIONS

Clinical Monitoring of Adverse Reactions

APO-CARBAMAZEPINE (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 APO-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, APO-CARBAMAZEPINE should be immediately discontinued until the case is carefully reassessed.

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 APO-CARBAMAZEPINE. However, treatment with APO-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.

Hepatic function

Baseline and periodic evaluations of hepatic function must be performed, particularly in elderly patients and patients with a history of liver disease. APO-CARBAMAZEPINE should be withdrawn immediately in cases of aggravated liver dysfunction or active liver disease.

Renal function

Pre-treatment and periodic complete urinalysis and BUN determinations should be performed.

Ophthalmic examinations

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

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 **Precautions - Drug Interactions**).

Hyponatremia

Hyponatremia is known to occur with carbamazepine. Although hyponatraemia occurs in 10 to 15% of patients taking carbamazepine, it is seldom symptomatic or severe enough to cause fluid retention. In patients with pre-existing renal conditions associated with low sodium or in patients

treated concomitantly with sodium-lowering medicinal products (*e.g.* diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to the elderly and renally-compromised patients. If hyponatraemia is observed, water restriction is an important counter-measurement if clinically indicated.

Hypothyroidism

Carbamazepine can reduce serum concentrations of thyroid hormones through enzyme induction requiring an increase in dose of thyroid replacement therapy in patients with hypothyroidism. In order to adjust the dosage of thyroid replacement therapy, evaluation of thyroid hormone status should be considered for patients treated with carbamazepine, particularly for pediatric patients, due to the potential risk of hypothyroidism and long-term adverse effects on development that can occur in relation to undetected changes in thyroid hormone status.

Increased Seizure Frequency

APO-CARBAMAZEPINE should be used with caution in patients with mixed seizures which includes absences, either typical or atypical. In all these conditions, APO-CARBAMAZEPINE may exacerbate seizures. In the event of exacerbation of seizures, APO-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**).

Anticholinergic effects

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 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.

Suicidalideation and behaviour

Suicidal ideation and behaviour 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 behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour 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 behaviour 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 behaviour 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 behaviour 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 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 APO-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

APO-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 APO-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 using Hazardous Machines

Patients' ability to react may be impaired by their medical condition resulting in seizures and adverse reactions reported with carbamazepine, including dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision. Patients should be advised not to drive or use complex machines, or engage in other hazardous activities, until they have gained sufficient experience on carbamazepine to gauge whether it affects their mental and/or motor performance adversely.

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 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.[§]

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

Coadministration of CYP3A4 inducers may increase the rate of APO-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[†], 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. Coadministration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations.

Effects of APO-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 APO-CARBAMAZEPINE:

Analgesics, anti-inflammatory agents: buprenorphine, methadone, paracetamol (long term administration of carbamazepine and paracetamol (acetaminophen) may be associated with hepatotoxicity), phenazone (antipyrine), tramadol.

Antibiotics: doxycycline, rifabutin.

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

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

Antidepressants: bupropion, citalopram, mianserin, nefadozone, sertraline, trazodone**,** tricyclic antidepressants (e.g. imipramine, amitriptyline, nortryptyline, clomipramine).

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. Phenytoin has also been shown to decrease carbamazepine plasma levels. To avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine, it is recommended to monitor the plasma concentration of both drugs during titration and adjust dosage accordingly. Mephenytoin plasma levels have been reported in rare instances to increase.

Antifungals: caspofungin, itraconazole, voriconazole (see CONTRAINDICATIONS). APO-CARBAMAZEPINE should not be used in combination with voriconazole or itraconazole.
Antihelmintics: praziquantel, albendazole.
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.
Bronchodilators or anti-asthma drugs: theophylline.
Contraceptives: hormonal contraceptives.
Cardiovascular drugs: calcium channel blockers (dihydropyridine group), e.g. felodipine, digoxin, disopyramide, quinidine, propranolol, simvastatin, atorvastatin, lovastatin, ivabradine.
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 result in adverse reactions (e.g., dizziness, drowsiness, ataxia, diplopia), the dosage of APO-

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, telithromycin), ciprofloxacine.

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

Antiepileptics: stiripentol, vigabatrin.

Antifungals: azoles (itraconazole, ketoconazole, fluconazole, voriconazole). APO-CARBAMAZEPINE should not be used in combination with voriconazole or itraconazole.

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. 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 APO-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, phenobarbital, phensuximide, phenytoin (to avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine, it is recommended to monitor

the plasma concentration of both drugs during titration (see also *Effects of APO-CARBAMAZEPINE on Plasma Levels of Concomitant Agents*) and fosphenytoin**,** primidone, progabide, and possibly by clonazepam, valproic acid or valpromide.

Antineoplastics: cisplatin or doxorubicin.

Antituberculosis: rifampicin.

Bronchodilators 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 APO-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 APO-CARBAMAZEPINE and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

APO-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 APO-CARBAMAZEPINE. Due to enzyme induction, APO-CARBAMAZEPINE may result in a failure of the therapeutic effect of oral contraceptive drugs containing estrogen and/or progesterone (e.g. failure of contraception).

Concomitant medication with APO-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.

The use of APO-CARBAMAZEPINE in combination with MAO inhibitors (MAOIs) is contraindicated. Before administering APO-CARBAMAZEPINE, MAOIs should be discontinued for a minimum of 2 weeks, or longer, if the clinical situation permits (see **Contraindications**).

Interference with serological testing

Carbamazepine may result in false positive perphenazine concentrations in HPLC analysis due to interference.

Carbamazepine and the 10,11-epoxide metabolite may result in false positive tricyclic antidepressant concentration in fluorescence polarized immunoassay method.

ADVERSE REACTIONS

The reactions which have been most commonly reported with carbamazepine tablets 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 tablets 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 APO-CARBAMAZEPINE may precipitate seizures, therefore carbamazepine should be withdrawn gradually over a 6-month period. In epileptic patients, the

switch to the new antiepileptic compound should be made under cover of a suitable drug. The following adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common: (≥1/100 to <1/10); uncommon: (≥1/1,000 to <1/100); rare: (≥1/10,000 to <1/1,000); very rare: (<1/10,000); frequency unknown:

Blood and lympathic system disorders

Very common: leucopenia;

Common: eosinophilia, thrombocytopenia;

Rare: leucocytosis, lymphadenopathy;

Very rare: agranulocytosis, aplastic anemia, pancytopenia, pure red cell aplasia, anemia, macrocytic anemia, megaloblastic anemia, reticulocytosis, thrombocytopenic purpura and hemolytic anemia. In a few instances, deaths have occurred;

Unknown: bone marrow failure.

Hepatobiliary disorders

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

Very rare: hepatic failure, granulomatous liver disease.

Skin and subcutaneous tissue disorders

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

Uncommon: exfoliative dermatitis;

Rare: systemic lupus erythematosus, pruritis;

Very rare: Steven Johnson syndrome[‡], toxic epidermal necrolysis (LyeIl's syndrome), photosensitivity reaction, erythema multiform, erythema nodosum, pigmentation disorder, purpura, acne, diaphoresis, alopecia, neurodermatitis, hirsutism.

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

Unknown: Acute Generalized Exanthematous Pustulosis (AGEP), lichenoid keratosis, onychomadesis.

Nervous system disorders

Very common: ataxia, dizziness, somnolence;
Common: an increase in motor seizures (see **Indications**), diplopia, headache;
Uncommon: abnormal involuntary movements (e.g., tremor, asterixis, dystonia, tics), nystagmus;
Rare: dyskinesia, paresis, eye movement disorder, speech disorders (e.g., dysarthria, slurred speech), choreoathetosis, peripheral neuropathy, paraesthesia, muscle weakness;
Very rare: neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia;
Unknown: sedation, memory impairment.

Cardiac disorders

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

Very rare: arrhythmias, Stokes-Adams in patients with atrioventricular block, bradycardia, congestive cardiac failure, aggravated coronary artery disease. Some of these cardiovascular complications have had fatal outcomes. Myocardial infarction and arrhythmia have been associated with other tricyclic compounds.

Vascular disorders

Rare: hypertension or hypotension;

Very Rare: circulatory collapse, thromboembolism (e.g. pulmonary embolism), thrombophlebitis.

Psychiatric disorders

Rare: hallucinations (visual or auditory), depression, 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: tubulointerstitial 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 retention, urinary frequency.

Reproductive system

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

Gastrointestinal disorders

Very common: vomiting, nausea;

Common: dry mouth and throat;

Uncommon: diarrhea, constipation;

Rare: abdominal pain;

Very rare: pancreatitis, glossitis, stomatitis;

Unknown: colitis

Eye disorders

Common: accommodation disorders (e.g. blurred vision);

Very rare: lenticular opacities, conjunctivitis, 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:*galactorrhea, gynecomastia.

Metabolism and nutrition disorders

Rare: folate deficiency, decreased appetite;
Very rare: acute porphyria (acute intermittent porphyria and variegate porphyria), non-acute porphyria (porphyria cutanea tarda).

Musculoskeletal, connective tissue and bone disorders
Very rare: bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms.
Unknown: fracture

Respiratory, thoracic and mediastinal system
Very rare: pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Infections and infestations
Unknown: reactivation of human herpesvirus 6 infection.

Immune system disorders
Rare: delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, 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: anaphylactic reaction, angioedema, hypogammaglobulinemia;.

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

General disorders and administration site conditions
Very common: fatigue.

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

Common: increased blood alkaline phosphatase;
Uncommon: increased transaminases;
Very rare: increased intraocular pressure, increased blood cholesterol, increased high density lipoprotein, increased blood triglycerides. Abnormal thyroid function test: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, increased blood prolactin (usually without clinical manifestations);
Unknown: bone density decreased.

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, as well as the adverse drug reactions mentioned under the Adverse Reaction section.

Central Nervous System: CNS depression, disorientation, depressed level of consciousness, 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.

Musculoskeletal system: There have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity.

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 APO-CARBAMAZEPINE (carbamazepine).

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

Hemodialysis is the effective treatment modality in the management of the carbamazepine overdose.

Vital signs, including electrocardiogram to detect any cardiac arrhythmias or conduction defects, should be watched and symptomatic treatment should be administered as required. Hyperirritability or convulsions should be appropriately managed by standard medical care.

Hyponatremia should be appropriately managed by standard medical care.

Shock (circulatory collapse) should be treated with supportive measures, including intravenous fluids, oxygen, and corticosteroids.

Charcoal hemoperfusion has been recommended.

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)

APO-CARBAMAZEPINE (carbamazepine) may be used alone or with other anticonvulsants. A low initial daily dosage of APO-CARBAMAZEPINE with a gradual increase in dosage is advised. To achieve adequate control of seizures, dosage should be adjusted to the needs of the individual patient. Determination of plasma levels may help in establishing the optimum dosage (see **Clinical Pharmacokinetics and Warnings-Pregnancy and Nursing**). APO-CARBAMAZEPINE should be taken with meals whenever possible.

APO-CARBAMAZEPINE tablets should be taken in 2 to 4 divided doses daily.

The controlled release characteristics of APO-CARBAMAZEPINE CR reduce the daily fluctuations of plasma carbamazepine. APO-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 should be prescribed as 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 **Precautions, Drug Interactions** and **Warnings, Pregnancy and Nursing**).

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. Maximum recommended dose is 1200 mg/day. 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 APO-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 ensure 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.

Special populations

Geriatrics

Due to drug interactions and different antiepileptic drug pharmacokinetics, the dosage of APO-CARBAMAZEPINE should be selected with caution in elderly patients.

Renal impairment / Hepatic impairment

No data are available on the pharmacokinetics of carbamazepine in patients with any degree of hepatic or renal impairment.

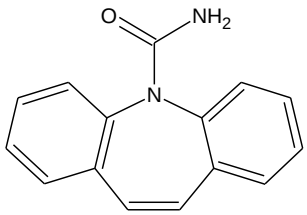
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Carbamazepine

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

Structural Formula:



Molecular Formula: $C_{15}H_{12}N_20$

Molecular Weight: 236.27

Description: White to off-white powder.

Solubility: Practically insoluble in water and in acetone.

Composition

APO-CARBAMAZEPINE: In addition to carbamazepine, each tablet contains the non-medicinal ingredients colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

APO-CARBAMAZEPINE CR: In addition to carbamazepine, each controlled release tablet contains the non-medicinal ingredients crospovidone, ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol, red ferric oxide, titanium dioxide and yellow ferric oxide.

Stability and Storage Recommendations

APO-CARBAMAZEPINE: Store in a dry place at room temperature 15-30°C (59-86°F). Protect from moisture.

APO-CARBAMAZEPINE CR: Store at room temperature 15-30°C (59-86°F). Keep bottle tightly closed. Protect from moisture.

Keep out of reach of children.

AVAILABILITY OF DOSAGE FORMS

APO-CARBAMAZEPINE 200 mg: Each round, white, flat-faced tablet, one side cross-scored, the other side engraved "APO" over "200", contains 200 mg carbamazepine. Available in bottles of 100 and 500, unit dose packages of 100.

APO-CARBAMAZEPINE CR 200 mg: Each light orange, capsule-shaped, film-coated tablet, scored and engraved "APO" bisect "200" on one side, plain with bisect on the other side, contains 200 mg carbamazepine. Available in bottles of 100 and 500, unit dose packages of 30 (aluminum blister 3 x 10), 60 (aluminum blister 6 x 10) and 100 (aluminum blister 10 x 10).

APO-CARBAMAZEPINE CR 400 mg: Each capsule-shaped, dark orange, film-coated tablet, scored and engraved "APO" bisect "400" on one side, plain with bisect on the other side, contains 400 mg carbamazepine. Available in bottles of 100 and 500, unit dose packages of 30 (aluminum blister 3 x 10), 60 (aluminum blister 6 x 10) and 100 (aluminum blister 10 x 10).

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 1×10^{-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. 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 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.

Carcinogenicity and Genotoxicity

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. Carbamazepine was not found to be genotoxic in various standard bacterial and mammalian mutagenicity studies. The carcinogencity findings in rats are considered to be not relevant to the use of carbamazepine in humans.

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 Toxicity

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.

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CONSUMER INFORMATION

PrAPO-CARBAMAZEPINE
Carbamazepine Tablets USP, 200 mg

PrAPO-CARBAMAZEPINE CR
Carbamazepine Controlled ReleaseTablets
Apotex Standard
200 mg and 400 mg

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

ABOUT THIS MEDICATION

What the medication is used for:
APO-CARBAMAZEPINE has been prescribed for you by your doctor:
- to reduce your number of seizures;
- to relieve the pain of trigeminal neuralgia;
- to treat your acute mania or bipolar disorder.

What it does:
APO-CARBAMAZEPINE belongs to the family of medicines called anticonvulsants for treating epilepsy. APO-CARBAMAZEPINE is also used for treating the pain of trigeminal neuralgia and for treating mania.

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

When it should not be used:
You should not use APO-CARBAMAZEPINE if:
- You are allergic (hypersensitive) to carbamazepine or to any of the other ingredients of APO-CARBAMAZEPINE (See **What the non-medicinal ingredients** are). If you think you may be allergic, ask your doctor for advice. Do not take APO-CARBAMAZEPINE if you are allergic to other tricyclic drugs such as amitriptyline, trimipramine, imipramine.
- You have severe heart disease (heart block).
- You have liver disease.
- You have a history of bone marrow depression.
- 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 medicines 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.
- APO-CARBAMAZEPINE 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 APO-CARBAMAZEPINE**.

What the medicinal ingredient is:
Carbamazepine.

What the important non-medicinal ingredients are:
APO-CARBAMAZEPINE 200 mg Tablets: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

APO-CARBAMAZEPINE CR 200 mg and 400 mg: crospovidone, ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol, red ferric oxide, titanium dioxide and yellow ferric oxide.

What dosage forms it comes in:
APO-CARBAMAZEPINE is available in the following forms:
- Round tablets containing 200 mg carbamazepine.
- Capsule-shaped CR tablets (controlled-release tablets, which can be divided) containing 200 mg or 400 mg carbamazepine.

WARNINGS AND PRECAUTIONS

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 APO-CARBAMAZEPINE. 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 APO-CARBAMAZEPINE in order to detect as early as possible any possible signs of a blood disorder. Your doctor should discontinue APO-CARBAMAZEPINE, 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 APO-CARBAMAZEPINE. Other serious skin reactions such as Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP) and Maculopapular Rash have also been reported. Although very rare, serious forms of DRESS and AGEP may also lead to death. Some cases of these skin reactions have been genetically linked. Your doctor may recommend a blood test to determine if you belong to an at-risk population.**
- **Contact your doctor immediately if you are developing any combination of:**
  - **a rash or any serious skin reactions such as red skin, blistering of the lips, eyes or mouth, and skin peeling accompanied by fever.**
  - **Swollen lymph nodes**

- **Joint pain**
- **Enlargement of the liver and/or the spleen**
- **Problems related to the lungs, kidneys, pancreas, heart, bone marrow, thymus, and colon.**

Your doctor will determine if it is indeed drug-related, and discontinue APO-CARBAMAZEPINE in this case.

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

BEFORE you use APO-CARBAMAZEPINE talk to your doctor or pharmacist if:

- About your medical conditions, especially if you have or have had any liver, kidney, heart or thyroid 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 APO-CARBAMAZEPINE (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 APO-CARBAMAZEPINE with your doctor. This is especially important during the first three months of pregnancy. The risk to a fetus may be less if APO-CARBAMAZEPINE:
  - the only drug used to control seizures
  - used at the lowest dose that still controls seizures
- Your doctor may recommend that you take folic acid before and during your pregnancy and vitamin K during the last weeks of pregnancy.
- The doctor may recommend that the newborn receive vitamin K and be observed for liver and gall bladder problems.
- If you are a women taking hormonal contraceptive (birth control medicine), APO-CARBAMAZEPINE may render this contraceptive ineffective. Therefore, you should use a different or additional non-hormonal method of contraception while you are taking APO-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.
- If you are breast-feeding. APO-CARBAMAZEPINE is known to pass into breast milk. You must discuss with your doctor the benefits of breastfeeding against any possible risks to the infant. If you decide to breastfeed, the baby must be observed for liver and gall gladder problems, drowsiness, and allergic skin reactions.
- APO-CARBAMAZEPINE may affect male fertility or cause abnormal sperm.
- Of any other medicines (prescription and non-prescription) 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**.
- If you have kidney problems associated with low sodium blood level or if you have kidney problems and you are also taking certain medicines that lower sodium blood level (diuretics such as hydrochlorothiazide, furosemide).

Periodic eye examinations are recommended while taking APO-CARBAMAZEPINE.

Do not drive a car or operate dangerous machinery until you are sure that APO-CARBAMAZEPINE does not cause dizziness, drowsiness, sleepiness, blurred or double vision, affect your muscular coordination 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 APO-CARBAMAZEPINE, 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 APO-CARBAMAZEPINE. The hormonal contraceptive may become less effective and you should use another contraceptive method (non-hormonal).

- Avoid alcohol consumption when taking APO-CARBAMAZEPINE.

- Do not drink grapefruit juice or eat grapefruit since this can increase the effect of APO-CARBAMAZEPINE. Other juices, like orange juice or apple juice, do not have this effect.

PROPER USE OF THIS MEDICATION

Usual dose:
Dosage should be individualised. It is very important that you take APO-CARBAMAZEPINE exactly as your doctor instructed.

- Never increase or decrease the recommended dose of APO-CARBAMAZEPINE you are taking unless your doctor tells you to.
- If you are taking APO-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
- APO-CARBAMAZEPINE tablets should be taken in 2-4 divided doses daily, with meals whenever possible.
- APO-CARBAMAZEPINE CR tablets should be swallowed unchewed with a little liquid during or after a meal.

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.

For the treatment of trigeminal neuralgia, the maximum dose is 1200 mg a day. Do not exceed maximum dose.

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 APO-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 not sure, ask your doctor or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- purple or reddish-purple bumps that may be itchy
- trembling, uncontrolled body movements, muscle spasm, loss of muscle coordination, weakness
- agitation or hostility (especially in the elderly), depression with restlessness, nervousness or other mood or mental changes, changes in behaviour, confusion, headache, memory loss
- blurred vision, double vision, itching with redness and swelling of the eye (conjunctivitis), uncontrolled eye movements
- difficulty speaking or slurred speech, taste disturbances, dry mouth, red and sore tongue, mouth sores
- ringing or other unexplained sounds in the ears, decreased hearing
- numbness, tingling in hands and feet
- unusual secretion of breast milk, breast enlargement in men, sexual disturbances (erectile dysfunction), male infertility
- increased sensitivity of the skin to sun, alterations in skin pigmentation, acne, increased sweating
- reactivation of herpes virus infection (can be serious when the immune system is depressed)
- complete loss of the nails, loss of hair, excessive body and facial hair
- vomiting, nausea, loss of appetite, constipation, diarrhea, abdominal pain
- dizziness, sleepiness, unsteadiness, drowsiness, fatigue
- weight gain
- aching joints or muscles

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, or fracture.

If any of these affects you severely, contact your doctor.

Carbamazepine can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

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

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug & seek immediate emergency medical treatment
		Only if severe	In all cases	
Very Common	***Decreased White Blood Cells:*** fever, sore throat, rash, ulcers in the mouth, swollen glands, or more easily getting infections).	√		
	Suicidal Thoughts or Actions: thoughts, plans and actions taken		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		**Talk with your doctor or pharmacist**		**Stop taking drug & seek immediate emergency medical treatment**
		Only if severe	**In all cases**	
	for the purpose of killing or harming yourself)			
Common	**Edema:** swelling of the ankles, feet or lower legs.	√		
Rare	**Systemic Lupus Erythematosus:** red blotchy rash mainly on the face which may be accompanied by fatigue, fever, nausea, loss of appetite).	√		
	Hallucination :see or hear things that are not there.	√		
	High Blood Pressure Low Blood Pressure: dizziness, fainting, light-headedness	√		
Very rare	**Glaucoma:** pressure / pain in the eye			√
	Thrombophlebitis: swelling and redness along a vein which is extremely tender or painful when touched.		√	
	Angioedema and Severe Allergic Reactions: swelling of the face, eyes, or tongue, difficulty swallowing, wheezing, hives and generalized			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		**Talk with your doctor or pharmacist**		**Stop taking drug & seek immediate emergency medical treatment**
		Only if severe	**In all cases**	
	itching, rash, fever, abdominal cramps, chest discomfort or tightness, difficulty breathing, unconscious-ness).			
	Serious Skin Reactions: any combination of itchy skin rash, redness, blistering of the lips, eyes or mouth, skin peeling, accompanied by fever, chills, headache, cough, body aches or swollen lymp nodes, joint pain, enlargement of the liver and/or the spleen. Any problems related to the lungs, kidneys, pancreas, heart, bone marrow, thymus, and colon.)			√
	Hepatitis: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting loss of appetite.		√	
	Meningitis: fever, nausea, vomiting, headache, stiff neck and			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug & seek immediate emergency medical treatment
		Only if severe	In all cases	
	extreme sensitivity to bright light).			
	Pancreatitis: severe upper abdominal pain, vomiting, loss of appetite).	√		
	Severe decreased urine output due to kidney disorders, blood in the urine. Frequent urination.	√		
	Porphyria> darkening of urine, severe abdominal pain, excessive sweating, vomiting, and anxiety.		√	
	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.	√		
	Neuroleptic Malignant Syndrome: muscular stiffness, high fever, altered consciousness, high blood pressure, excessive salivation			√
	Irregular heartbeat, chest pain, fast or unusually slow heartbeat, trouble breathing.	√		
	Thromboembolism (blood clot): swelling, pain and redness in an arm or a leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.			√
	Circulatory Collapse: the body is unable to circulate blood to the organs. This is very serious and can lead to death.			√
	Disturbed consciousness, fainting.		√	
	Hyponatremia (low sodium in the blood): lethargy, confusion, muscular twitching or significant worsening of convulsions	√		
Unknown	**Inflammation of the colon:** diarrhea, abdominal pain and fever.		√	

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

HOW TO STORE IT

- Store at room temperature 15-30°C (59-86°F).
- Keep bottle tightly closed. Protect from moisture.
- Protect from humidity, such as in bathrooms where 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 0701E
    Ottawa, ON 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

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at: http://www.apotex.ca/products.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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