Product Monograph

Pr TARO- CARBAMAZEPINE Tablets 200 mg
(Carbamazepine Tablets, USP)

Pr TARO- CARBAMAZEPINE Chewable Tablets 100 & 200 mg
(Carbamazepine Chewable Tablets)

Pr TARO- CARBAMAZEPINE CR Tablets 200 & 400 mg
(Carbamazepine Extended-Release Tablets, Taro Standard)

Anticonvulsant

For Symptomatic Relief Of Trigeminal Neuralgia

Antimanic

Taro Pharmaceuticals Inc.
130 East Drive
Brampton, Ontario
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THERAPEUTIC CLASSIFICATION

1. Anticonvulsant

2. For Symptomatic Relief of Trigeminal Neuralgia

3. Antimanic

ACTIONS AND CLINICAL PHARMACOLOGY

TARO-CARBAMAZEPINE(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 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.

Pharmacokinetics: The absorption of carbamazepine in man is relatively slow. When taken in a single oral dose, the 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 nonprotein-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.

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

BIOEQUIVALENCE STUDIES:

CR tablets:

Three bioavailability studies were performed in order to establish bioequivalence between Taro-Carbamazepine CR tablets and the brand product.

The results of the three studies are summarized in the tables below:

Two-way, Crossover, Multiple Dose, Fasting Study
Carbamazepine CR tablets (1 x 400 mg)
Carbamazepine (from measured data)

Geometric Mean
Arithmetic Mean (CV%)

PARAMETER	**Taro-Carbamazepine CR 400 mg tablets (Taro Pharmaceuticals Inc.)**	**Tegretol® CR * 400 mg tablets (Ciba Geigy Canada)**	**RATIO OF MEANS**
AUC_{0-12} (ng hr/mL)	83516 84836 (18%)	84588 85802 (17%)	99
C_{max} 0-12 (ng/mL)	7744 7877 (18%)	7793 7913 (18%)	99
C_{min} 0-12 (ng/mL)	6093 6197 (18%)	6257 6374 (20%)	97
T_{max} 0-12 (hr)	3 (45%)	4 (42%)	
Fluctuation (% Cav)	22 (28%)	21 (27%)	

for T_{max} and Fluctuation arithmetic mean (CV%) are presented
* purchased in Canada

Three-way, Crossover, Single Dose, Fasting Study
Carbamazepine CR tablets (1 x 400 mg)
Carbamazepine (from measured data)

Geometric Mean
Arithmetic Mean (CV%)

PARAMETER	Taro-Carbamazepine CR 400 mg tablets (Taro Pharmaceuticals Inc.)	Tegretol® CR * 400 mg tablets (Ciba Geigy Canada)	RATIO OF MEANS
AUC_{0-72} (ng hr/mL)	120626 123331 (20%)	133019 135128 (17%)	91
AUC_{inf} (ng hr/mL)	203889 212158 (28%)	214872 221344 (24%)	95
C_{max} (ng/mL)	2236.5 2287 (21%)	2387 2413 (15%)	94
T_{max} (hr)	33 (34%)	28 (33%)	
$T_{½}$ (hr)	41.2 (20%)	40.9 (21%)	

for T_{max} and $T_{½}$ arithmetic mean (CV%) are presented
* purchased in Canada

Two-way, Crossover, Single Dose, Food-Effect Study
Carbamazepine CR tablets (1 x 400 mg)
Carbamazepine (from measured data)

Geometric Mean
Arithmetic Mean (CV%)

PARAMETER	Taro-Carbamazepine CR 400 mg tablets (Taro Pharmaceuticals Inc.)	Tegretol® CR * 400 mg tablets (Ciba Geigy Canada)	RATIO OF MEANS
AUC_{0-72} (ng hr/mL)	165181 167536 (17%)	154065 156613 (17%)	107
AUC_{inf} (ng hr/mL)	250337 256308 (23%)	230331 236139 (22%)	109
C_{max} (ng/mL)	3055.4 3097.7 (17%)	2896.0 2921.4 (13%)	106
T_{max} (hr)	24.1 (28%)	23.1 (25%)	
$T_{½}$ (hr)	38.0 (21%)	37.6 (18%)	

for T_{max} and $T_{½}$ arithmetic mean (CV%) are presented
* purchased in Canada

Chewable Tablets:

Two bioavailability studies were performed in order to establish bioequivalence between Taro-Carbamazepine Chewable Tablets and the brand product.

The results of these two studies are summarized in the tables below:

Two-way, Crossover, Single Dose, Fasting Study
1 x 200 mg Chewable Tablet
Carbamazepine(From measured and ln-transformed data)
uncorrected for potency
Geometric Least-Squares Mean
Arithmetic Mean (CV%)

PARAMETER	**Taro-Carbamazepine Chewable Tablets 200 mg (Taro Pharmaceuticals Inc.)**	**Tegretol Chewtabs® * 200 mg (Novartis Canada)**	**RATIO OF GEOMETRIC MEANS**
AUC_{0-72} (ng hr/mL)	115138.04 116314.33 (13.64)	109777.59 113494.35 (22.97)	104.88
AUC_{inf} (ng hr/mL)	168714.69 176283.08 (31.03)	153523.09 162040.20 (30.34)	109.90
C_{max} (ng/mL)	2467.54 2480.22 (9.64)	2450.08 2507.89 (18.07)	100.71
T_{max} (hr)	7.38 (44.68)	6.00 (49.42)	
$T_{½\ el}$ (hr)	41.13 (30.11)	38.53 (21.30)	

for T_{max} and $T_{½}$ arithmetic mean (CV%) are presented
* purchased in Canada

Two-way, Crossover, Single Dose, Food-effect Study
1 x 200 mg Chewable Tablet
Carbamazepine (From measured and ln-transformed data)
uncorrected for potency
Geometric Least-Squares Mean
Arithmetic Mean (CV%)

PARAMETER	Taro-Carbamazepine Chewable Tablets 200 mg (Taro Pharmaceuticals Inc.)	Tegretol Chewtabs® * 200 mg (Novartis Canada)	RATIO OF GEOMETRIC MEANS
AUC_{0-72} (ng hr/mL)	113415.24 114203.16 (11.81)	111361.80 111985.11 (10.97)	101.84
AUC_{inf} (ng hr/mL)	163327.59 166626.79 (21.83)	160232.71 163078.43 (19.84)	101.93
C_{max} (ng/mL)	2644.22 2652.59 (8.05)	2578.64 2589.71 (9.74)	102.54
T_{max} (hr)	7.95 (32.51)	7.20 (31.99)	
$T_{½\ el}$ (hr)	40.08 (26.97)	40.81(21.71)	

for T_{max} and $T_{½}$ arithmetic mean (CV%) are presented
* purchased in Canada

INDICATIONS AND CLINICAL USE

A. Epilepsy: TARO-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: TARO-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 TARO-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: TARO-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

TARO-CARBAMAZEPINE (carbamazepine) should not be administered to patients with hepatic disease, a history of bone-marrow depression, a history of acute intermittent porphyria, or serious blood disorder.

Because it is structurally related to tricyclic antidepressants, TARO-CARBAMAZEPINE should not be administered immediately before, in conjunction with, or immediately after a monoamine oxidase inhibitor. When it seems desirable to administer TARO-CARBAMAZEPINE to a patient who has been receiving an MAO inhibitor, there should be as long a drug-free interval as the clinical condition allows, but in no case should this be less than 14 days. Then the dosage of TARO-CARBAMAZEPINE should be low initially, and increased very gradually.

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

TARO-CARBAMAZEPINE should not be administered to patients with known hypersensitivity to carbamazepine, to any 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

ALTHOUGH REPORTED INFREQUENTLY, SERIOUS ADVERSE EFFECTS HAVE BEEN OBSERVED DURING THE USE OF CARBAMAZEPINE. AGRANULOCYTOSIS AND APLASTIC ANEMIA HAVE OCCURRED IN A FEW INSTANCES WITH A FATAL OUTCOME. 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 TARO-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. TARO-CARBAMAZEPINE SHOULD BE DISCONTINUED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION APPEARS. (See PRECAUTIONS).

SHOULD SIGNS AND SYMPTOMS SUGGEST A SEVERE SKIN REACTION SUCH AS STEVEN-JOHNSON SYNDROME OR LYELL'S SYNDROME, TARO-CARBAMAZEPINE SHOULD BE WITHDRAWN AT ONCE.

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 TARO-CARBAMAZEPINE TO INDIVIDUAL PATIENTS.

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

In women of childbearing potential, TARO-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 TARO-CARBAMAZEPINE, or if the problem of initiating TARO-CARBAMAZEPINE arises during pregnancy, the drug's potential benefits must be weighed against its hazards, particularly during the first 3 months of pregnancy. TARO-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. There are rare reports on developmental

disorders and malformations, including spina bifida, in association with carbamazepine. Conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. The patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

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 the newborn, has been recommended.

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

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

PRECAUTIONS

Clinical Monitoring of Adverse Reactions: TARO-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 TARO-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, TARO-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. Nonprogressive fluctuating asymptomatic leucopenia, which is encountered, does not generally call for the withdrawal of TARO-CARBAMAZEPINE. However, treatment with TARO-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. TARO-CARBAMAZEPINE should be withdrawn immediately in cases of aggravated liver dysfunction or active liver disease.

- Kidney function: Pretreatment 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: TARO-CARBAMAZEPINE should be used with caution in patients with a mixed seizures which includes absences, either typical or atypical. In all these conditions, carbamazepine may exacerbate seizures. In case of exacerbation of seizures, TARO-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 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 Lyell's syndrome occurring (see WARNINGS).

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.

Occurrence of Behavioural Disorders: 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.

Use in Patients with Cardiovascular Disorders: TARO-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 TARO-CARBAMAZEPINE, in order to exclude patients with atrioventricular block.

Occupational Hazards:

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

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.

Drug Interactions: Cytochrome P450 3A4 (CYP3A4) is the main enzyme responsible for metabolizing carbamazepine. Coadministration of CYP3A4 inhibitors may increase plasma concentrations and induce adverse reactions. Coadministration of CYP3A4 inducers may increase the rate of carbamazepine metabolism leading to a potential decrease in carbamazepine serum levels and a potential decrease in therapeutic effect.

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 TARO-CARBAMAZEPINE: clobazam, clonazepam, ethosuximide, primidone, valproic acid, alprazolam; corticosteroids (e.g. prednisolone, dexamethasone), cyclosporin, digoxin, doxycycline, felodipine, haloperidol, imipramine, methadone, oral contraceptives, theophylline, and oral anticoagulants (warfarin, phenprocoumon, dicumarol), felbamate, lamotrigine, zonisamide, tiagabine, topiramate, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortryptyline, clomipramine), clozapine.

Phenytoin plasma levels have been reported both to be raised and to be lowered by carbamazepine, and mephenytoin plasma levels have been reported in rare instances to increase.

The following drugs have been shown to raise plasma carbamazepine levels: isoniazid, verapamil, diltiazem, dextropropoxyphene, viloxazine, fluoxetine, cimetidine,

acetazolamide, danazol, possibly desipramine, fluvoxamine, nefadozone, macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin), azoles (itraconazole, ketoconazole, fluconazole), terfenidine, loratadine. Nicotinamide raises carbamazepine plasma levels in children, but only at high dosage in adults. Since an increase in carbamazepine plasma levels may result in adverse reaction (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of TARO-CARBAMAZEPINE should be adjusted accordingly and the blood levels monitored.

The plasma levels of carbamazepine may be reduced by phenobarbitone, phenytoin, primidone, progabide, theophylline, methsuximide, phensuximide, rifampicin, cisplatin or doxorubicin and possibly by clonazepam, valproic acid or valpromide. On the other hand, valproic acid, valpromide, and primidone have been reported to raise plasma levels of the pharmacologically active metabolite, carbamazepine-10,11 epoxide. The dose of TARO-CARBAMAZEPINE may consequently have to be adjusted. Felbamate might decrease the carbamazepine serum concentrations associated with an increase in carbamazepine epoxide levels, and might decrease the serum felbamate levels.

Combined use of TARO-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 TARO-CARBAMAZEPINE and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

Coadministration of carbamazepine and paracetamol/acetaminophen may reduce the bioavailability of paracetamol/acetaminophen.

TARO-CARBAMAZEPINE, like other anticonvulsants, may adversely affect the reliability of oral contraceptives; breakthrough bleeding may occur. Patients should accordingly be advised to use some alternative, non-hormonal method of contraception, while taking carbamazepine.

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

Carbamazepine may antagonize the effects of nondepolarising 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 its active 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.

TARO-CARBAMAZEPINE should not be administered in conjunction with an MAO inhibitor. (See CONTRAINDICATIONS).

Information to be Provided to the Patient: See INFORMATION FOR THE PATIENT.

ADVERSE REACTIONS

The reactions which have been most commonly 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 reaction observed are the hematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy.

Abrupt withdrawal of Taro-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. phenytoin i.v.).

The following adverse reactions have been reported (Frequency estimate: Very common: ≥10%; common: ≥ 1% to < 10%; uncommon: ≥0.1% to <1%; rare: ≥0.01% to <0.1%, very rare: <0.01%):

Hematologic: Very common: leucopenia; Common: eosinophilia, thrombocytopenia; rare - leucocytosis, lymphadenopathy, folic acid deficiency; Very rare: agranulocytosis, aplastic anemia, pure red cell aplasia, macrocytic anemia, megaloblastic anemia, acute intermittent porphyria, reticulocytosis, thrombocytopenia purpura, and possibly hemolytic anemia. In a few instances, deaths have occurred.

Hepatic: Very common: elevated gamma-GT (due to hepatic enzyme induction), usually not clinically relevant; Common: elevated alkaline phosphatase; Uncommon: elevated transaminases; Rare: jaundice, hepatitis of a cholestatic, parenchymal (hepatocellular), or mixed type; Very rare: granulomatous hepatitis.

Dermatologic: Very common: skin sensitivity reactions and rashes, erythematous rashes, urticaria; Uncommon: exfoliative dermatitis and erythroderma; Rare: systemic lupus erythematosus-like syndrome, pruritis; Very rare: Steven Johnson syndrome, toxic epidermal

necrolysis (Lyell's syndrome), photosensitivity, erythema multiforme and nodosum, skin pigmentation changes, purpura, acne, diaphoresis, alopecia and neurodermatitis. Very rare cases of hirsuitism have been reported, however the causal relationship is not clear.

Neurologic: Very common: vertigo, somnolence, ataxia and fatigue; Common: an increase in motor seizures (see INDICATIONS), headache, diplopia, accommodation disorders (e.g. blurred vision); Uncommon: abnormal involuntary disorders (e.g. tremor, asterixis, dystonia, tics), nystagmus; Rare: orofacial dyskinesia, paretic symptoms, oculomotor disturbances, speech disorders (e.g. dysarthria or slurred speech), peripheral neuritis, paraesthesia, muscle weakness, choreoathetosis disorders. There have been some reports of neuromalignant syndrome and paralysis and other symptoms of cerebral arterial insufficiency but no conclusive relationship to the administration of carbamazepine could be established.

Cardiovascular: Rare: disturbances of cardiac conduction, hypertension or hypotension; Very rare: bradycardia, arrhythmias, Stokes-Adams in patients with AV-block, collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thromboembolism. Some of these complications (including myocardial infarction and arrhythmia) have been associated with other tricyclic compounds.

Psychiatric: Rare: hallucinations (visual or acoustic), depression with agitation, talkativeness, agitation, loss of appetite, restlessness, aggressive behaviour, confusion; Very Rare: activation of psychosis.

Genitourinary: Very Rare: interstitial nephritis and renal failure, renal dysfunction (e.g. albuminuria, glycosuria, hematuria, oliguria sometimes associated with elevated blood pressure, and elevated BUN/azotemia), urinary frequency, urinary retention and sexual disturbances/impotence.

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

Sense Organs: Very rare: lens opacities, conjunctivitis, retinal changes, taste disturbances, hearing disorders(e.g. tinnitus, hyperacusis, hypoacusis), change in pitch perception.

Endocrine System and Metabolism: Common: edema, fluid retention, weight increase, hyponatremia and reduced plasma osmolality due to antidiuretic hormone (ADH)-like effect occurs, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities; Very rare: increase in prolactin with or without clinical manifestations (e.g. galactorrhea), gynecomastia, abnormal thyroid function tests (decreased L-thyroxine i.e. FT_4, T_4,T_3, and increased TSH, usually without

clinical manifestations), disturbances of bone metabolism (decrease in plasma calcium and 25-OH-calciferol), leading to osteomalacia, as well as reports of elevated levels of cholesterol, including HDL cholesterol and triglycerides.

Musculoskeletal system: Vary rare: arthralgia, muscle pain or cramp.

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

Hypersensitivity reactions: Rare: delayed multiorgan hypersensitivity disorder with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking 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 eosinophilia; anaphylactic reaction, angioedema. Treatment should be discontinued should such hypersensitivity reactions occur.

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: There is no known specific antidote to carbamazepine.

Evacuate the stomach, with an emetic or by gastric lavage, then administer activated charcoal. Delay in evacuating the stomach may results 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): TARO-CARBAMAZEPINE (carbamazepine) may be used alone or with other anticonvulsants. A low initial daily dosage of TARO-CARBAMAZEPINE with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient.

TARO-CARBAMAZEPINE tablets should be taken in 2 to 4 divided doses daily, with meals whenever possible. TARO-CARBAMAZEPINE chewable tablets are particularly suitable for patients who have difficulty swallowing tablets.

The controlled release characteristics of TARO-CARBAMAZEPINE CR reduce the daily fluctuations of plasma carbamazepine. TARO-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 Drug Interactions under Precautions and Pregnancy and nursing 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 TARO-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.

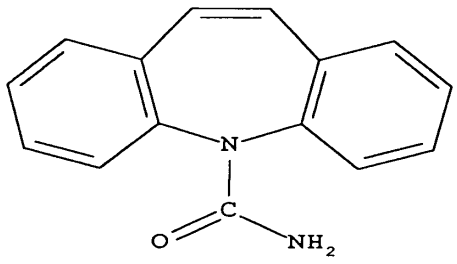
Use in Mania and Bipolar (Manic-Depressive) Disorders: The initial daily dosage should be low, 200 to 400 mg/day, administered in divided doses, although higher starting doses of 400 to 600 mg/day may be used in acute mania. This dose may be gradually increased until patient symptomatology is controlled 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

Carbamazepine



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

Molecular Weight: 236.27

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

Description: Carbamazepine is a white to off-white powder, freely soluble in methylene chloride, sparingly soluble in acetone and in alcohol, practically insoluble in water and in ether.

Specific Rotation: Optically inactive

Melting Point: 189 ˚C to 193 ˚C

AVAILABILITY OF DOSAGE FORMS:

	TARO-CARBAMAZEPINE TABLETS	**TARO-CARBAMAZEPINE CR TABLETS**	
	200 mg	**200 mg**	**400 mg**
Colour	White	White to off-white	White to off-white
Shape	Round, quadrisect	Capsule shaped	Capsule shaped
Imprint	embossed "TARO"	"T12" engraved on one side, scored on both sides	"T17" engraved on one side, scored on both sides
Medical Content	200 mg carbamazepine	200 mg carbamazepine	400 mg carbamazepine
Non-medicinal Ingredients	Microcrystalline Cellulose, Povidone, Sodium Lauryl Sulphate, Sodium Starch Glycollate, Magnesium Stearate	Eudragit RS30D, Diethyl Phthalate, Microcrystalline Cellulose, Lactose Monohydrate, Maize Starch, Sodium Starch Glycolate, Magnesium Stearate	

Availability	Bottles of 100's and 500's	
Storage Conditions	Protect from heat and humidity.	Store at room temperature (15-25 ˚C). Protect from humidity.

TARO-CARBAMAZEPINE CHEWABLE TABLETS		
	100 mg	**200 mg**
Colour and Odour	White with pink speckles, cherry odour	
Shape	Round, flat	Oval, flat
Imprint	Scored on one side, engraved "TARO" above the score and "16" under the score.	Both sides scored, one side "T"engraved above the score line and "27" under the score line
Medical Content	100 mg carbamazepine	200 mg carbamazepine
Non-medicinal ingredients	Eudragit RS 30D, Diethyl Phthalate, FD & C Red No.40 Lake, Microcrystalline Cellulose, Pregelatinized Starch, Croscarmellose Sodium, Natural Cherry Flavour, Sorbitol, Magnesium Stearate	
Availability	Bottles of 100's and 500's, blister packs of 50's and 100's	Bottles of 100's and 400's
Storage Conditions	Store at room temperature (15-30 ˚C). Protect from light and humidity	

Information for the Patient:

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 Taro-Carbamazepine:

- Carbamazepine belongs to the family of medicines called anticonvulsants for treating epilepsy. Taro-Carbamazepine is also used for treating the pain of t r i g e m i n a l neuralgia and for treating mania.
- Taro-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 you doctor before taking Taro-Carbamazepine:

- Tell about your medical conditions, especially if you have or have had any liver or kidney disease, heart disease or blood disorders.
- If you are pregnant or thinking about becoming pregnant, or if you are breast-feeding.
- Any other medicines (prescription and nonprescription) you are taking.
- Inform your doctor of your usual alcohol consumption.
- Inform your doctor of any allergies you may have.

How to take Taro-Carbamazepine:

- It is very important you take Taro-Carbamazepine exactly as your doctor instructed.
- Never increase or decrease the amount of Taro-Carbamazepine you are taking unless your doctor tells you to.
- Do not stop taking it abruptly, because your seizures may increase.

- If you miss a dose, take your Taro-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.
- Taro-Carbamazepine tablets and chewable tablets should be taken in 2 to 4 divided doses daily, with meals whenever possible. Taro-Carbamazepine CR should be swallowed unchewed with a little liquid during or after a meal.

When not to use Taro-Carbamazepine:

- If you are allergic to it or any of the components in the tablets (see list of components at the end of this leaflet).
- You have severe heart disease.
- You have had serious blood illness in the past.
- You have a disturbance in the production of porphyrin, a pigment important for liver function and blood formation.
- You are also taking drugs belonging to a special group of antidepressants called monoaminooxidase inhibitors (MAOIs).

Precautions when taking Taro-Carbamazepine:

- Call your doctor immediately if your seizures get worse.
- Contact your doctor immediately if you experience any severe, unusual or allergic reactions.

- If you experience any side effects such as drowsiness, headache, unsteadiness of the feet, double vision, dizziness, nausea or vomiting, consult your doctor.
- Do not drive a car or operate dangerous machinery until you are sure that Taro-Carbamazepine does not affect your alertness.
- Avoid alcoholic drinks when taking Taro-Carbamazepine.

What to do in case of overdose of Taro-Carbamazepine:

- Contact your doctor or nearest hospital emergency ward, even though you may not feel sick.

How to store Taro-Carbamazepine:

- Taro-Carbamazepine Tablets and CR Tablets: Store at 15 - 25 ˚C.
- Taro-Carbamazepine Chewable Tablets: Store at 15 - 30 ˚C. Protect from light.
- Protect from humidity, such as in bathrooms where you shower often.
- Keep out of reach of children.

What does Taro- Carbamazepine contain:

- Taro-Carbamazepine 200 mg Tablets: Microcrystalline Cellulose, Povidone, Sodium Lauryl Sulphate, Sodium Starch Glycolate, Magnesium Stearate
- Taro-Carbamazepine Chewable Tablets 100 & 200 mg: Eudragit RS 30D, Diethyl Phthalate, FD & C Red No.40 Lake, Microcrystalline Cellulose, Pregelatinized

Starch, Croscarmellose Sodium, Natural Cherry Flavour, Sorbitol, Magnesium Stearate

- Taro-Carbamazepine CR 200 and 400 mg Tablets: Eudragit RS30D, Diethyl Phthalate, Microcrystalline Cellulose, Lactose Monohydrate, Maize Starch, Sodium Starch Glycolate, Magnesium Stearate

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.

TARO Pharmaceuticals Inc., Canada

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 tranquillizing 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 SGPT and histological changes in the livers. At a dosage of 400 mg/kg/day, 25 of 50 animals died, beginning at the 15th week. SGPT and BUN levels were slightly increased. The relative organ/body weight ratios were increased for the hearts, livers 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 grey 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.

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