

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE-CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

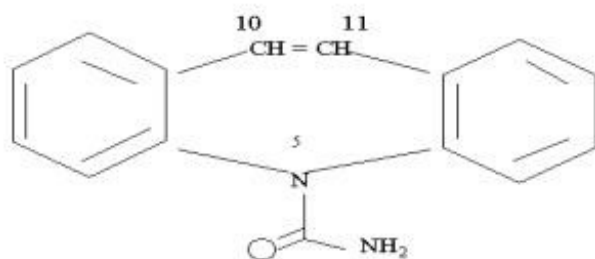
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Carbatrol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

CARBATROL* is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as 100 mg, 200 mg and 300 mg extended-release capsules of Carbamazepine, USP. Carbamazepine is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27. Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and its structural formula is:



CARBAMAZEPINE

Carbatrol is a multi-component capsule formulation consisting of three different types of beads: immediate-release beads, extended-release beads, and enteric-release beads. The three bead types are combined in a specific ratio to provide twice daily dosing of Carbatrol.

Inactive ingredients: citric acid, colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, talc, triethyl citrate and other ingredients.

CLINICAL PHARMACOLOGY

In controlled clinical trials, carbamazepine has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Carbamazepine has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Carbamazepine greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Carbamazepine is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of carbamazepine, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several *in vivo* animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of carbamazepine has not been established.

Pharmacokinetics

Carbamazepine (CBZ): Taken every 12 hours, carbamazepine extended-release capsules provide steady state plasma levels comparable to immediate-release carbamazepine tablets given every 6 hours, when administered at the same total mg daily dose.

Following a single 200 mg oral extended-release dose of carbamazepine, peak plasma concentration was $1.9 \pm 0.3 \mu\text{g/mL}$ and the time to reach the peak was 19 ± 7 hours. Following chronic administration (800 mg every 12 hours), the peak levels were $11.0 \pm 2.5 \mu\text{g/mL}$ and the time to reach the peak was 5.9 ± 1.8 hours. The pharmacokinetics of extended-release carbamazepine is linear over the single dose

range of 200-800 mg.

Carbamazepine is 76% bound to plasma proteins. Carbamazepine is primarily metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide. Since carbamazepine induces its own metabolism, the half-life is also variable. Following a single extended-release dose of carbamazepine, the average half-life range from 35-40 hours and 12-17 hours on repeated dosing. The apparent oral clearance following a single dose was 25 ± 5 mL/min and following multiple dosing was 80 ± 30 mL/min.

After oral administration of ^{14}C -carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

Carbamazepine-10,11-epoxide (CBZ-E): Carbamazepine-10,11-epoxide is considered to be an active metabolite of carbamazepine. Following a single 200 mg oral extended-release dose of carbamazepine, the peak plasma concentration of carbamazepine-10,11-epoxide was 0.11 ± 0.012 $\mu\text{g/mL}$ and the time to reach the peak was 36 ± 6 hours. Following chronic administration of a extended-release dose of carbamazepine (800 mg every 12 hours), the peak levels of carbamazepine-10,11-epoxide were 2.2 ± 0.9 $\mu\text{g/mL}$ and the time to reach the peak was 14 ± 8 hours. The plasma half-life of carbamazepine-10,11-epoxide following administration of carbamazepine is 34 ± 9 hours. Following a single oral dose of extended-release carbamazepine (200-800 mg) the AUC and C_{max} of carbamazepine-10,11-epoxide were less than 10% of carbamazepine. Following multiple dosing of extended-release carbamazepine (800-1600 mg daily for 14 days), the AUC and C_{max} of carbamazepine-10,11-epoxide were dose related, ranging from 15.7 $\mu\text{g}\cdot\text{hr/mL}$ and 1.5 $\mu\text{g/mL}$ at 800 mg/day to 32.6 $\mu\text{g}\cdot\text{hr/mL}$ and 3.2 $\mu\text{g/mL}$ at 1600 mg/day, respectively, and were less than 30% of carbamazepine. Carbamazepine-10,11-epoxide is 50% bound to plasma proteins.

Food Effect: A high fat meal diet increased the rate of absorption of a single 400 mg dose (mean T_{max} was reduced from 24 hours, in the fasting state, to 14 hours and C_{max} increased from 3.2 to 4.3 $\mu\text{g/mL}$) but not the extent (AUC) of absorption. The elimination half-life remains unchanged between fed and fasting state. The multiple dose study conducted in the fed state showed that the steady-state C_{max} values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

Special Populations

Hepatic Dysfunction: The effect of hepatic impairment on the pharmacokinetics of carbamazepine is not known. However, given that carbamazepine is primarily metabolized in the liver, it is prudent to proceed with caution in patients with hepatic dysfunction.

Renal Dysfunction: The effect of renal impairment on the pharmacokinetics of carbamazepine is not known.

Gender: No difference in the mean AUC and C_{max} of carbamazepine and carbamazepine-10,11-epoxide was found between males and females.

Age: Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide in young children than adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age.

Race: No information is available on the effect of race on the pharmacokinetics of carbamazepine.

INDICATIONS AND USAGE

Epilepsy

Carbatrol is indicated for use as an anticonvulsant drug. 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 complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvements than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by carbamazepine (see PRECAUTIONS, General).

Trigeminal Neuralgia

Carbatrol is indicated in the treatment of the pain associated with true trigeminal neuralgia. Beneficial results have also been reported in glossopharyngeal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

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

WARNINGS

Patients should be made aware that Carbatrol contains carbamazepine and should not be used in combination with any other medications containing carbamazepine.

Usage in Pregnancy

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy.

In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5-4 times the MHDD on a mg/m² basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect defects using current accepted procedures should be considered a part of routine

prenatal care in childbearing women receiving carbamazepine.

General

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with carbamazepine. These reactions have been extremely rare. However, a few fatalities have been reported.

In patients with seizure disorder, carbamazepine should not be discontinued abruptly because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered.

Co-administration of carbamazepine and delavirdine may lead to loss of virologic response and possible resistance to PRESCRIPTOR or to the class of non-nucleoside reverse transcriptase inhibitors.

PRECAUTIONS

General

Before initiating therapy, a detailed history and physical examination should be made.

Carbamazepine should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients carbamazepine has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reaction to other drugs; or interrupted courses of therapy with carbamazepine.

Information for Patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

If necessary, the Carbatrol capsules can be opened and the contents sprinkled over food, such as a teaspoon of applesauce or other similar food products. Carbatrol capsules or their contents should not be crushed or chewed.

Carbatrol may interact with some drugs. Therefore, patients should be advised to report to their doctors the use of any other prescription or non-prescription medication or herbal products.

Laboratory Tests

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Increases in total cholesterol, LDL and HDL have been observed in some patients taking anticonvulsants. Therefore, periodic evaluation of these parameters is also recommended.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with carbamazepine administered alone.

Hyponatremia has been reported in association with carbamazepine use, either alone or in combination with other drugs.

Interference with some pregnancy tests has been reported.

Drug Interactions

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to the following:

Agents Highly Bound to Plasma Protein:

Carbamazepine is not highly bound to plasma proteins; therefore, administration of Carbatrol® to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Agents that Inhibits Cytochrome P450 Isoenzymes and/or Epoxide Hydrolase:

Carbamazepine is metabolized mainly by cytochrome P450 (CYP) 3A4 to the active carbamazepine 10,11-epoxide, which is further metabolized to the trans-diol by epoxide hydrolase. Therefore, the potential exists for interaction between carbamazepine and any agent that inhibits CYP3A4 and/or epoxide hydrolase. Agents that are CYP3A4 inhibitors that have been found, or are expected, to increase plasma levels of Carbatrol® are the following:

Acetazolamide, azole antifungals, cimetidine, clarithromycin⁽¹⁾, dalfopristin, danazol, delavirdine, diltiazem, erythromycin⁽¹⁾, fluoxetine, fluvoxamine, grapefruit juice, isoniazid, itraconazole, ketoconazole, loratadine, nefazadone, niacinamide, nicotinamide, protease inhibitors, propoxyphene, quinine, quinupristin, troleandomycin, valproate⁽¹⁾, verapamil, zileuton.

⁽¹⁾also inhibits epoxide hydrolase resulting in increased levels of the active metabolite carbamazepine 10, 11- epoxide

Thus, if a patient has been titrated to a stable dosage of Carbatrol®, and then begins a course of treatment with one of these CYP3A4 or epoxide hydrolase inhibitors, it is reasonable to expect that a dose reduction for Carbatrol® may be necessary.

Agents that Induce Cytochrome P450 Isoenzymes:

Carbamazepine is metabolized by CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent that induces CYP3A4. Agents that are CYP inducers that have been found, or are expected, to decrease plasma levels of Carbatrol® are the following:

Cisplatin, doxorubicin HCL, felbamate, rifampin, phenobarbital, phenytoin⁽²⁾, primidone, methsuximide, and theophylline

⁽²⁾Phenytoin plasma levels have also been reported to increase and decrease in the presence of carbamazepine, see below.

Thus, if a patient has been titrated to a stable dosage on Carbatrol®, and then begins a course of

treatment with one of these CYP3A4 inducers, it is reasonable to expect that a dose increase for Carbatrol® may be necessary.

Agents with Decreased Levels in the Presence of Carbamazepine due to Induction of Cytochrome P450 Enzymes:

Carbamazepine is known to induce CYP1A2 and CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent metabolized by one (or more) of these enzymes. Agents that have been found, or are expected to have decreased plasma levels in the presence of Carbatrol® due to induction of CYP enzymes are the following:

Acetaminophen, alprazolam, amitriptyline, bupropion, buspirone, citalopram, clobazam, clonazepam, clozapine, cyclosporin, delavirdine, desipramine, diazepam, dicumarol, doxycycline, ethosuximide, felbamate, felodipine, glucocorticoids, haloperidol, itraconazole, lamotrigine, levothyroxine, lorazepam, methadone, midazolam, mirtazapine, nortriptyline, olanzapine, oral contraceptives⁽³⁾, oxcarbazepine, phenytoin⁽⁴⁾, praziquantel, protease inhibitors, quetiapine, risperidone, theophylline, topiramate, tiagabine, tramadol, triazolam, trazodone⁽⁵⁾, valproate, warfarin⁽⁶⁾, ziprasidone, and zonisamide.

⁽³⁾Break through bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

⁽⁴⁾Phenytoin has also been reported to increase in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels following co-medication with carbamazepine is advised.

⁽⁵⁾Following co-administration of carbamazepine 400mg/day with trazodone 100mg to 300mg daily, carbamazepine reduced trough plasma concentrations of trazodone (as well as meta-chlorophenylpiperazine [mCPP]) by 76 and 60% respectively, compared to precarbamazepine values.

⁽⁶⁾Warfarin's anticoagulant effect can be reduced in the presence of carbamazepine.

Thus, if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of treatment with Carbatrol®, it is reasonable to expect that a dose increase for the concomitant agent may be necessary.

Agents with Increased Levels in the Presence of Carbamazepine:

Carbatrol® increases the plasma levels of the following agents:

Clomipramine HCl, phenytoin⁽⁷⁾, and primidone

⁽⁷⁾Phenytoin has also been reported to decrease in the presence of carbamazepine. Careful monitoring of phenytoin plasma levels following co-medication with carbamazepine is advised.

Thus, if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of the treatment with Carbatrol®, it is reasonable to expect that a dose decrease for the concomitant agent may be necessary.

Pharmacological/Pharmacodynamic Interactions with Carbamazepine

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Given the anticonvulsant properties of carbamazepine, Carbatrol® may reduce the thyroid function as has been reported with other anticonvulsants. Additionally, anti-malarial drugs, such as chloroquine and mefloquine, may antagonize the activity of carbamazepine.

Thus if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of treatment with Carbatrol®, it is reasonable to expect that a dose adjustment may be necessary.

Because of its primary CNS effect, caution should be used when Carbatrol® is taken with other centrally acting drugs and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of carbamazepine to Sprague-Dawley rats for two years in the diet at doses of 25, 75,

and 250 mg/kg/day (low dose approximately 0.2 times the maximum human daily dose of 1200 mg on a mg/m² basis), resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of 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.

Usage in Pregnancy

Pregnancy Category D (See WARNINGS)

Labor and Delivery

The effect of carbamazepine on human labor and delivery is unknown.

Nursing Mothers

Carbamazepine and its epoxide metabolite are transferred to breast milk and during lactation. The concentrations of carbamazepine and its epoxide metabolite are approximately 50% of the maternal plasma concentration. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Substantial evidence of carbamazepine effectiveness for use in the management of children with epilepsy (see INDICATIONS for specific seizure types) is derived from clinical investigations performed in adults and from studies in several *in vitro* systems which support the conclusion that (1) the pathogenic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children.

Taken as a whole, this information supports a conclusion that the generally acceptable therapeutic range of total carbamazepine in plasma (i.e., 4-12 µg/mL) is the same in children and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months. No longer term data from clinical trials is available.

Geriatric Use

No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

General: If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive patient with epilepsy may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions previously observed with carbamazepine were reported in the hemopoietic system (see BOX WARNING), the skin, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.

The following additional adverse reactions were previously reported with carbamazepine:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of

disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy. Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving carbamazepine orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg/day and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills, inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion have been reported in association with carbamazepine use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with carbamazepine, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD₅₀ in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920. Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention

Laboratory Findings: Isolated instances of overdose have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. ECG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with carbamazepine may be aggravated or modified.

Treatment

For the most up to date information on management of carbamazepine overdose, please contact the poison center for your area by calling 1-800-222-1222. The prognosis in cases of carbamazepine poisoning is generally favorable. Of 5,645 cases of carbamazepine exposures reported to US poison centers in 2002, a total of 8 deaths (0.14% mortality rate) occurred. Over 39% of the cases reported to these poison centers were managed safely at home with conservative care. Successful management of large or intentional carbamazepine exposures requires implementation of supportive care, frequent monitoring of serum drug concentrations, as well as aggressive but appropriate gastric decontamination.

Elimination of the Drug: The primary method for gastric decontamination of carbamazepine overdose is use of activated charcoal. For substantial recent ingestions, gastric lavage may also be considered. Administration of activated charcoal prior to hospital assessment has the potential to significantly reduce drug absorption. There is no specific antidote. In overdose, absorption of carbamazepine may be prolonged and delayed. More than one dose of activated charcoal may be beneficial in patients that have evidence of continued absorption (e.g., rising serum carbamazepine levels).

Measures to Accelerate Elimination:

The data on use of dialysis to enhance elimination in carbamazepine is scarce. Dialysis, particularly high flux or high efficiency hemodialysis, may be considered in patients with severe carbamazepine poisoning associated with renal failure or in cases of status epilepticus, or where there are rising serum drug levels and worsening clinical status despite appropriate supportive care and gastric decontamination. For severe cases of carbamazepine overdose unresponsive to other measures, charcoal hemoperfusion may be used to enhance drug clearance.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within 1 week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet, and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2)⁵⁹Fe-ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A₂ and F hemoglobin, and (7) serum folic acid and B₁₂ levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patients. A low initial daily dosage with gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. The Carbatrol capsules may be opened and the beads sprinkled over food, such as a teaspoon of applesauce or other similar food products if this method of administration is preferred. Carbatrol capsules or their contents should not be crushed or chewed. Carbatrol can be taken with or without meals.

Carbatrol is an extended-release formulation for twice a day administration. When converting patients from immediate release carbamazepine to Carbatrol extended-release capsules, the same total daily mg dose of carbamazepine should be administered.

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age. Initial: 200 mg twice daily. Increase at weekly intervals by adding up to 200 mg/day until the optimal response is obtained. Dosage generally should not exceed 1000 mg per day in children 12-15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults. **Maintenance:** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children under 12 years of age: Children taking total daily dosages of immediate-release carbamazepine of 400 mg or greater may be converted to the same total daily dosage of Carbatrol extended-release capsules, using a twice daily regimen. Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of Carbatrol for use at doses above 35 mg/kg/24 hours can be made.

Combination Therapy: Carbatrol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see

PRECAUTIONS, Drug Interactions, and Pregnancy Category D).
Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, start with one 200 mg capsule. This daily dose may be increased by up to 200 mg/day every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily.

Maintenance: Control of pain can be maintained in most patients with 400-800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Carbatrol (carbamazepine) extended-release capsules is supplied in three dosage strengths. 300 mg-Two-piece hard gelatin capsule (black opaque body with bluish green opaque cap) printed with the Shire logo in white ink.

Supplied in bottles of 120NDC 54868-5432-0

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature]. PROTECT FROM LIGHT AND MOISTURE.

Manufactured for:

Shire US Inc.

725 Chesterbrook Blvd, Wayne PA 19087

1-800-828-2088, Made in U.S.A. © 2011 Shire US Inc.

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Physicians Total Care, Inc.
Tulsa, OK 74146

Medication Guide
CARBATROL (CAR-BA-TROL)
(carbamazepine)
Extended-Release Capsules

Read this Medication Guide before you start taking CARBATROL and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about CARBATROL?

Do not stop taking CARBATROL without first talking to your healthcare provider.

Stopping CARBATROL suddenly can cause serious problems.

CARBATROL can cause serious side effects, including:

1. CARBATROL may cause rare but serious rashes that may lead to death. These serious skin reactions are more likely to happen within the first four months of CARBATROL treatment but

may occur at later times. These reactions can happen in anyone, but are more likely in people of Asian descent. If you are of Asian descent you may need a genetic blood test before you take CARBATROL to see if you are at a higher risk for serious skin reactions with this medicine.

Symptoms may include:

- skin rash
- hives
- sores in your mouth
- blistering or peeling of the skin

2. CARBATROL may cause rare but serious blood problems. Symptoms may include:

- fever, sore throat or other infections that come and go or do not go away
- easy bruising
- red or purple spots on your body
- bleeding gums or nose bleeds
- severe fatigue or weakness

3. Like other antiepileptic drugs, CARBATROL may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempt to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop CARBATROL without first talking to a healthcare provider.

Stopping CARBATROL suddenly can cause serious problems.

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

What is CARBATROL?

CARBATROL is a medicine used to treat:

- certain types of seizures (partial, tonic-clonic, mixed)
- certain types of nerve pain (trigeminal and glossopharyngeal neuralgia).

CARBATROL is not a regular pain medicine and should not be used for aches or pains.

Who should not take CARBATROL?

Do not take CARBATROL if you:

- have a history of bone marrow depression
- are allergic to carbamazepine or any of the ingredients in CARBATROL. See the end of this Medication Guide for a complete list of ingredients in CARBATROL.
- take nefazodone
- are allergic to antidepressant medications called tricyclic (TCAs).
- have taken a medicine called Monoamine Oxidase Inhibitor (MAOI) in the last 14 days.

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

What should I tell my healthcare provider before taking CARBATROL?

Before you take CARBATROL, tell your healthcare provider if you:

- have or ever had heart problems
- have or ever had blood problems
- have or ever had liver or kidney problems
- have or ever had allergic reactions to medicines
- have or ever had increased pressure in your eye
- have or have had suicidal thoughts or actions, depression or mood problems
- have any other medical conditions
- drink grapefruit juice or eat grapefruit
- use birth control. CARBATROL may make your birth control less effective. Tell your healthcare provider if your menstrual bleeding changes while you take birth control and CARBATROL.
- are pregnant or plan to become pregnant. CARBATROL may harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking CARBATROL. You and your healthcare provider should decide if you should take CARBATROL while you are pregnant.

- If you become pregnant while taking CARBATROL, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy. You can enroll in this registry by calling 1-888-233-2334.

- are breastfeeding or plan to breastfeed. CARBATROL passes into your breast milk. You and your healthcare provider should discuss whether you should take CARBATROL or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Taking CARBATROL with certain other medicines can cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take CARBATROL?

- Take CARBATROL exactly as prescribed. Your doctor will tell you how much CARBATROL to take.
- Your healthcare provider may change your dose. Do not change your dose of CARBATROL without talking to your healthcare provider.
- Do not stop taking CARBATROL without first talking to your healthcare provider. Stopping CARBATROL suddenly can cause serious problems. Stopping seizure medicine suddenly in a patient who has epilepsy can cause seizures that will not stop (status epilepticus).
- Take CARBATROL with or without food.

- **Do not crush, chew, or break** CARBATROL capsules or the beads inside of the capsules. But, CARBATROL capsules can be opened and sprinkled over food such as a teaspoon of applesauce. Tell your healthcare provider if you can not swallow CARBATROL whole.
- If you take too much CARBATROL, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking CARBATROL?

- Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking CARBATROL until you talk to your healthcare provider. CARBATROL taken with alcohol or drugs may make your sleepiness or dizziness worse.
- Do not drive, or operate heavy machinery, or do other dangerous activities until you know how CARBATROL affects you. CARBATROL can slow your thinking and motor skills.

What are the possible side effects of CARBATROL?

See "**What is the most important information I should know about CARBATROL?**"

CARBATROL may cause other serious side effects including:

Irregular heartbeat - symptoms include:

- Fast, slow, or pounding heartbeat
- Shortness of breath
- Feeling lightheaded
- Fainting

Liver problems - symptoms include:

- yellowing of your skin or the whites of your eyes
- dark urine
- pain on the right side of your stomach area (abdominal pain)
- easy bruising
- loss of appetite
- nausea or vomiting

Get medical help right away if you have any of the symptoms listed above or listed in "**What is the most important information I should know about CARBATROL**".

The most common side effects of CARBATROL include:

- dizziness
- drowsiness
- problems with walking and coordination (unsteadiness)
- nausea
- vomiting

These are not all the side effects of CARBATROL. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you, or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CARBATROL?

- Store CARBATROL between 59°F to 86°F (15°C to 30°C).
- Keep CARBATROL out of the light.
- Keep CARBATROL capsules dry.

Keep CARBATROL and all medicines out of the reach of children.

General information about CARBATROL

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CARBATROL for a condition for which it was not prescribed. Do not give CARBATROL to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about CARBATROL. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about CARBATROL that is written for health professionals.

For more information go to www.carbatrol.com or call 1-800-828-2088.

What are the ingredients in CARBATROL?

Active ingredient: carbamazepine

Inactive ingredients: citric acid, colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, talc, triethyl citrate and Eudragit.

In addition:

- the 100 mg capsules contain gelatin-NF, FD&C Blue #2, Yellow Iron Oxide, and titanium dioxide and are imprinted with white ink
- the 200 mg capsules contain gelatin-NF, FD&C Red #3, FD&C Yellow #6, Yellow Iron Oxide, FD&C Blue #2, and titanium dioxide, and are imprinted with white ink
- the 300 mg capsules contain gelatin-NF, FD&C Blue #2, FD&C Yellow #6, Red Iron Oxide, Yellow Iron Oxide, and titanium dioxide, and are imprinted with white ink

This Medication Guide has been approved by the US Food and Drug Administration.

Shire US Inc.

Wayne, PA 19087

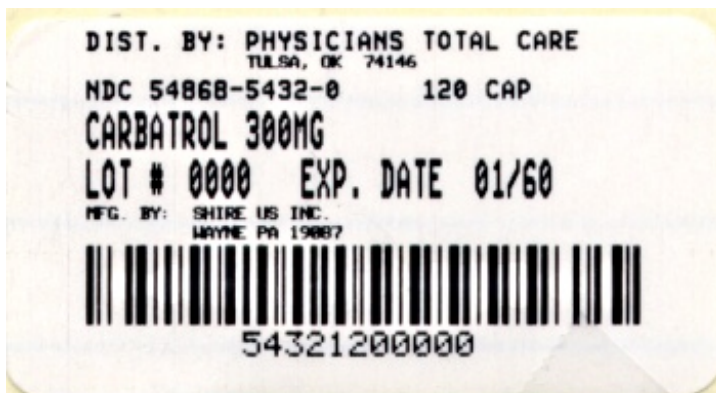
Issued [01/2011]

PRINCIPAL DISPLAY PANEL

CARBATROL (CAR-BA-TROL)

(carbamazepine)

300 mg



CARBATROL

carbamazepine capsule, extended release

Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-5432(NDC:54092-173)	
Route of Administration	ORAL			
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
CARBAMAZEPINE (UNII: 33CM23913M) (CARBAMAZEPINE - UNII:33CM23913M)		CARBAMAZEPINE	300 mg	
Inactive Ingredients				
Ingredient Name			Strength	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)				
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)				
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)				
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)				
POLYETHYLENE GLYCOL (UNII: 3WJQ0SDW1A)				
POVIDONE (UNII: FZ989GH94E)				
SODIUM LAURYL SULFATE (UNII: 368GB5141J)				
TALC (UNII: 7SEV7J4R1U)				
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)				
GELATIN (UNII: 2G86QN327L)				
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)				
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)				
FERRIC OXIDE RED (UNII: 1K09F3G675)				
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)				
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)				
Product Characteristics				
Color	black (BLACK) , green (GREEN)	Score	no score	
Shape	CAPSULE (CAPSULE)	Size	22mm	
Flavor		Imprint Code		
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-5432-0	120 in 1 BOTTLE		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA020712	10/15/2009		

Establishment

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	relabel

Revised: 3/2012

Physicians Total Care, Inc.