Prescribing Information

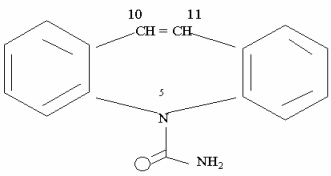
EQUETRO™
Rx only
(carbamazepine) extended release capsules
100 mg, 200 mg and 300 mg

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 EQUETRO™, 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

EQUETRO™ is 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

EQUETRO™ 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 EQUETRO™.

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

The 100 mg capsule shells contain gelatin-NF, FD&C Blue #2, Yellow Iron Oxide, Titanium Dioxide and are imprinted with white ink; the 200 mg capsule shells contain gelatin-NF, Yellow Iron Oxide, FD&C Blue #2, and Titanium Dioxide, and are imprinted with white ink; and the 300 mg capsule shells contain gelatin-NF, FD&C Blue #2, Yellow Iron Oxide, and Titanium Dioxide, and are imprinted with white ink.

CLINICAL PHARMACOLOGY

In controlled clinical trials, carbamazepine has been shown to be effective in the treatment of Bipolar I Disorder.

Mechanism of Action

The mechanism(s) of action of carbamazepine in the treatment of bipolar disorder has not been elucidated. Although numerous pharmacological effects of carbamazepine have been described in the published literature (e.g., modulation of ion channels [sodium and calcium], receptor-mediated neurotransmission [GABAergic, glutamatergic, and monoaminergic], and intracellular signaling pathways in experimental preparations), the contribution of these effects to the efficacy of carbamazepine in bipolar disorder is unknown.

Pharmacokinetics

Carbamazepine (CBZ):

Following a single 200 mg oral extended-release dose of carbamazepine, peak plasma concentration was 1.9 ± 0.3 µg/mL and the time to reach the peak was 19 ± 7 hours. Following repeat dose administration (800 mg every 12 hours), the peak levels were 11.0 ± 2.5 µg/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 ranged from 35-40 hours and 12-17 hours following 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 µg/mL and the time to reach the peak was 36 ± 6 hours. Following chronic administration of an extended-release dose of carbamazepine (800 mg every 12 hours), the peak levels of carbamazepine-10,11-epoxide were 2.2 ± 0.9 µg/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 Cmax 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 µg.hr/mL and 1.5 µg/mL at 800 mg/day to 32.6 µg.hr/mL and 3.2 µg/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 µg/mL) but not the extent (AUC) of absorption. The elimination half-life remained 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. The safety and effectiveness of EQUETRO in pediatric and adolescent patients have not been established.

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

CLINICAL STUDIES

The effectiveness of EQUETRO™ in the acute treatment of manic and mixed symptoms in patients with Bipolar I Disorder was established in 2 (3 week) multicenter, randomized, double-blind, flexible dose, placebo controlled studies in adult patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episode. In both studies, patients were titrated to a dose range from 400 mg/day to 1600 mg/day, given in divided doses, twice daily. The mean carbamazepine ER dose during the last week was 952 mg/day in the first study, and 726 mg/day in the second.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the YMRS total score.

EQUETRO™ was significantly more effective than placebo in reduction of the YMRS total score for both studies.

INDICATIONS AND USAGE

EQUETRO™ is indicated for the treatment of acute manic and mixed episodes associated with Bipolar I Disorder.

A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. A mixed episode is characterized by the criteria for a manic episode in conjunction with those for a major depressive episode (depressed mood, loss of interest or pleasure in nearly all activities).

The efficacy of EQUETRO™ in acute mania was established in 2 placebo-controlled, double-blind, 3-week studies in patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode (see **CLINICAL PHARMACOLOGY**).

The effectiveness of EQUETRO™ for longer-term use and for prophylactic use in mania has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use EQUETRO™ for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

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 EQUETRO™ 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 a human daily dosage of 1200 mg on a mg/kg basis or 1.5-4 times the human daily dosage on a mg/m^2 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.

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 RESCRIPTOR or to the class of non-nucleoside reverse transcriptase inhibitors.

PRECAUTIONS

General

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

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.

Suicide: The possibility of suicide attempt is inherent in Bipolar Disorder and close supervision of high risk patients should accompany drug therapy. Prescriptions for EQUETRO™ should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

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

EQUETRO™ 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) may be useful for verification of drug compliance, assessing safety and determining the cause of toxicity including 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 EQUETRO™ to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

Agents that Inhibit 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 EQUETRO™ are the following:

Acetazolamide, azole antifungals, cimetidine, clarithromycin[(1)], dalfopristin, danazol, delavirdine, diltiazem, erythromycin[(1)], fluoxetine, fluvoxamine, grapefruit juice, isoniazid, itraconazole, ketoconazole, loratadine, nefazodone, 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 EQUETRO™, 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 EQUETRO™ 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 EQUETRO™ 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 EQUETRO™, and then begins a course of treatment with one of these CYP3A4 inducers, it is reasonable to expect that a dose increase for EQUETRO™ 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 EQUETRO™ 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, valproate, warfarin[5], 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]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 EQUETRO™, 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:
EQUETRO™ increases the plasma levels of the following agents:

Clomipramine HCl, Phenytoin[6], and primidone

[6]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 EQUETRO™, 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, EQUETRO™ 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 EQUETRO™, it is reasonable to expect that a dose adjustment may be necessary.

Because of its primary CNS effect, caution should be used when EQUETRO™ 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 human daily dose of 1200 mg on a mg/m^2 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. 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
The safety and effectiveness of EQUETRO in pediatric and adolescent patients have not been established.

Geriatric Use
No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS
General:
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 most commonly observed adverse experiences (5% and at least twice placebo) seen in association with the use of EQUETRO™ (400 to 1600 mg/day, dose adjusted in 200mg daily increments in week 1 in Bipolar I Disorder in the double-blind, placebo-controlled trials of 3 weeks' duration are included in Table 3 below:

Table 3. Most Common Adverse Events Reported in Double-Blind, Placebo Controlled Trials
(Incidence >=5% and at least twice Placebo)

Adverse Events	EQUETRO™ (N = 251)	Placebo (N = 248)
DIZZINESS	44%	12%
SOMNOLENCE	32%	13%
NAUSEA	29%	10%
VOMITING	18%	3%
ATAXIA	15%	0%
PRURITUS	8%	2%
DRY MOUTH	8%	3%
AMBLYOPIA*	6%	2%
SPEECH DISORDER	6%	0%

* reported as blurred vision

EQUETRO™ and placebo-treated patients from the two double-blind, placebo-controlled studies were enrolled in a 6-month open-label study. The table below summarizes the most common adverse events with an incidence of 5% or more.

Table 4. Most Common Adverse Events Reported in Open Label
(Incidence >=5%)

Body As A Whole	**% events reported**
Headache	22%
Infection	12%
Pain	12%
Asthenia	8%
Accidental Injury	7%
Chest Pain	5%
Back Pain	5%
Digestive	
Diarrhea	10%
Dyspepsia	10%
Nausea	10%
Constipation	5%
Nervous System	

Dizziness	16%
Somnolence	12%
Amnesia^	8%
Anxiety	7%
Depression*	7%
Manic Depressive Reaction	7%
Ataxia	5%
Skin Appendages	
Rash	13%
Pruritis	5%

^Amnesia includes poor memory, forgetful and memory disturbance
*Depression includes suicidal ideation

Other significant adverse events seen in less than 5% of patients include:

Suicide Attempt, Manic Reaction, Insomnia, Nervousness, Depersonalization and Extrapyramidal Symptoms

Infections (Fungal, Viral, Bacterial), Pharyngitis, Rhinitis, Sinusitis, Bronchitis, Urinary Tract Infection, Leukopenia and Lymphadenopathy

Liver Function Tests Abnormal, Edema, Peripheral Edema, Allergic Reaction, Photosensitivity Reaction, Alopecia, Diplopia and Ear Pain

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 LD_{50} 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 overdosage have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. EEG 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) ^{59}Fe-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 A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

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

DOSAGE AND ADMINISTRATION

The recommended initial dose of EQUETRO™ is 400 mg/day given in divided doses, twice daily. The dose should be adjusted in 200 mg daily increments to achieve optimal clinical response. Doses higher than 1600mg/day have not been studied.
Monitoring of blood levels (see PRECAUTIONS), Laboratory Tests may be useful for verification of drug compliance, assessing safety and determining the cause of toxicity including when more than one medication is being used.
The EQUETRO™ 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. EQUETRO™ capsules or their contents should not be crushed or chewed. EQUETRO™ can be taken with or without meals.

HOW SUPPLIED

EQUETRO™ (carbamazepine) extended-release capsules is supplied in three dosage strengths.

100 mg -Two-piece hard gelatin capsule yellow opaque cap with bluish green opaque body printed with the Shire logo on the cap, SPD417 and 100 mg on the body in white ink

Supplied in bottles of 120 NDC 54092-419-12

200 mg-Two-piece hard gelatin capsule yellow opaque cap with blue opaque body printed with the Shire logo on the cap and SPD417 and 200 mg on the body in white ink

Supplied in bottles of 120 ..... NDC 54092-421-12

300 mg-Two-piece hard gelatin capsule yellow opaque cap with blue body printed with the Shire logo on the cap and SPD417 and 300 mg on the body in white ink

Supplied in bottles of 120 ..... NDC 54092-423-12

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

Manufactured for:
Shire US Inc.
One River Front Place, Newport, KY 41071
1-800-828-2088, Made in U.S.A.

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