TARO
Taro Pharmaceuticals U.S.A., Inc.

February 28, 2003

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned submits this petition pursuant to section 505 (j) (2) (c) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Parts 314.55 (d) (2) and 10.30 of the Food and Drug Administration's regulations, to request the Commissioner of the Food and Drug Administration to make a determination of ANDA suitability for Carbamazepine Tablets, 100 mg, 300 mg and 400 mg based on the reference-listed drug, Tegretol Tablets, 200 mg of Novartis Pharmaceuticals Corporation. [See Exhibit 1]

A. Action Requested

The petitioner requests the Commissioner of the Food, and Drug Administration for a change to a listed drug to allow the undersigned to submit an Abbreviated New Drug Application for Carbamazepine Tablets, 100 mg, 300 mg and 400 mg. The reference-listed drug is Tegretol Tablets, 200 mg manufactured by Novartis Pharmaceuticals Corporation. The safety of the proposed strengths will be supported by a bioequivalence study conducted comparing the reference Tegretol Tablets, 200 mg of Norvatis and Carbamazepine Tablets, 400 mg by Taro. In the study, 1 x 400-mg tablet will be dosed on healthy adult male subjects (as the Carbamazepine Tablets, 100 mg, 300 mg and 400 mg will be dose proportional, a bioequivalence study on the highest strength, 400 mg will cover the lower strengths 100 mg and 300 mg tablets). Furthermore, safety is supported by the fact that single or multiple tablets of 200 mg are the routine oral dosage strength of this product. Also, this product is dose proportional to Taro's Carbamazepine Tablets USP, 200 mg for which an ANDA (76-525) was submitted on October 31,2002.

03P-0083

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B. Statement of Grounds

Carbamazepine dosage should be adjusted to the needs of the individual patients. Carbamazepine Tablets are approved for use at daily doses up to 1200 mg per day, with a usual maintenance dose of 400 mg per day. Because of the unique pharmacokinetic properties and potential severity of the side effects if patients are improperly monitored, Carbamazepine should be administered at the lowest effective dosage and should be closely monitored by the physicians. The availability of 100 mg, 300 mg and 400 mg tablets will provide the physicians with greater flexibility in prescribing the drug, as well as enabling the patients to take dose appropriate tablets, which will improve patient compliance.

The proposed Carbamazepine Tablets, 100 mg, 300 mg and 400 mg will be the same as the reference-listed product, Tegretol Tablets, 200 mg of Novartis Pharmaceuticals Corporation in respect of:

- Active ingredient, Carbamazepine USP
- Indications
- Dosing regimen
- Bioequivalence: the proposed strengths, 100 mg, 300 mg and 400 mg will be dose proportional to Taro's 200 mg potency which was filed on October 31, 2002, ANDA 76-525. A bioequivalence study will be conducted comparing Taro's Carbamazepine Tablets, 400 mg tablets to the reference-listed product, Tegretol Tablets, 200 mg of Novartis Pharmaceuticals Corporation. Bioequivalence studies under fast condition was also conducted on Taro's 200 mg by comparing to the reference Tegretol Tablets, 200 mg, and submitted on October 31, 2002 (ANDA 76-525). *In-Vitro* dissolution profiles and assay will also be conducted on Taro's Carbamazepine Tablets, 100 mg and 300 mg by comparing them to Taro's 400 mg.

Copies of the approved labeling for Tegretol Tablets, 200 mg of Novartis Pharmaceuticals Corporation [see Exhibit 1]. The proposed labeling for Taro's Carbamazepine Tablets 100 mg, 200 mg, 300 mg and 400 mg with highlighting of the changes is provided [see Exhibit 2].

C. Environmental Impact

The undersigned, hereby requests a categorical exclusion under 21 CFR 25.24 (c) (1). The proposed drug product will not be administered at higher dosage levels, for longer duration, or for different indications than for the reference-listed product.

D. Economic Impact

This information will be submitted on request of the Commissioner.

E. Advantages

The proposed Carbamazepine Tablets, 100 mg, 300 mg and 400 mg will provide the physicians a greater flexibility in prescribing the drug.

F. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

A. Yacobi

Avraham Yacobi, Ph.D.
President, Taro Research Institute

Exhibit 1

Tegretol Tablets, 200 mg

Approved Package Insert

89007002

NOVARTIS

T2000-04
89007002

Tegretol®

carbamazepine USP

Chewable Tablets of 100 mg - red-speckled, pink
Tablets of 200 mg - pink
Suspension of 100 mg/5 mL

Tegretol®-XR

(carbamazepine extended-release tablets)
100 mg, 200 mg, 400 mg

Rx only

Prescribing Information

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. 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.

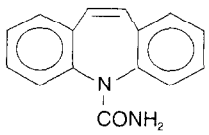
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE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

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, XR tablets of 100, 200, and 400 mg, and as a suspension of 100 mg/5 mL (teaspoon). Its chemical name is 5*H*-dibenz[*b,f*]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients: Tablets: Colloidal silicon dioxide, D&C Red No. 30 Aluminum Lake (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Suspension: Citric acid, FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum. Tegretol-XR tablets: cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200-mg tablets only).

CLINICAL PHARMACOLOGY

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

Mechanism of Action

Tegretol 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. Tegretol 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. Tegretol 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 Tegretol, 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 Tegretol has not been established.

Pharmacokinetics

In clinical studies, Tegretol suspension, conventional tablets, and XR tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the XR tablet slightly slower, than the conventional tablet. The bioavailability of the XR tablet was 89% compared to suspension. Following a b.i.d. dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Following a b.i.d. dosage regimen, Tegretol-XR tablets afford steady-state plasma levels comparable to conventional Tegretol tablets given q.i.d., when administered at the same total mg daily dose. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 µg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 µg/mL. In polytherapy, the concentration of Tegretol and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see PRECAUTIONS, Drug Interactions). Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4-5 hours after administration of conventional Tegretol tablets, and 3-12 hours after administration of Tegretol-XR tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound Tegretol in serum. Because Tegretol induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3-5 weeks of a fixed dosing regimen. Initial half-life values range from 25-65 hours, decreasing to 12-17 hours on repeated doses. Tegretol is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from Tegretol. 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 Tegretol.

The pharmacokinetic parameters of Tegretol disposition are similar in children and in adults. However, there is a poor correlation between plasma concentrations of carbamazepine and Tegretol dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide (a metabolite shown to be equipotent to carbamazepine as an anticonvulsant in animal screens) in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10-15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated.

INDICATIONS AND USAGE

Epilepsy

Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol 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 improvement 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 Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia

Tegretol 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

Tegretol 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, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

WARNINGS

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 Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol 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 borne in mind.

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. In treating or counseling women of childbearing potential, the prescribing physician will wish to weigh the benefits of therapy against the risks. 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. Therefore, if therapy is to be continued, monotherapy may be preferable for pregnant women.

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/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

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 currently accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal Tegretol and other concomitant anticonvulsant drug use A few cases of neonatal vomiting, diarrhea, and/or decreased feeding have also been reported in association with maternal Tegretol use These symptoms may represent a neonatal withdrawal syndrome

PRECAUTIONS

General

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

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol 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 or hypersensitivity reaction to other drugs, including reactions to other anticonvulsants, or interrupted courses of therapy with Tegretol

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure have been reported (see ADVERSE REACTIONS and PRECAUTIONS, Laboratory Tests) In some cases, hepatic effects may progress despite discontinuation of the drug

Multi-organ hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases (see ADVERSE REACTIONS, Other and PRECAUTIONS, Information for Patients)

Discontinuation of carbamazepine should be considered if any evidence of hypersensitivity develops

Hypersensitivity reactions to carbamazepine have been reported in patients who previously experienced this reaction to anticonvulsants including phenytoin and phenobarbital A history of hypersensitivity reactions should be obtained for a patient and the immediate family members If positive, caution should be used in prescribing carbamazepine

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION)

Information for Patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, as well as dermatologic hypersensitivity or hepatic reactions These symptoms may include but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting or jaundice The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use

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

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 (see PRECAUTIONS General and ADVERSE REACTIONS) Carbamazepine should be discontinued, based on clinical judgment if indicated by newly occurring or worsening clinical or laboratory evidence of liver dysfunction or hepatic damage, or in the case of 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

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 Tegretol administered alone

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

Interference with some pregnancy tests has been reported

Drug Interactions

There has been a report of a patient who passed an orange rubbery precipitate in his stool the day after ingesting Tegretol suspension immediately followed by Thorazine® solution Subsequent testing has shown that mixing Tegretol suspension and chlorpromazine solution (both generic and brand name) as well as Tegretol suspension and liquid Mellaril® resulted in the occurrence of this precipitate Because the extent to which this occurs with other liquid medications is not known, Tegretol suspension should not be administered simultaneously with other liquid medicinal agents or diluents (see DOSAGE AND ADMINISTRATION)

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

Agents That May Affect Tegretol Plasma Levels

CYP 3A4 inhibitors inhibit Tegretol metabolism and can thus increase plasma carbamazepine levels Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include

cimetidine, danazol, diltiazem, macrolides erythromycin, troleandomycin, clarithromycin, fluoxetine, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketaconazole, itraconazole, verapamil, valproate *

CYP 3A4 inducers can increase the rate of Tegretol metabolism Drugs that have been shown, or that would be expected, to decrease plasma carbamazepine levels include

cisplatin, doxorubicin HCl, felbamate,† rifampin, phenobarbital, phenytoin, primidone, theophylline

*increased levels of the active 10,11-epoxide

†decreased levels of carbamazepine and increased levels of the 10,11-epoxide

Effect of Tegretol on Plasma Levels of Concomitant Agents

Increased levels clomipramine HCl, phenytoin, primidone

Tegretol induces hepatic CYP activity Tegretol causes, or would be expected to cause, decreased levels of the following

acetaminophen, alprazolam, clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, lamotrigine, methsuximide, oral contraceptives, phensuximide, phenytoin, theophylline, tiagabine, topiramate, valproate, warfarin

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

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications

Breakthrough bleeding has been reported among patients receiving concomitant oral and subdermal implant contraceptives and their reliability may be adversely affected

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carbamazepine, when administered to Sprague-Dawley rats for two 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 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 Tegretol on human labor and delivery is unknown

Nursing Mothers

Tegretol and its epoxide metabolite are transferred to breast milk The ratio of the concentration in breast milk to that in maternal plasma is about 0 4 for Tegretol and about 0 5 for the epoxide The estimated doses given to the newborn during breast feeding are in the range of 2-5 mg daily for Tegretol and 1-2 mg daily for the epoxide

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 Tegretol's 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 pathogenetic 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 accepted therapeutic range of total carbamazepine in plasma (i e 4-12 mcg/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

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 epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin liver and the cardiovascular system

The most frequently observed adverse reactions particularly during the initial phases of therapy are dizziness drowsiness, unsteadiness, nausea and vomiting

Tegretol® carbamazepine USP
Tegretol®-XR (carbamazepine extended-release tablets)

To minimize the possibility of such reactions therapy should be initiated at the low dosage recommended

The following additional adverse reactions have been reported

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, very rare cases of hepatic failure

Pancreatic: Pancreatitis

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 Tegretol orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day Additionally, rats receiving Tegretol 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 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 sydrome has been reported Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests) Decreased levels of plasma calcium have been reported

Other. Multi-organ hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases Signs or symptoms may include, but are not limited to fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests These signs and symptoms may occur in various combinations and not necessarily concurrently Signs and symptoms may initially be mild Various organs, including but not limited to, liver, skin, immune system, lungs, kidneys, pancreas, myocardium, and colon may be affected (see PRECAUTIONS, General and PRECAUTIONS, Information for Patients)

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 dicarbamazepine

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose adults 3 2 g (a 24-year-old woman died of a cardiac arrest and a 24-year-old man died of pneumonia and hypoxic encephalopathy), children, 4 g (a 14-year-old girl died of a cardiac arrest), 1 6 g (a 3-year-old girl died of aspiration pneumonia)

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 Tegretol may be aggravated or modified

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded There is no specific antidote

Elimination of the Drug Induction of vomiting

Gastric lavage Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol

Measures to Reduce Absorption: Activated charcoal, laxatives

Measures to Accelerate Elimination: Forced diuresis

Dialysis is indicated only in severe poisoning associated with renal failure Replacement transfusion is indicated in severe poisoning in small children

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 (see table below)

Tegretol suspension in combination with liquid chlorpromazine or thioridazine results in precipitate formation, and in the case of chlorpromazine, there has been a report of a patient passing an orange rubbery precipitate in the stool following coadministration of the two drugs (see Drug Interactions) Because the extent to which this occurs with other liquid medications is not known, Tegretol suspension should not be administered simultaneously with other liquid medications or diluents

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 patient A low initial daily dosage with a gradual increase is advised As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level Medication should be taken with meals

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years 1/2 teaspoon q i d) and to increase slowly to avoid unwanted side effects

Conversion of patients from oral Tegretol tablets to Tegretol suspension Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i e , b i d tablets to t i d suspension)

Tegretol-XR is an extended-release formulation for twice-a-day administration When converting patients from Tegretol conventional tablets to Tegretol-XR, the same total daily mg dose of Tegretol-XR should be administered **Tegretol-XR tablets must be swallowed whole and never crushed or chewed** Tegretol-XR tablets should be inspected for chips or cracks Damaged tablets or tablets without a release portal should not be consumed Tegretol-XR tablet coating is not absorbed and is excreted in the feces, these coatings may be noticeable in the stool

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age - Initial Either 200 mg b i d for tablets and XR tablets, or 1 teaspoon q i d for suspension (400 mg/day) Increase at weekly intervals by adding up to 200 mg/day using a b i d regimen of Tegretol-XR or a t i d or q i d regimen of the other formulations until the optimal response is obtained Dosage generally should not exceed 1000 mg daily 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 in rare instances

Maintenance Adjust dosage to the minimum effective level, usually 800-1200 mg daily

Children 6-12 years of age - Initial: Either 100 mg b i d for tablets or XR tablets or 1/2 teaspoon q i d for suspension (200 mg/day) Increase at weekly intervals by adding up to 100 mg/day using a b i d regimen of Tegretol-XR or a t i d or q i d regimen of the other formulations until the optimal response is obtained Dosage generally should not exceed 1000 mg daily ***Maintenance:*** Adjust dosage to the minimum effective level usually 400-800 mg daily

Children under 6 years of age - Initial: 10-20 mg/kg/day b i d or t i d as tablets or q i d as suspension Increase weekly to achieve optimal clinical response administered t i d or q i d ***Maintenance*** 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 carbamazepine for use at doses above 35 mg/kg/24 hours can be made

Combination Therapy: Tegretol 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, either 100 mg b i d for tablets or XR tablets, or 1/2 teaspoon q i d for suspension, for a total daily dose of 200 mg This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours for tablets or XR tablets, or 50 mg (1/2 teaspoon) q i d for suspension, 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

Chewable Tablets 100 mg - round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100 . NDC 0083-0052-30
Unit Dose (blister pack)
Box of 100 (strips of 10) . . NDC 0083-0052-32

Do not store above 30°C (86°F) *Protect from light and moisture Dispense in tight, light-resistant container (USP)*

Tablets 200 mg - capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

Bottles of 100 NDC 0083-0027-30
Bottles of 1000 NDC 0083-0027-40
Unit Dose (blister pack)
Box of 100 (strips of 10) NDC 0083-0027-32

Do not store above 30°C (86°F) *Protect from moisture Dispense in tight container (USP)*

XR Tablets 100 mg - round, yellow, coated (imprinted T on one side and 100 mg on the other), release portal on one side

Bottles of 100 . . NDC 0083-0061-30
Unit Dose (blister pack)
Box of 100 (strips of 10) NDC 0083-0061-32

XR Tablets 200 mg - round, pink, coated (imprinted T on one side and 200 mg on the other), release portal on one side

Bottles of 100 NDC 0083-0062-30
Unit Dose (blister pack)
Box of 100 (strips of 10) NDC 0083-0062-32

XR Tablets 400 mg - round, brown, coated (imprinted T on one side and 400 mg on the other), release portal on one side

Bottles of 100 . NDC 0083-0060-30
Unit Dose (blister pack)
Box of 100 (strips of 10) NDC 0083-0060-32

Store at controlled room temperature 15°C-30°C (59°F-86°F) *Protect from moisture Dispense in tight container (USP)*

Suspension 100 mg/5 mL (teaspoon) - yellow-orange, citrus-vanilla flavored

Bottles of 450 mL . NDC 0083-0019-76

Shake well before using
Do not store above 30°C (86°F) *Dispense in tight, light-resistant container (USP)*

Dosage Information

	Initial Dose			Subsequent Dose			Maximum Daily Dose		
Indication	Tablet*	XR†	Suspension	Tablet*	XR†	Suspension	Tablet*	XR†	Suspension
Epilepsy									
Under 6 yr	10-20 mg/kg/day b i d or t i d		10-20 mg/kg/day q i d	Increase weekly to achieve optimal clinical response, t i d or q i d		Increase weekly to achieve optimal clinical response, t i d or q i d	35 mg/kg/24 hr (see Dosage and Administration section above)		35 mg/kg/24 hr (see Dosage and Administration section above)
6-12 yr	100 mg b i d (200 mg/day)	100 mg b i d (200 mg/day)	1/2 tsp q i d (200 mg/day)	Add up to 100 mg/day at weekly intervals, t i d or q i d	Add 100 mg/day at weekly intervals, b i d	Add up to 1 tsp (100 mg)/day at weekly intervals, t i d or q i d	1000 mg/24 hr		
Over 12 yr	200 mg b i d (400 mg/day)	200 mg b i d (400 mg/day)	1 tsp q i d (400 mg/day)	Add up to 200 mg/day at weekly intervals, t i d or q i d	Add up to 200 mg/day at weekly intervals, b i d	Add up to 2 tsp (200 mg)/day at weekly intervals, t i d or q i d	1000 mg/24 hr (12-15 yr) 1200 mg/24 hr (>15 yr) 1600 mg/24 hr (adults, in rare instances)		
Trigeminal Neuralgia	100 mg b i d (200 mg/day)	100 mg b i d (200 mg/day)	1/2 tsp q i d (200 mg/day)	Add up to 200 mg/day in increments of 100 mg every 12 hr	Add up to 200 mg/day in increments of 100 mg every 12 hr	Add up to 2 tsp (200 mg)/day in increments of 50 mg (1/2 tsp) q i d	1200 mg/24 hr		

*Tablet = Chewable or conventional tablets
†XR = Tegretol®-XR extended-release tablets

Tegretol Suspension Manufactured by
Novartis Pharmaceuticals Canada Inc
Dorval (Québec), Canada H9S 1A9

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

REV FEBRUARY 2000

2249-25-00A

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Exhibit 2

Taro's Carbamazepine Tablets
100 mg, 200 mg, 300 mg and 400 mg

Proposed Package Insert

(Highlighting the Changes in Arial Black)
Draft Package Insert

Carbamazepine Tablets USP, 100 mg, 200 mg, 300 mg and 400 mg
Rx only
Prescribing Information

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 TO 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.

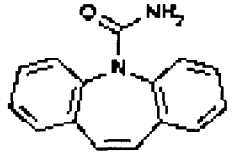
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED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

Carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as tablets of **100 mg,** 200 mg, **300 mg and 400 mg**. Its chemical name is 5*H*-dibenz[*b,f*]azepine-5-carboxamide, and its structural formula is:
Per USP Monograph



$C_{15}H_{12}N_2O$

Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive ingredients: **100 mg,** 200 mg, **300 mg and 400 mg** tablets – colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, povidone.

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

In clinical studies, carbamazepine suspension, conventional tablets, and carbamazepine extended-release tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the carbamazepine extended-release tablet slightly slower, than the conventional tablet. The bioavailability of the carbamazepine extended-release tablet was 89% compared to suspension. Following a b.i.d. dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, carbamazepine suspension affords steady-state plasma levels comparable to carbamazepine tablets given b.i.d. when administered at the same total mg

daily dose. Following a b.i.d. dosage regimen, carbamazepine extended-release tablets afford steady-state plasma levels comparable to conventional carbamazepine tablets given q.i.d., when administered at the same total mg daily dose. Carbamazepine in blood is 76% bound to plasma proteins. Plasma levels of carbamazepine are variable and may range from 0.5 to 25 mcg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 mcg/mL. In polytherapy, the concentration of carbamazepine and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see PRECAUTIONS, Drug Interactions). Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4 to 5 hours after administration of conventional carbamazepine tablets, and 3 to 12 hours after administration of carbamazepine extended-release tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound carbamazepine in serum. Because carbamazepine induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3 to 5 weeks of a fixed dosing regimen. Initial half-life values range from 25 to 65 hours, decreasing to 12 to 17 hours on repeated doses. Carbamazepine is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine. 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.

The pharmacokinetic parameters of carbamazepine disposition are similar in children and in adults. However, there is a poor correlation between plasma concentrations of carbamazepine and carbamazepine dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide (a metabolite shown to be equipotent to carbamazepine as an anticonvulsant in animal screens) in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10 to 15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated.

INDICATIONS AND USAGE

Epilepsy: Carbamazepine 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 improvement 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: Carbamazepine 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, nortriptyline, etc. 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 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.

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 borne in mind.

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. In treating or counseling women of childbearing potential, the prescribing physician will wish to weigh the benefits of therapy against the risks. 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. Therefore, if therapy is to be continued, monotherapy may be preferable for pregnant women.

In humans, transplacental passage of carbamazepine is rapid (30 to 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 to 25 times the maximum human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5 to 4 times the MHDD 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.

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 currently accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal carbamazepine and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhea, and/or decreased feeding have also been reported in association with maternal carbamazepine use. These symptoms may represent a neonatal withdrawal syndrome.

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 or hypersensitivity or reactions to other drugs, including reactions to other anticonvulsants; or interrupted courses of therapy with carbamazepine.

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure have been reported (see ADVERSE REACTIONS and PRECAUTIONS, Laboratory Tests). In some cases, hepatic effects may progress despite discontinuation of the drug.

Multi-organ hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases (see ADVERSE REACTIONS, Other and PRECAUTIONS, Information for Patients).

Discontinuation of carbamazepine should be considered if any evidence of hypersensitivity develops.

Hypersensitivity reactions to carbamazepine have been reported in patients who previously experienced this reaction to anticonvulsants including phenytoin and phenobarbital. A history of hypersensitivity reactions should be obtained for a patient and the immediate family members. If positive, caution should be used in prescribing carbamazepine.

Since a given dose of carbamazepine suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, as well as dermatologic, hypersensitivity or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use.

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.

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 (see PRECAUTIONS, General and ADVERSE REACTIONS). Carbamazepine should be discontinued, based on clinical judgment, if indicated by newly occurring or worsening clinical or laboratory evidence of liver dysfunction or hepatic damage, or in the case of 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.

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: There has been a report of a patient who passed an orange rubbery precipitate in his stool the day after ingesting carbamazepine suspension immediately followed by Thorazine® (chlorpromazine hydrochloride) solution. Subsequent testing has shown that mixing carbamazepine suspension and chlorpromazine solution (both generic and brand name) as well as carbamazepine suspension and liquid Mellaril® (thioridizine) resulted in the occurrence of this precipitate. Because the extent to which this occurs with other liquid medications is not known, carbamazepine suspension should not be administered simultaneously with other liquid medicinal agents or diluents. (See DOSAGE AND ADMINISTRATION).

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

Agents That May Affect Carbamazepine Plasma Levels

CYP 3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include:

cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketoconazole, itraconazole, verapamil, valproate.*

CYP 3A4 inducers can increase the rate of carbamazepine metabolism. Drugs that have been shown, or that would be expected, to decrease plasma carbamazepine levels include:

cisplatin, doxorubicin HCl, felbamate†, rifampin, phenobarbital, phenytoin, primidone, theophylline.

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* increased levels of the active 10,11-epoxide

†decreased levels of carbamazepine and increased levels of the 10,11-epoxide

Effect of Carbamazepine on Plasma Levels of Concomitant Agents

Increased levels: clomipramine HCl, phenytoin, primidone.

Carbamazepine induces hepatic CYP activity. Carbamazepine causes, or would be expected to cause, decreased levels of the following:

acetaminophen, alprazolam, clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, lamotrigine, metheuximide, oral and other hormonal contraceptives, phensiximide, phenytoin, theophylline, tiagabine, topiramate, valproate, warfarin.

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

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Concomitant use of carbamazepine with hormonal contraceptive products (e.g. oral, and levonogestrel subdermal implant contraceptives) may render the contraceptives less effective because the plasma concentrations of the hormones may be decreased. Breakthrough bleeding and unintended pregnancies have been reported. Alternative or back-up methods of contraception should be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two 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 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. The ratio of the concentration in breast milk to that in maternal plasma is about 0.4 for carbamazepine and about 0.5 for the epoxide. The estimated doses given to the newborn during breast feeding are in the range of 2 to 5 mg daily for carbamazepine and 1 to 2 mg daily for the epoxide.

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's effectiveness for use in the management of children with epilepsy (see INDICATIONS AND USAGE 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 pathogenetic 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 accepted therapeutic range of total carbamazepine in plasma (i.e., 4 to 12 mcg/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

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 epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin, liver, 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 low dosage recommended.

The following additional adverse reactions have been reported:

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, very rare cases of hepatic failure.

Pancreatic: Pancreatitis.

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 to 52 weeks at dosage levels of 50 to 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 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: Multi-organ hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases. Signs or symptoms may include, but are not limited to fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthraigia, leukopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests. These signs and symptoms may occur in various combinations and not necessarily concurrently. Signs and symptoms may initially be mild. Various organs, including but not limited to, liver, skin, immune system, lungs, kidneys, pancreas, myocardium, and colon may be affected (see PRECAUTIONS, General and PRECAUTIONS, Information for Patients).

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, 3.2 g (a 24 year-old woman died of a cardiac arrest and a 24 year-old man died of pneumonia and hypoxic encephalopathy); children, 4 g (a 14 year-old girl died of a cardiac arrest), 1.6 g (a 3 year-old girl died of aspiration pneumonia).

Oral LD_{50} in animals (mg/kg): mice, 1100 to 3750; rats, 3850 to 4025; rabbits, 1500 to 2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1 to 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

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

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 one 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 (see table below)

Carbamazepine suspension in combination with liquid chlorpromazine or thioridazine results in precipitate formation, and, in the case of chlorpromazine, there has been a report of a patient passing an orange rubbery precipitate in the stool following coadministration of the two drugs. (See Drug Interactions.) Because the extent to which this occurs with other liquid medications is not known, carbamazepine suspension should not be administered simultaneously with other liquid medications or diluents.

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 patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of carbamazepine suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6 to 12 years; ½ teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral carbamazepine tablets to carbamazepine suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Epilepsy: (See INIDCATIONS AND USAGE.)

Adults and Children over 12 Years of Age

Initial: Either 200 mg b.i.d. for tablets, or 1 teaspoon q.i.d. for suspension (400 mg/day). Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage should generally not exceed 1000 mg daily in children 12 to 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 in rare instances. ***Maintenance***: Adjust dosage to the minimum effective level, usually 800 to 1200 mg daily.

Children 6 to 12 Years of Age

Initial: Either 100 mg b.i.d. for tablets, or 1/2 teaspoon q.i.d. for suspension (200 mg/day). Increase at weekly intervals by adding up to 100 mg per day using a t.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance***: Adjust dosage to the minimum effective level, usually 400 to 800 mg daily.

Children Under 6 Years of Age

Initial: 10 to 20 mg/kg/day b.i.d. or t.i.d. Increase weekly to achieve optimal clinical response administered t.i.d or q.i.d. ***Maintenance***: 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 carbamazepine for use at doses above 35 mg/kg/24
Hours can be made.

Combination Therapy: Carbamazepine 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 Usage in Pregnancy, Pregnancy Category D).

Trigeminal Neuralgia: (See INDICATIONS AND USAGE.)

Initial: On the first day, 100 mg b.i.d. for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg 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 to 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.

Dosage Information

	Initial Dose		Subsequent Dose		Maximum Daily Dose	
Indication	Tablet*	Suspension	Tablet*	Suspension	Tablet*	Suspension
Epilepsy Under 6 yr	10 to 20 mg/kg/day b.i.d. or t.i.d.	10 to 20 mg/kg/day q.i.d.	Increase weekly to achieve optimal clinical response, t.i.d. or q.i.d.	Increase weekly to achieve optimal clinical response, t.i.d. or q.i.d.	35 mg/kg/24 hr (see Dosage and Administration section below)	35 mg/kg/24 hr (see Dosage and Administration section below)
6 to 12 yr	100 mg b.i.d. (200 mg/day)	½ tsp q.i.d. (200 mg/day)	Add up to 100 mg/day at weekly intervals, t.i.d. or q.i.d.	Add up to 1 tsp (100 mg)/day at weekly intervals t.i.d. or q.i.d.	1000 mg/24 hr	
Over 12 yr	200 mg b.i.d. (400 mg/day)	1 tsp q.i.d. (400 mg/day)	Add up to 200 mg/day at weekly intervals t.i.d. or q.i.d.	Add up to 2 tsp (200 mg)/day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hr (12 to 15 yr) 1200 mg/24 hr (> 15 yr) 1600 mg/24 hr (adults, in rare instances)	
Trigeminal Neuralgia	100 mg b.i.d. (200 mg/day)	½ tsp q.i.d. (200 mg/day)	Add up to 200 mg/day in increments of 100 mg every 12 hr	Add up to 2 tsp (200 mg)/day in increments of 50 mg (1/2 tsp) q.i.d.	1200 mg/24 hr	

* Tablet = chewable or conventional tablets

HOW SUPPLIED

Carbamazepine Tablets USP, 100 mg - - White to off-white round tablet, scored on one side, and engraved "T" above the score line and "23" below the score line, plain on the other side.

Bottles of 60.....NDC 51672-4076-6
Bottles of 100.....NDC 51672-4076-1
Bottles of 500.....NDC 51672-4076-2
Bottles of 1000.....NDC 51672-4076-3
Unit Dose of 50 ...NDC 51672-4076-9
Unit Dose of 100...NDC 51672-4076-0

Carbamazepine Tablets USP, 200 mg - - White, round, flat beveled-edge, one side scored and engraved TARO above the score and 11 below the score.
Bottles of 100.....NDC 51672-4068-1
Bottles of 500.....NDC 51672-4068-2
Bottles of 1000.....NDC 51672-4068-3

Carbamazepine Tablets USP, 300 mg - - White to off-white capsule shaped tablet, scored on both sides, engraved on one side "CFN 250" through the score line.

Bottles of 60.....NDC 51672-4077-6
Bottles of 100.....NDC 51672-4077-1
Bottles of 500.....NDC 51672-4077-2
Bottles of 1000.....NDC 51672-4077-3
Unit Dose of 50 ...NDC 51672-4077-9
Unit Dose of 100...NDC 51672-4077-0

Carbamazepine Tablets USP, 400 mg - - White to off-white capsule shaped tablet, scored on both sides, engraved "T" on one side above, and "29" below the score line.

Bottles of 60.....NDC 51672-4078-6
Bottles of 100.....NDC 51672-4078-1
Bottles of 500.....NDC 51672-4078-2
Bottles of 1000.....NDC 51672-4078-3
Unit Dose of 50 ...NDC 51672-4078-9
Unit Dose of 100...NDC 51672-4078-0

Do not store above 30°C (86°F).
Protect from moisture.
Dispense in tight, preferably glass.

Manufactured by:
Taro Pharmaceutical Industries Ltd.,
Haifa Bay, Israel 26110
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