

Tegretol[®]
carbamazepine USP

Prescribing Information

Tablets of 200 mg

(7/79) 667104
C79-19

APPROVED

WARNING

SERIOUS AND SOMETIMES FATAL ABNORMALITIES OF BLOOD CELLS (APLASTIC ANEMIA, AGRANULOCYTOSIS, THROMBOCYTOPENIA AND LEUKOPENIA) HAVE BEEN REPORTED FOLLOWING TREATMENT WITH TEGRETOL, CARBAMAZEPINE.

EARLY DETECTION OF HEMATOLOGIC CHANGE IS IMPORTANT SINCE IN SOME PATIENTS, APLASTIC ANEMIA IS REVERSIBLE.

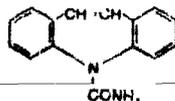
COMPLETE PRETREATMENT BLOOD COUNTS, INCLUDING PLATELET AND POSSIBLY RETICULOCYTE AND SERUM IRON, SHOULD BE OBTAINED. ANY SIGNIFICANT ABNORMALITIES SHOULD RULE OUT USE OF THE DRUG. THESE SAME TESTS SHOULD BE REPEATED AT FREQUENT INTERVALS, POSSIBLY WEEKLY DURING THE FIRST THREE MONTHS OF THERAPY AND MONTHLY THEREAFTER FOR AT LEAST TWO TO THREE YEARS. THE DRUG SHOULD BE STOPPED IF ANY EVIDENCE OF BONE MARROW DEPRESSION DEVELOPS.

PATIENTS SHOULD BE MADE AWARE OF THE EARLY TOXIC SIGNS AND SYMPTOMS OF A POTENTIAL HEMATOLOGIC PROBLEM SUCH AS FEVER, SORE THROAT, ULCERS IN THE MOUTH, EASY BRUISING, PETECHIAL OR PURPURIC HEMORRHAGE AND SHOULD BE ADVISED TO DISCONTINUE THE DRUG AND TO REPORT TO THE PHYSICIAN IMMEDIATELY IF ANY SUCH SIGNS OR SYMPTOMS APPEAR.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains. Treatment of epilepsy should be restricted to those classifications listed under "Indications."

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 is an iminostilbene derivative, 5H-dibenz (b,f)azepine 5-carboxamide, and has the following chemical structure:



It is a white, crystalline substance which is insoluble in water but soluble in propylene glycol. It melts within a range of no more than 3°C between 187°-193°C. Its molecular weight is 236.28.

Actions Tegretol has demonstrated anticonvulsant properties in rats and mice with convulsions induced by electrical and chemical methods.

Early animal screening tests demonstrated that Tegretol depressed the inquemamandibular reflexes in cats. Pain induced by stimulation of the infraorbital nerve of cats and rats was greatly reduced or abolished. Tegretol, brand of carbamazepine, is chemically unrelated to other anticonvulsants or other agents used to control the severe pain of trigeminal neuralgia. Its mechanism of action is obscure.

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants. Plasma levels of Tegretol are variable and may range from 0.5-25 mcg/ml with no apparent relationship to the daily intake of the drug. Therapeutic levels in the adult range should be between 4-12 mcg/ml. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values have been reported to range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. In oral studies with ¹⁴C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces.

Indications *Epilepsy* Tegretol is indicated for the following conditions in patients who have not responded satisfactorily to treatment with other agents such as phenytoin, phenobarbital, and/or primidone:

- 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.

Because of the necessity for frequent laboratory evaluation for potentially serious side effects, Tegretol is not recommended as the drug of first choice in seizure disorders. It should be reserved for patients whose seizures are difficult to control and/or patients experiencing marked side effects (e.g., excessive sedation).

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.

Contraindications Tegretol should not be used in patients with a history of previous bone marrow depression and/or hypersensitivity to the drug, or in patients with a 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. When administering Tegretol to pa-

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lients receiving MAO inhibitors. The MAO inhibitors should be discontinued and at least a drug free interval should elapse as the clinical situation permits with a minimum of fourteen days.

Warnings: The drug should be discontinued if evidence of significant bone marrow depression occurs. In general, Tegretol should be discontinued if a patient sustains evidence of marrow suppression as follows:

- 1) Erythrocytes less than 4.0 m cmm
Hematocrit less than 32%
Hemoglobin less than 11 gm%
- 2) Leukocytes less than 4000 cmm
- 3) Platelets less than 100,000 cmm
- 4) Reticulocytes less than 0.3% (20,000 cmm)
- 5) Serum iron greater than 150 µgm%

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

Usage in Pregnancy: The effects of Tegretol in human pregnancy and nursing infants are unknown. Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to diphenylhydantoin and phenobarbital but these are also the most commonly prescribed anticonvulsants. Less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

The reports suggesting an elevated incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause-and-effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors, e.g. genetic factors or the epileptic condition itself, may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants.

It is important to note that anticonvulsant drugs should not be discontinued 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 the 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.

Adverse effects have been observed in reproduction studies in animals given Tegretol orally. In rat teratology studies, 2 of 130 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 reproduc-

tion studies, nursing rats demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential. Use of Tegretol in women of childbearing potential should be considered only when the clinical situation warrants the risk. It is inadvisable for mothers taking Tegretol to nurse.

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 aivation of a latent psychosis and in elderly patients of confusion or agitation should be borne in mind. 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.

Precautions: Before initiating therapy, the following procedures are recommended:

Detailed history and physical examination.

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

Complete pretreatment blood count, including platelet and possibly reticulocyte and serum iron, should be obtained. Any significant abnormalities should rule out use of the drug. These same tests should be repeated at frequent intervals, possibly weekly, during the first three months of therapy and monthly thereafter for at least two to three years.

Baseline evaluations of liver function, particularly in patients with a history of liver disease. Liver function tests must be performed at regular intervals 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. These are recommended for patients being treated with this drug since many phenothiazines and related drugs have been shown to cause eye changes. Baseline and periodic complete ophthalmic and BUN determinations. These are recommended for patients treated with this agent because of observed renal dysfunction.

Carcinogenesis and Mutagenesis: 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 in benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Extensive 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.

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

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ever, seizures which are life-threatening hazards.

The adverse reactions most frequently observed 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:

Hematopoietic System: Aplastic anemia, leukopenia, agranulocytosis, eosinophilia, leukocytosis, thrombocytopenia, purpura.

Hepatic: Abnormalities in liver function tests and cholestatic and hepatocellular jaundice.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, renal failure, azotemia 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 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. 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 and oculomotor disturbances, speech disturbances, and abnormal involuntary movements; peripheral neuritis and paresthesias, depression with agitation, alkalineosis, nystagmus, 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.

Skin: Pruritic and erythematous rashes, urticaria, Stevens-Johnson syndrome, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme and nodosum, and aggravation of disseminated lupus erythematosus. In certain cases, discontinuation of therapy may be necessary.

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

Cardiovascular System: Congestive heart failure, aggravation of hypertension, hypotension, syncope and collapse, edema, primary thrombophlebitis, recurrence of thrombophlebitis, aggravation of coronary artery disease, and adenopathy or lymphadenopathy.

Some of the above cardiovascular complications have resulted in fatalities. Arrhythmias and A-V block have been reported. Myocardial infarction has been associated with other tricyclic compounds.

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

changes.

Musculoskeletal: Aching joints and muscles, and leg cramps.

Metabolic: Fever and chills. Inappropriate antidiuretic hormone syndrome has been reported. Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications. Thyroid function tests have been reported to have decreased values with Tegretol alone.

Dosage and Administration: Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see **Actions**). 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.

Epilepsy (see Indications):

Adults and children over 12 years of age—Initial: One tablet (200 mg) b.i.d. on the first day. Increase gradually by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the best 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 4-6 tablets (800-1200 mg) daily.

Children 6-12 years of age—Initial: One-half tablet (100 mg) b.i.d. on the first day. Increase gradually by adding 100 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg.

Maintenance: Adjust dosage to the minimum effective level, usually 2-4 tablets (400-800 mg) daily.

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.

Trigeminal Neuralgia (see Indications):

Initial: One-half tablet (100 mg) b.i.d. on the first day for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of one-half tablet every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily. Tablets should be taken with meals.

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some cases 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.

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Overdosage Symptoms and Treatment. These include dizziness, ataxia, drowsiness, stupor, nausea, vomiting, restlessness, agitation, disorientation, tremor, involuntary movements, opisthotonus, abnormal reflexes (slowed or hyperactive), mydriasis, nystagmus, flushing, cyanosis, urinary retention. Hypotension or hypertension may develop. Coma may ensue.

Laboratory findings in reported instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Treatment. Experience with cases of accidental overdosage is limited. However, since the drug is related to the tricyclic antidepressants, the treatment recommendations suggested for overdosage with Tofranil[®], imipramine hydrochloride, may be helpful.

There is no specific antidote. Induced emesis and gastric lavage are recommended. Vital signs should be watched and symptomatic treatment administered. Parenteral barbiturates may be employed to treat hyperirritability. 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).

Barbiturates may induce respiratory depression, particularly in children. It is therefore advisable to have equipment available for artificial ventilation and resuscitation when barbiturates are employed.

Paraldehyde may be used in children to counteract muscular hypertonus without producing respiratory depression.

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

Because of the relationship of Tegretol to the tricyclic antidepressants, it is recommended that the ECG be monitored, particularly in children, to detect any cardiac arrhythmias or conduction defects.

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

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

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

How Supplied: Round, white, single-scored tablets of 200 mg in bottles of 100 and 1000, and Unit Dose Packages of 100.

Dispense in tight container (USP)

Printed in U.S.A. 667104 (7/79)

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Geigy

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