

TEGRETOL®

(Carbamazepine tablets)

THERAPEUTIC CLASSIFICATION

1. Anticonvulsant
2. For Symptomatic Relief of Trigeminal Neuralgia
3. Antimanic

INDICATIONS AND CLINICAL USE

A. Epilepsy: TEGRETOL (carbamazepine) is indicated for use as an anticonvulsant drug either alone or in combination with other anticonvulsant drugs.

Carbamazepine is not effective in controlling absence, myoclonic or atonic seizures, and does not prevent the generalization of epileptic discharge. Moreover, exacerbation of seizures may occasionally occur in patients with atypical absences.

B. Trigeminal Neuralgia: TEGRETOL is indicated for the symptomatic relief of pain of trigeminal neuralgia during periods of exacerbation of true or primary trigeminal neuralgia (tic douloureux). It should not be used preventively during periods of remission. In some patients, TEGRETOL has relieved glossopharyngeal neuralgia. For patients who fail to respond to TEGRETOL, or who are sensitive to the drug, other accepted measures must be considered.

Carbamazepine is not a simple analgesic and should not be used to relieve trivial facial pains or headaches.

C. Treatment of Acute Mania and Prophylaxis in Bipolar (Manic-Depressive) Disorders: TEGRETOL may be used as monotherapy or as an adjunct to lithium in the treatment of acute mania or prophylaxis of bipolar (manic-depressive) disorders in patients resistant to or intolerant of conventional antimanic drugs. Carbamazepine may be a useful alternative to neuroleptics in such patients. Patients with severe mania, dysphoric mania or rapid cycling who are non-responsive to lithium may show a positive response when treated with carbamazepine.

Recommendations are based on extensive clinical experience and some clinical trials versus active comparison agents.

CONTRAINDICATIONS

TEGRETOL (carbamazepine) should not be administered to patients with hepatic disease, a history of acute intermittent porphyria, or serious blood disorder.

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

TEGRETOL should not be administered to patients presenting atrioventricular heart block.

TEGRETOL should not be administered to patients with known hypersensitivity to carbamazepine or any tricyclic compound, such as amitriptyline, trimipramine, imipramine, or their analogues or metabolites, because of the similarity in chemical structure.

WARNINGS

ALTHOUGH REPORTED INFREQUENTLY, SERIOUS ADVERSE EFFECTS HAVE BEEN OBSERVED DURING THE USE OF TEGRETOL (carbamazepine). AGRANULOCYTOSIS AND APLASTIC ANEMIA HAVE OCCURRED IN A FEW INSTANCES WITH A FATAL OUTCOME. LEUCOPENIA, THROMBOCYTOPENIA, HEPATOCELLULAR AND CHOLESTATIC JAUNDICE, AND HEPATITIS HAVE ALSO BEEN REPORTED. IN THE MAJORITY OF CASES, LEUCOPENIA AND THROMBOCYTOPENIA WERE TRANSIENT AND DID NOT SIGNAL THE ONSET OF EITHER APLASTIC ANEMIA OR AGRANULOCYTOSIS. TEGRETOL SHOULD BE USED CAREFULLY AND CLOSE CLINICAL AND FREQUENT LABORATORY SUPERVISION SHOULD BE MAINTAINED THROUGHOUT TREATMENT IN ORDER TO DETECT AS EARLY AS POSSIBLE SIGNS AND SYMPTOMS OF A POSSIBLE BLOOD DYSCRASIA. TEGRETOL SHOULD BE DISCONTINUED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION APPEARS. (See PRECAUTIONS).

SHOULD SIGNS AND SYMPTOMS SUGGEST A SEVERE SKIN REACTION SUCH AS STEVEN-JOHNSON SYNDROME OR LYELL SYNDROME, WITHDRAW TEGRETOL AT ONCE. LONG-TERM TOXICITY STUDIES IN RATS INDICATED A POTENTIAL CARCINOGENIC RISK. THEREFORE WEIGH THE POSSIBLE RISK AGAINST THE POTENTIAL BENEFITS BEFORE PRESCRIBING TEGRETOL TO INDIVIDUAL PATIENTS

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

In women of childbearing potential, TEGRETOL should, whenever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with more than one antiepileptic drug is greater than in those of women receiving a single antiepileptic. Minimum effective doses should be given and the plasma levels monitored.

If pregnancy occurs in a woman receiving TEGRETOL, or if the problem of initiating TEGRETOL arises during pregnancy, the drug's potential benefits must be weighed against its hazards, particularly during the first 3 months of pregnancy. TEGRETOL should not be discontinued or withheld if required to prevent major seizures because of the risks posed, to mother and fetus, by status epilepticus with attendant hypoxia.

The possibility that carbamazepine, like all major antiepileptic drugs, increases the risk of malformations has been reported. There are rare reports on developmental disorders and malformations, including spina bifida, in association with carbamazepine. Conclusive evidence from controlled studies with carbamazepine monotherapy is lacking.

Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate folic acid deficiency, which may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy. To prevent neonatal bleeding disorders, Vitamin K₁ administration to the mother the last weeks of pregnancy, as well as to the newborn, has been recommended.

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

The reliability of oral contraceptives may be adversely affected by carbamazepine (see PRECAUTIONS, Drug Interactions).

PRECAUTIONS

Clinical Monitoring of Adverse Reactions: TEGRETOL (carbamazepine) should be prescribed only after a critical risk-benefit appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematological reactions to other drugs, or interrupted courses of therapy with TEGRETOL. Careful clinical and laboratory supervision should be maintained throughout treatment. Should any signs, symptoms or abnormal laboratory findings be suggestive of blood dyscrasia or liver disorder, TEGRETOL should be immediately discontinued until the case is carefully reassessed.

(a) **Bone marrow function:** Complete blood counts, including platelets and possibly reticulocytes and serum iron, should be carried out before treatment is instituted. Suggested guidelines for monitoring are weekly for the first month, then monthly for the next five months, thereafter 2 - 4 times a year.

If low or decreased white blood cell or platelet counts are observed during treatment, the patient and the complete blood count should be monitored closely. Non-progressive fluctuating asymptomatic leucopenia, which is encountered, does not generally call for the withdrawal of TEGRETOL. Treatment should be discontinued if the patient develops leucopenia which is progressive or accompanied by clinical manifestations, e.g. fever or sore throat, as this could indicate the onset of significant bone marrow depression.

Because the onset of potentially serious blood dyscrasias may be rapid, patients should be made aware of early toxic signs and symptoms of a potential hematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage appear, the patient should be advised to consult his/her physician immediately.

(b) **Hepatic function:** Baseline and periodic evaluations of hepatic function must be performed, particularly in the elderly and patients with a history of liver disease. Withdraw TEGRETOL immediately in cases of aggravated liver dysfunction or active liver disease.

(c) **Kidney function:** Pretreatment and periodic complete urinalysis and BUN determinations should be performed.

(d) **Ophthalmic examinations:** Carbamazepine has been associated with pathological eye changes. Periodic eye examinations, including slit-lamp funduscopy and tonometry are recommended.

(e) **Plasma levels:** Although correlations between dosage

and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring plasma levels may be useful in the following conditions: dramatic increase in seizure frequency/verification of patient compliance; during pregnancy; when treating children or adolescents; in suspected absorption disorders; in suspected toxicity, especially where more than one drug is being used (see Drug Interactions).

Increased seizure frequency: TEGRETOL should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since its use has been associated with increased frequency of generalized convulsions. In case of exacerbation of seizures, discontinue TEGRETOL.

Dermatologic: Mild skin reactions, e.g. isolated macular or maculopapular exanthema, usually disappear within a few days or weeks, either during continued course of treatment or following a decrease in dosage. However, the patient should be kept under close surveillance because of the rare possibility of Steven-Johnson syndrome or Lyell's syndrome occurring (see WARNINGS).

Urinary Retention and Increased Intraocular Pressure: Because of its anticholinergic action, carbamazepine should be given cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Follow such patients closely.

Occurrence of Behavioral Disorders: Because it is closely related to the other tricyclic drugs, there is some possibility that carbamazepine might activate a latent psychosis, or, in elderly patients, produce agitation or confusion, especially when combined with other drugs. Exercise caution in alcoholics.

Use in Patients with Cardiovascular Disorders: Use TEGRETOL cautiously in patients with a history of coronary artery disease, organic heart disease, or congestive failure. If a defective conductive system is suspected, an ECG should be performed before administering TEGRETOL, to exclude patients with atrioventricular block.

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

Drug Interactions: Induction of hepatic enzymes in response to carbamazepine may diminish or abolish the activity of certain drugs that are also metabolized in the liver. Dosage of the following drugs may have to be adjusted when administered with TEGRETOL: clobazam, clonazepam, ethosuximide, primidone, valproic acid, alprazolam, corticosteroids (e.g. prednisolone, dexamethasone), cyclosporin, digoxin, doxycycline, felodipine, haloperidol, thioridazine, imipramine, methadone, oral contraceptives, theophylline, and oral anticoagulants (warfarin, phenprocoumon, dicumarol). Phenytoin plasma levels have been reported both to be raised and lowered by carbamazepine, and mephenytoin plasma levels have been reported in rare instances to increase.

The following drugs have been shown to raise plasma carbamazepine levels: erythromycin, troleandomycin, possibly josamycin, isoniazid, verapamil, diltiazem, propoxyphene, viloxazine, fluoxetine, cimetidine, acetazolamide, danazol, and possibly desipramine. Nicotinamide raises carbamazepine plasma levels in children, but only at high dosage in adults. Since an increase in carbamazepine plasma levels may result in unwanted effects (e.g. dizziness, drowsiness, ataxia, diplopia and nystagmus), the dosage of TEGRETOL should be adjusted accordingly and the blood levels monitored.

Plasma levels of carbamazepine may be reduced by phenobarbitone, phenytoin, primidone, progabide, or theophylline, and possibly by clonazepam. Valproic acid, valpromide, and primidone have been reported to raise plasma levels of the pharmacologically active metabolite, carbamazepine-10,11 epoxide. The dose of TEGRETOL may consequently have to be adjusted.

Combined use of TEGRETOL with lithium, metoclopramide, or haloperidol, may increase the risk of neurotoxic side effects (even in the presence of "therapeutic plasma levels").

Concomitant use of TEGRETOL and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

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

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

Carbamazepine may antagonize the effects of non-depolarising muscle relaxants (e.g. pancuronium); their dosage may need to be raised and patients should be monitored

closely for more rapid recovery from neuromuscular blockade than expected.

Isotretinoin has been reported to alter the bioavailability and/or clearance of carbamazepine and its active 10,11-epoxide; carbamazepine plasma levels should be monitored.

Carbamazepine, like other psycho-active drugs, may reduce alcohol tolerance; it is advisable to abstain from alcohol during treatment.

TEGRETOL should not be administered in conjunction with a MAO inhibitor. (See CONTRAINDICATIONS).

ADVERSE REACTIONS

The reactions most frequently reported with TEGRETOL (carbamazepine) are CNS (e.g. drowsiness, headache, unsteadiness on the feet, diplopia, dizziness), gastrointestinal disturbances (nausea, vomiting), and allergic skin reactions. These usually occur only during the initial phase of therapy, if the initial dose is too high, or when treating elderly patients. They have rarely necessitated discontinuing TEGRETOL therapy, and can be minimized by initiating treatment at a low dosage.

The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels and possibly lower the daily dose and/or divide it into 3 - 4 fractional doses.

The more serious adverse reactions observed are the hematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy.

If treatment with TEGRETOL has to be withdrawn abruptly, the change-over to another antiepileptic drug should be effected under cover of diazepam.

The following adverse reactions have been reported:

Hematologic: Occasional or frequent - leucopenia; occasional eosinophilia, thrombocytopenia; rare - leucocytosis, lymphadenopathy; isolated cases - agranulocytosis, aplastic anaemia, pure red cell aplasia, macrocytic anaemia, megaloblastic anaemia, acute intermittent porphyria, reticulocytosis, folic acid deficiency, thrombocytopenic purpura, and possibly hemolytic anaemia. In a few instances, deaths have occurred.

Hepatic: Frequent - elevated gamma-GT (due to hepatic enzyme induction), usually not clinically relevant; occasional - elevated alkaline phosphatase; rarely transaminases; rare - jaundice, hepatitis of cholestatic, parenchymal (hepatocellular), or mixed type; isolated cases - granulomatous hepatitis.

Dermatologic: Occasional to frequent - skin sensitivity reactions and rashes, erythematous rashes, urticaria; rare - exfoliative dermatitis and erythroderma, Steven-Johnson syndrome, systemic lupus erythematosus-like syndrome; isolated cases - toxic epidermal necrolysis (Lyell's syndrome), photosensitivity, erythema multiforme and nodosum, skin pigmentation changes, pruritus, purpura, acne, diaphoresis, alopecia and neurodermatitis. Isolated cases of hirsutism have been reported, however the causal relationship is not clear.

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

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

Psychiatric: Isolated cases - hallucinations (visual or acoustic), depression, sometimes with talkativeness, agitation, loss of appetite, restlessness, aggressive behaviour, confusion, activation of psychosis.

Genitourinary: Isolated cases - interstitial nephritis and renal failure, as well as signs of renal dysfunction (e.g. albuminuria, glycosuria, hematuria, oliguria sometimes associated with elevated blood pressure, and elevated BUN/azotemia), urinary frequency, urinary retention and sexual disturbances/impotence.

Gastrointestinal: Occasional or frequent - nausea, vomiting; occasional - dryness of the mouth and throat; rare - diarrhea or constipation; isolated cases - abdominal pain, glossitis, stomatitis, anorexia.

Sense organs: Isolated cases - lens opacities, conjunctivi-

tis, retinal changes, tinnitus, hyperacusis, and taste disturbances.

Endocrine system and metabolism: Occasionally edema, fluid retention, weight increase, hyponatremia and reduced plasma osmolality due to antidiuretic hormone (ADH)-like effect occurs, leading in isolated cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities. Isolated cases of gynecostasia or galactorrhea have been reported, as well as abnormal thyroid function tests (decreased L-thyroxine i.e. FT_4 , T_4 , T_3 , and increased TSH, usually without clinical manifestations), disturbances of bone metabolism (decrease in plasma calcium and 25-OH-calciferol), leading in isolated cases to osteomalacia, as well as reports of elevated levels of cholesterol, including HDL cholesterol and triglycerides.

Musculoskeletal system: Isolated cases - arthralgia, muscle pain or cramp.

Respiratory: Isolated cases - pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Hypersensitivity reactions: A rare delayed multi-organ hypersensitivity disorder with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopenia, eosinophilia, hepatosplenomegaly and abnormal liver function tests, occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium). Isolated cases: aseptic meningitis, with myoclonus and eosinophilia; anaphylactic reaction. Discontinue treatment should such hypersensitivity reactions occur.

DOSAGE AND ADMINISTRATION

Use in Epilepsy (See INDICATIONS): TEGRETOL may be used alone or with other anticonvulsants. A low initial daily dosage of TEGRETOL with a gradual increase in dosage adjusted to the needs of the individual patient, is advised. TEGRETOL tablets and CHEWTABS should be taken in 2 to 4 divided doses daily, with meals whenever possible.

The controlled release characteristics of TEGRETOL CR reduce the daily fluctuations of plasma carbamazepine. TEGRETOL CR tablets (either whole or, if so prescribed, only half a tablet) should be swallowed unchewed with a little liquid during or after a meal. Controlled release tablets should be prescribed as a twice-daily dosage. If necessary, three divided doses may be prescribed. Some patients have been reported to require a dosage increase when switching from tablets to CR tablets. Dosage adjustments should be individualized based on clinical response and, if necessary, plasma carbamazepine levels.

Adults and Children Over 12 Years of Age: Initially, 100 to 200 mg once or twice a day depending on the severity of the case and previous therapeutic history. The initial dosage is progressively increased, in divided doses, until the best

response is obtained. The usual optimal dosage is 800 to 1200 mg daily. In rare instances some adult patients have received 1600 mg. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

Children 6-12 Years of Age: Initially, 100 mg in divided doses, increased gradually by 100 mg per day until the best response is obtained. Dosage should generally not exceed 1000 mg daily. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

Combination Therapy: When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except for phenytoin, which may be increased (See Precautions, Drug Interactions and Warnings, Pregnancy and nursing).

Use in Trigeminal Neuralgia: Initial daily dosage of 200 mg taken in 2 doses of 100 mg each is recommended. The total daily dosage can be increased by 200 mg/day until relief of pain is obtained. This is usually achieved at dosage of 200-800 mg daily; occasionally up to 1200 mg/day may be necessary. As soon as relief of pain has been obtained and maintained, progressive reduction in dosage should be attempted until a minimal effective dosage is reached. Because trigeminal neuralgia is characterized by periods of remission, attempts should be made to reduce or discontinue the use of TEGRETOL at intervals of not more than 3 months, depending upon the individual clinical course. Prophylactic use of the drug in trigeminal neuralgia is not recommended.

Use in Mania and Bipolar (Manic-Depressive) Disorders: The initial daily dosage should be low, 200 to 400 mg/day, administered in divided doses, although higher starting doses of 400 to 600 mg/day may be used in acute mania. This dose may be gradually increased until patient symptomatology is controlled or a total daily dose of 1600 mg is achieved. Increments in dosage should be adjusted to provide optimal patient tolerability. The usual dose range is 400 to 1200 mg/day administered in divided doses. Doses used to achieve optimal acute responses and tolerability should be continued during maintenance treatment. When given in combination with lithium and neuroleptics, the initial dosage should be low, 100 mg to 200 mg daily, and then increased gradually. A dose higher than 800 mg/day is rarely required when given in combination with neuroleptics and lithium, or with other psychotropic drugs such as benzodiazepines. Plasma levels are probably not helpful for guiding therapy in bipolar disorders.

Stability and Storage Recommendations

Protect from heat and humidity. Keep out of reach of children.

AVAILABILITY OF DOSAGE FORM

	TEGRETOL tablets 200 mg	TEGRETOL CHEWTABS 100 mg	TEGRETOL CHEWTABS 200mg	TEGRETOL CR 200 mg	TEGRETOL CR 400 mg
Colour	White	White with red specks	White with red specks	Beige-orange	Brownish-orange
Shape	Round, flat-faced and bevel-edged	Round, flat-faced and bevel-edged	Oval, biconvex	Oval, slightly biconvex	Oval, slightly biconvex
Imprint	Engraved GEIGY on one side and quadrased on the other	Engraved GEIGY on one side and M/R with bisect on the other	Engraved GEIGY on one side and P/U with bisect on the other	C/G engraved on one side and H/C engraved on the other. Fully bisected on both sides	CG/CG engraved on one side and ENE/ENE engraved on the other. Fully bisected on both sides
Carbamazepine	200 mg	100 mg	200 mg	200 mg	400mg
Availability	Bottles of 100 & 500	Bottles of 100	Bottles of 100	Bottles of 100	Bottles of 100

Tegretol is a schedule F drug and can only be obtained by prescription from a licensed practitioner. Product Monograph available on request. September 23, 1994

REFERENCES

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For brief prescribing information see pages S79, S80.



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