

Intermediate Prescribing Information

TEGRETOL® (carbamazepine tablets)
TEGRETOL® 200 mg

TEGRETOL Chewtabs®
(carbamazepine chewable tablets)
TEGRETOL® Chewtabs™ 100 mg
TEGRETOL® Chewtabs™ 200 mg

TEGRETOL CR
(carbamazepine controlled release tablets)
TEGRETOL® CR 200 mg TEGRETOL® CR 400 mg
Anticonvulsant
For symptomatic relief of trigeminal neuralgia
Antimanic

INDICATIONS A. Management of psychomotor (temporal lobe) epilepsy. As an adjunct in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when combined with other anti-epileptic agents.

As an alternative in patients with generalized tonic-clonic seizures and marked side effects or who fail to respond to other anticonvulsant drugs.

Ineffective for controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent generalization of epileptic discharge. Exacerbation of seizures may occur in patients with atypical absences.

B. Symptomatic relief of pain of true or primary trigeminal neuralgia (tic douloureux). Not for prophylactic use. Glossopharyngeal neuralgia has been relieved in some patients. Other measures must be considered for patients failing to respond or who are sensitive to TEGRETOL.

C. Treatment of Acute Mania and Prophylaxis in Bipolar (Manic-Depressive) Disorders: may be used as monotherapy or adjunct to lithium in patients who are resistant to or are intolerant of conventional antimaniacs. Possibly an alternative to neuroleptics in such patients. Patients with severe mania, dysphoric mania or rapid cycling who are non-responsive to lithium may respond positively to carbamazepine. Recommendations are based on extensive clinical experience and some comparative trials.

CONTRAINDICATIONS History of hepatic disease, acute intermittent porphyria or serious blood disorder, in patients with AV heart block (see Precautions), hypersensitivity to carbamazepine or to tricyclic compounds, or their analogues or metabolites.

Do not give with, immediately before or immediately after treatment with monoamine oxidase inhibitors. There should be as long a drug free interval as the clinical condition allows, in no case less than 14 days. Then TEGRETOL dosage should be low initially, increased very gradually.

WARNINGS Although reported infrequently, serious adverse effects have been observed during 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 also reported. It is important that TEGRETOL be used carefully and close clinical and frequent laboratory supervision be maintained throughout treatment to detect signs and symptoms of possible blood dyscrasia, as early as possible. Discontinue TEGRETOL 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's syndrome, withdraw TEGRETOL at once. Long-term toxicity studies in rats indicated a potential carcinogenic risk. Weigh possible risk of TEGRETOL against potential benefits before prescribing.

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

If woman receiving TEGRETOL becomes pregnant, or if the problem of initiating TEGRETOL arises during pregnancy, weigh the drug's potential benefits against its hazards, particularly during the first 3 months of pregnancy. Do not discontinue TEGRETOL or withhold from patients if required to prevent major seizures because of the risks posed, to both mother and fetus, by status epilepticus with attendant hypoxia.

Possibility that carbamazepine, like all major antiepileptic drugs, increases the risk of malformations has been reported. 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 increased incidence of birth defects in offspring of treated epileptic women. Folic acid supplementation is recommended before and during pregnancy.

Vitamin K₁ administration to mother during last weeks of pregnancy, and to newborn, has been recommended to prevent neonatal bleeding disorders.

Carbamazepine passes into breast milk in concentrations of

about 25-60% of the plasma level. No reports available on long-term effect of breast feeding. Weigh benefits of breast feeding against possible risks to infant. Observe infant for possible adverse reactions, e.g., somnolence, should mother taking carbamazepine nurse.

A severe hypersensitivity skin reaction in a breast-fed baby has been reported.

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

PRECAUTIONS Clinical Monitoring of Adverse Reactions: Prescribe TEGRETOL 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. Maintain careful clinical and laboratory supervision throughout treatment. Should any signs or symptoms or abnormal laboratory findings be suggestive of blood dyscrasia or liver disorder, discontinue TEGRETOL immediately until case is carefully reassessed.

(a) **Bone marrow function:** Carry out complete blood counts, including platelets and possibly reticulocytes and serum iron, before treatment is instituted. Suggested guidelines for monitoring are weekly for the first month, monthly for the next 5 months, thereafter 2-4 times/year.

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

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

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

(c) **Kidney function:** Perform pretreatment and periodic complete urinalysis and BUN determinations.

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

(e) **Plasma levels:** Although correlations between dosage and plasma levels, 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; pregnancy; when treating children or adolescents; suspected absorption disorders; suspected toxicity, especially where more than one drug is used (see "Interactions").

Increased Seizure Frequency: Use TEGRETOL with caution in patients with mixed seizure disorder that includes atypical absence seizures, since 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 dosage decrease. However, patient should be kept under close surveillance because of 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 while on the drug.

Occurrence of Behavioural Disorders: Because it is closely related to other tricyclic drugs, there is a possibility that carbamazepine might activate 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 history of coronary artery disease, organic heart disease, or congestive failure. If defective conductive system suspected, perform an ECG before administering TEGRETOL, to exclude patients with atrioventricular block.

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

Drug Interactions: Induction of hepatic enzymes in response to carbamazepine may diminish or abolish activity of certain drugs also metabolized in the liver. Dosage of the following drugs may have to be adjusted: clobazam, clonazepam, ethosuximide, primidone, valproic acid, aprazolam, 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 reported to be both raised and lowered by carbamazepine, and mephenytoin plasma levels reported to increase in rare instances.

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), adjust TEGRETOL dosage accordingly and monitor the blood levels.

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

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

Concomitant use with isoniazid 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.

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

Carbamazepine, may reduce tolerance to alcohol; advisable to abstain from alcohol consumption during treatment.

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

ADVERSE REACTIONS Reactions most frequently reported are CNS (e.g. drowsiness, headache, unsteadiness on feet, diplopia, dizziness), gastrointestinal disturbances (nausea, vomiting), and allergic skin reactions. These reactions usually occur only during the initial phase of therapy, if 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 low dosage.

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

More serious adverse reactions observed are hematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy. If treatment is to be withdrawn abruptly, effect the change-over to another antiepileptic under cover of diazepam.

Adverse reactions reported:

Hematologic: Occasional or frequent - leucopenia; occasional - eosinophilia, thrombocytopenia; rare - leucocytosis, lymphadenopathy; isolated cases - agranulocytosis, aplastic anemia, pure red cell aplasia, macrocytic anemia, acute intermittent porphyria, reticulocytosis, folic acid deficiency, thrombocytopenic purpura, and possibly hemolytic anemia. In few instances, deaths 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 multiform and nodosum, skin pigmentation changes, pruritus, purpura, acne, diaphoresis, alopecia and neurodermatitis.

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, asterix, orofacial dyskinesia, choreoathetosis disorders, dystonia, tics); isolated cases - oculomotor disturbances, speech disorders (e.g. dysarthria or slurred speech), peripheral neuritis, paraesthesiae. 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: Disturbances of cardiac conduction, 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 renal failure.

Isolated reports – sexual disturbances/impotence.

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

Sense Organs: Isolated cases – lens opacities, conjunctivitis, 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, leading in isolated cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities. Isolated cases of gynecomastia or galactorrhea have been reported, as well as abnormal thyroid function tests (decreased L-thyroxine, i.e., 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:** Rare delayed multi-organ hypersensitivity disorder with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly 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. Treatment should be discontinued should such hypersensitivity reactions occur.

SYMPTOMS AND TREATMENT OF OVERDOSAGE Lowest Known Lethal Dose: estimated 3.2g (24 year old woman). Highest known doses survived: 80g (34 year old man); 34g (13 year old girl); 1.4g (23 month old girl).

Symptoms of Overdosage: The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular, and respiratory systems.

Central Nervous System: CNS depression, disorientation, tremor, restlessness, somnolence, agitation, hallucination, coma, blurred vision, nystagmus, mydriasis, slurred speech, dysarthria, ataxia, dyskinesia, abnormal reflexes (slow/hyperactive), convulsions, psychomotor disturbances, myoclonus, opisthotonia, hypothermia/hyperthermia, flushed skin/cyanosis, EEG changes.

Respiratory System: Respiratory depression, pulmonary edema.

Cardiovascular System: Tachycardia, hypotension/hypertension, conduction disturbance with widening of QRS complex, syncope in association with cardiac arrest.

Gastrointestinal System: Nausea, vomiting, delayed gastric emptying, reduced bowel motility.

Renal Function: Urinary retention, oliguria or anuria; fluid retention, and water intoxication.

Laboratory Findings: Hyponatremia, hypokalemia, leukocytosis, reduced white cell count, metabolic acidosis, hyperglycemia, glycosuria, acetonuria, increased muscle creatinine phosphokinase.

Treatment of Overdosage: There is no known specific antidote to TEGRETOL (carbamazepine).

Evacuate the stomach, with an emetic or by gastric lavage, then administer activated charcoal.

Observe vital signs and administer symptomatic treatment as required. Hyperirritability or convulsions may be controlled by the administration of parenteral diazepam or barbiturates but they may induce respiratory depression, particularly in children. Paraldehyde may be used to counteract muscular hypertonus without producing respiratory depression.

When barbiturates are employed, it is advisable to have equipment available for artificial ventilation and resuscitation. Barbiturates should not be used if drugs that inhibit monoamine oxidase have been taken by the patient, either in overdosage or in recent therapy (within two weeks).

Hyponatremia should be treated by restricting fluids and a slow and careful NaCl 0.9% infusion i.v. These measures may be useful in preventing brain damage.

Shock (circulatory collapse) should be treated with supportive measures, including intravenous fluids, oxygen, and corticosteroids. For hypotension unresponsive to measures taken to increase plasma volume, dopamine or dobutamine i.v. may be administered.

It is recommended that ECG be monitored, particularly in children, to detect cardiac arrhythmias or conduction defects. Charcoal hemoperfusion has been recommended. Forced diuresis, hemodialysis, and peritoneal dialysis reported to be ineffective.

Relapse and aggravation of the symptomatology on the 2nd or 3rd day after overdosage, due to delayed absorption, should be anticipated.

DOSAGE AND ADMINISTRATION Use in Epilepsy (See INDICATIONS): Low initial daily dosage of TEGRETOL (carbamazepine) with a gradual increase in dosage is advised. Adjust dosage to the needs of the individual patient.

TEGRETOL tablets and CHEWTABS should be taken in 2 to 4 divided doses daily, with meals when possible.

Controlled release characteristics of TEGRETOL CR reduce the daily fluctuations of plasma carbamazepine. TEGRETOL CR tablets (either whole or, if so prescribed, half a tablet) should be swallowed unchewed with a little liquid during or after a meal. Controlled release tablets should be prescribed as a b.i.d. dosage. If necessary, 3 divided doses may be prescribed.

Adults and Children Over 12 Years: Initially, 100 to 200 mg once or twice a day depending on the severity of the case and previous therapeutic history. Initial dosage is progressively increased, in divided doses, until best response is obtained. 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, reduce dosage very gradually until reaching minimum effective dose.

Children 6-12 Years: Initially, 100 mg in divided doses on first day. Increase gradually by adding 100 mg/day until best response is obtained. Dosage should generally not exceed 1000 mg daily. As soon as disappearance of seizures has been obtained and maintained, reduce dosage very gradually until reaching minimum effective dose.

Use in Trigeminal Neuralgia: Initial daily dosage 200 mg taken in 2 doses of 100 mg is recommended. Total daily dosage can be increased by 200 mg/day until relief of pain is obtained, usually achieved at dosage 200-800 mg daily; occasionally up to 1200 mg/day necessary. As soon as relief of pain has been obtained and maintained, attempt progressive reduction in dosage until reaching minimal effective dosage. 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 on individual clinical course. Prophylactic use in trigeminal neuralgia is not recommended.

Use in Mania and Bipolar (Manic Depressive) Disorders: Low initial dosage of 200-400 mg/day, in divided doses, higher starting doses of 400-600 mg/day may be used in acute mania. May be gradually increased until symptomatology is controlled or a total daily dose of 1600 mg. Adjust dosage increments for optimal tolerability. Usual dose is 400-1200 mg/day in divided doses. For maintenance, continue with doses used to achieve optimal acute responses and tolerability. In combination with lithium, neuroleptics: initially a low dosage of 100-200 mg/day; gradually increase. Daily dose > 800 mg is rarely required when given in combination with neuroleptics, lithium or other psychotropics, e.g., benzodiazepines. Plasma levels are probably not helpful for guidance in bipolar disorders.

AVAILABILITY TEGRETOL Tablets 200 mg: Each white, round, flat, bevelled-edge double-scored tablet engraved GEIGY on one side contains 200 mg carbamazepine. Protect from heat (store below 30°C) and humidity. Bottles of 100/500. **TEGRETOL CHEWTABS 100 mg:** Pale pink, round, flat, bevelled-edge tablets with distinct red spots. GEIGY engraved on one side and MR on the other. Fully bisected between the M and R. Each contains 100 mg carbamazepine. Protect from heat (store below 30°C), light and humidity. Bottles of 100. **TEGRETOL CHEWTABS 200 mg:** Pale pink, oval, biconvex tablets with distinct red spots. GEIGY engraved on one side and PU engraved on the other. Fully bisected between the P and U. Each contains 200 mg carbamazepine. Protect from heat (store below 30°C), light and humidity. Bottles of 100. **TEGRETOL CR 200 mg:** Beige-orange, oval, slightly biconvex tablet, engraved CG on one side and HC on the other. Fully bisected on both sides. Each contains 200 mg carbamazepine. Protect from heat (store below 25°C) and humidity. Bottles of 100. **TEGRETOL CR 400 mg:** Brownish-orange, oval, slightly biconvex tablet, engraved CG/CG on one side and ENE/ENE on the other. Fully bisected on both sides. Each contains 400 mg carbamazepine. Protect from heat (store below 25°C) and humidity. Bottles of 100. TEGRETOL is available to patients only by prescription. Product Monograph available on request. January 4, 1993

REFERENCES

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See pages OBC, xv.

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Epival[®]

divalproex sodium

THERAPEUTIC CLASSIFICATION Anticonvulsant.

INDICATIONS AND CLINICAL USE Sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal; useful in primary generalized seizures with tonic-clonic manifestations. May also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

In accordance with the International Classification of Seizures, simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds) accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS Should not be administered to patients with hepatic disease or significant dysfunction. Contraindicated in patients with known hypersensitivity to the drug.

WARNINGS Hepatic failures resulting in fatalities have occurred in patients receiving valproic acid and its derivatives. These incidences usually have occurred during the first six months of treatment with valproic acid. A recent survey study of valproate use in the United States in nearly 400,000 patients between 1978 and 1984, has shown that children under two years of age who received the drug as part of multiple anticonvulsant therapy were at greatest risk (nearly 20-fold increase) of developing fatal hepatotoxicity. These patients typically had other medical conditions such as congenital metabolic disorders, mental retardation or organic brain disease, in addition to severe seizure disorders. The risk in this age group decreased considerably in patients receiving valproate as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received only valproate. Risk generally declined with increasing age. No deaths have been reported in patients over 10 years of age who received valproate alone.

Epival is to be used in children two years old or younger. It should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risk.

Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, and vomiting. Patients and parents should be instructed to report such symptoms. Because of the non-specific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking Epival (divalproex sodium).

Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed in patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

In high-risk patients, it might also be useful to monitor serum fibrinogen and albumin for decrease in concentrations and serum ammonia for increases in concentration. If changes occur, the drug should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.

The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of the drug. The frequency of adverse effects, particularly elevated liver enzymes, may increase with increasing dose. Therefore, the benefit gained by improved seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Use in Pregnancy: According to recent reports in the medical literature, valproic acid may produce teratogenicity in the offspring of women receiving the drug during pregnancy. The incidence of neural tube defects in the fetus may be increased in mothers receiving valproic acid during the first trimester of pregnancy. Based upon a single report, it was estimated that the risk of valproic acid exposed women having children with spina bifida is approximately 1.2%. This risk is similar to that which applies to non-epileptic women who have had children with neural tube defects (anencephaly and spina bifida). Animal studies have demonstrated valproic acid induced teratogenicity, and studies in human females have demonstrated placental transfer of the drug.

Multiple reports in the clinical literature indicate an association between the use of anti-epileptic drugs and an increased incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women, this incidence may be increased 2- to 3-fold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, cleft lip or palate, and neural tube defects. Nevertheless, the great majority of mothers receiving anti-epileptic medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anti-epileptics. Some reports indicate a possible similar association with the use of other anti-epileptic drugs, including trimethadione, paramethadione, and valproic acid. However, the possibility also exists that other factors, e.g. genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

Anti-epileptic drugs should not be discontinued in patients to whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risks to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of child-bearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of anti-epileptic medication is in doubt, appropriate consultation is indicated.

Nursing Mothers: Valproic acid is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentrations. As a general rule, nursing should not be undertaken while a patient is receiving Epival (divalproex sodium).

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses of valproic acid greater than 200 mg/kg/day in rats and 90 mg/kg/day in dogs. Segment 1 fertility studies in rats have shown that doses up to 350 mg/kg/day for 60 days have no effect on fertility. The effect of divalproex sodium and valproic acid on the development of the testes and on sperm production and fertility in humans is unknown.

LONG-TERM TOXICITY STUDIES IN RATS AND MICE INDICATED A POTENTIAL CARCINOGENIC RISK.

PRECAUTIONS Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

General: Because of reports of thrombocytopenia and inhibition of platelet aggregation, platelet counts and bleeding-time determination are recommended before instituting therapy and at periodic intervals. It is recommended that patients be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of dosage or withdrawal of therapy pending investigation.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests; if elevation occurs the drug should be discontinued.

Because Epival (divalproex sodium) may interact with other anti-epileptic drugs, periodic serum level determinations of concurrently administered anti-epileptics are recommended during the early part of therapy. (See DRUG INTERACTIONS.) There have been reports of breakthrough seizures occurring with the combination of valproic acid and phenytoin.

Epival (divalproex sodium) is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproic acid; the clinical significance of these is unknown.

Driving and Hazardous Occupations: May produce CNS depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions: May potentiate the CNS depressant action of alcohol.

There is evidence that valproic acid may cause an increase in serum phenobarbital levels, by impairment of non-renal clearance. This phenomenon can result in severe CNS depression. The combination of valproic acid and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproic acid serum levels. Patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate drug levels should be obtained, if possible, and the barbiturate dosage decreased, if indicated.

Primidone is metabolized into a barbiturate, and therefore, may also be involved in a similar or identical interaction.

There is conflicting evidence regarding the interaction of valproic acid with phenytoin (See PRECAUTIONS - General). It is not known if there is a change in unbound (free) phenytoin serum levels. The dosage of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clonazepam may produce absence status.

ADVERSE REACTIONS The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since valproic acid has usually been used with other anti-epileptics, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drugs.

Gastrointestinal: Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and

constipation have also been reported. Anorexia with some weight loss and increased appetite with some weight gain have also been seen.

CNS Effects: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients on combination therapy. Sedation usually disappears upon reduction of other anti-epileptic medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been reported in patients receiving valproic acid alone or in conjunction with phenobarbital.

Dermatologic: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Endocrine: There have been reports of irregular menses and secondary amenorrhea in patients receiving valproic acid.

Abnormal thyroid function tests have been reported (See PRECAUTIONS).

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioural deterioration have been reported.

Musculoskeletal: Weakness has been reported.

Hematopoietic: Thrombocytopenia has been reported. Valproic acid inhibits the second phase of platelet aggregation (See PRECAUTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (eg. SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory tests also show increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (See WARNINGS).

Metabolic: Hyperammonemia (See PRECAUTIONS). Hyperglycemia has been reported and associated with a fatal outcome in a patient with pre-existing non-ketotic hyperglycinemia.

Pancreatic: There have been reports of acute pancreatitis occurring in association with therapy with valproic acid.

Other: Edema of the extremities has been reported.

DOSE AND ADMINISTRATION The recommended initial dosage is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases.

The maximal recommended dosage is 60 mg/kg/day. When the total daily dose exceeds 125 mg, it should be given in a divided regimen (See Table).

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by improving seizure control must be weighed against the increased incidence of adverse effects.

As the dosage is raised, blood levels of phenobarbital or phenytoin may be affected (See PRECAUTIONS).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. The tablets should be swallowed without chewing.

AVAILABILITY Epival (divalproex sodium) enteric-coated tablets are available as salmon-pink coloured tablets of 125 mg supplied in bottles of 100 tablets; peach-coloured tablets of 250 mg and lavender-coloured tablets of 500 mg are supplied in bottles of 100 and 500 tablets.

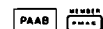
Table of Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total daily dose (mg)	Dosage (mg) Equivalent to valproic acid		
kg	lb		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	125	0	125
25-39.9	55-87.9	500	250	0	250
40-59.9	88-131.9	750	250	250	250
60-74.9	132-164.9	1,000	250	250	500
75-89.9	165-197.9	1,250	500	250	500

Product monograph available on request.

REFERENCES:

- Bourgeois B. Am J Med 1988;84(Suppl 1A):29-33.
- Drug Interaction Facts. JB Lippincott, St. Louis, MO, 1992.
- Dreifuss FE, Langer OH. Am J Med 1988;84(Suppl 1A):34-41.
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- Chadwick DW. Epilepsia 1987;28(Suppl 2):S12-S17.
- Brodie MJ. The Lancet 1990;336:350-4.
- Wilder BJ, Rangell RJ. Am J Med 1988;84(Suppl 1A):7-13.
- Loiseau P. In: Epileptic syndromes in infancy, childhood and adolescence. John Libbey Eurotext Ltd, 1985.
- Compendium of Pharmaceuticals and Specialties, 1992.



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See page xvi.

IN EPILEPSY, ADD

Frisium[®] 10 mg

(clobazam)

TO ACHIEVE SEIZURE CONTROL

Frisium (clobazam) Tablets 10 mg.

THERAPEUTIC CLASSIFICATION Anticonvulsant for adjunctive therapy. **INDICATIONS** Frisium (clobazam) has been found to be of value as adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anti-convulsant therapy. **CONTRAINDICATIONS** Hypersensitivity to clobazam, severe muscle weakness (myasthenia gravis) and narrow angle glaucoma. **WARNINGS** Use in the elderly: Frisium (clobazam) should be used with caution in elderly and debilitated patients, and those with organic brain disorders, with treatment initiated at the lowest possible dose. [See Precautions]. **Potential of drug effects:** Patients should be cautioned about the possibility of additive effects when Frisium is combined with alcohol or other drugs with central nervous system depressant effects. Patients should be advised against consumption of alcohol during treatment with Frisium. [See Precautions]. **Physical and psychological dependence:** Physical and psychological dependence are known to occur in persons taking benzodiazepines. Caution must be exercised if it is at all necessary to administer Frisium to individuals with a history of drug misuse or those who may increase the dose on their own initiative. Such patients must be placed under careful surveillance. Signs and symptoms of withdrawal may follow discontinuation of use of Frisium; thus it should not be abruptly discontinued after prolonged use. [See Precautions]. **Use in pregnancy:** Frisium should not be used in the first trimester of pregnancy and thereafter only if strictly indicated. Nursing mothers in whom therapy with Frisium is indicated should cease breast-feeding, since clobazam passes into breast milk. Several studies have suggested an increased risk of congenital malformations associated with the use of minor tranquilizers (chloridiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy. If Frisium is prescribed to a woman of child-bearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become, or suspects she might be, pregnant. **Anterograde amnesia:** Anterograde amnesia is known to occur after administration of benzodiazepines. **Use in patients with depression or psychosis:** Frisium is not recommended for use in patients with depressive disorders or psychosis. **PRECAUTIONS Driving and Hazardous Activities:** Frisium (clobazam) possesses a mild central nervous system depressant effect, therefore patients should be cautioned against driving, operating dangerous machinery or engaging in other hazardous activities, particularly in the dose adjustment period, or until it has been established that they do not become drowsy or dizzy. **Use in the Elderly:** Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to the CNS depressant activity of benzodiazepines even after low doses. Manifestations of this CNS depressant activity include ataxia, oversedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation, neurological impairment and other possible adverse reactions. **Dependence Liability:** Frisium should not be administered to individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. Withdrawal symptoms have been observed after abrupt discontinuation of benzodiazepines. These include irritability, nervousness, insomnia, agitation, tremors, convulsions, diarrhea, abdominal cramps, vomiting and mental impairment. As with other benzodiazepines, Frisium should be withdrawn gradually. **Tolerance:** Loss of part or all of the anti-convulsant effectiveness of clobazam has been described in patients who have been receiving the drug for some time. There is no absolute or universal definition for the phenomenon and reports vary widely on its development. The reported success of clobazam in intermittent therapy in catamenial epilepsy implies that tolerance may be minimized by intermittent treatment but long-term follow-up is unreported. No studies have identified or predicted which patients are likely to develop tolerance or precisely when this might occur. **Use in Mental and Emotional Disorders:** It should be recognized that suicidal tendencies may be present in patients with emotional disorders; particularly those depressed. Protective measures and appropriate treatment may be necessary and should be instituted without delay. Since excitement and other paradoxical reactions can result from the use of benzodiazepines in psychotic patients, Clobazam should not be used in patients suspected of having psychotic tendencies. **Use in Patients with Impaired Renal or Hepatic Function:** Clobazam requires dealkylation and hydroxylation before conjugation. Usual precautions should be taken if Frisium is used in patients who may have some impairment of renal or hepatic function. It is suggested that the dose in such cases be carefully titrated. In patients for whom prolonged

therapy with Frisium is indicated, blood counts and liver function should be monitored periodically. **Use in Patients with Acute, Severe Respiratory Insufficiency:** In patients with acute, severe respiratory insufficiency, respiratory function should be monitored. **Laboratory Tests:** If Frisium is administered for repeated cycles of therapy, periodic blood counts and liver and thyroid function tests are advisable. **Drug Interactions:** Most studies of the potential interactions of clobazam with other anti-epileptic agents have failed to demonstrate significant interactions with phenytoin, phenobarbital, or carbamazepine. However, one study noted that the addition of clobazam caused a 25% increase in serum drug levels in 29% of patients taking carbamazepine, 63% of patients taking phenytoin, 13% of those taking valproate and 14% of those on phenobarbital. The contradictory findings in different studies are presumably due to variations in patient susceptibility, and although clinically significant interactions are unusual, they may occur. Alcohol may also significantly increase plasma clobazam levels. **Several of the established anti-epileptic agents:** carbamazepine, diphenylhydantoin, phenobarbital, valproic acid, cause the blood levels of clobazam to decrease slightly. Findings are less consistent with regard to N-desmethyloclobazam: serum levels are lower with concurrent valproic acid, but higher with carbamazepine and diphenylhydantoin. **Toxicologic Studies:** In mouse, clobazam was associated with hepatomas in high-dose males. In rat, an increased incidence of thyroid adenomas was seen in males. There were three malignancies: two (male and female) in the thyroid and one (female) in the liver. The relevance of these findings to man has not been established. **ADVERSE REACTIONS** From 19 published studies of Frisium (clobazam) use in epileptic patients, the overall incidence of side-effects was 33% of which drowsiness, dizziness and fatigue were most frequently reported. Canadian experience provides a similar overall incidence (32%) with drowsiness reported in 17.3% of patients, and 12% of patients terminating treatment because of side-effects. The incidence of side-effects was lower in patients under 16 years of age (23.7%) than the incidence in adults (43.1%); $p < 0.05$, whereas treatment discontinuation incidences were similar across age groups: 10.6% and 13.8% respectively. The following side-effects occurred at incidences of greater than 1% (ataxia [3.9%], weight gain [2.2%], dizziness [1.8%], nervousness [1.6%], behaviour disorder [1.4%], hostility and blurred vision [1.3%]) while other effects occurred at a less than 1% incidence. Symptoms of tiredness may sometimes appear, especially at the beginning of treatment with Frisium and when higher doses are used. Also in rare instances and usually only temporarily, the patient may experience dryness of the mouth, constipation, loss of appetite, nausea, dizziness, muscle weakness, disorientation, tiredness, or a fine tremor of the fingers, but also paradoxical reactions, e.g., restlessness and irritability. After prolonged use of benzodiazepines, impairment of consciousness combined with respiratory disorders has been reported in very rare cases, particularly in elderly patients; it sometimes persisted for some length of time. Under experimental conditions, impairment of alertness has been observed to be less pronounced after therapeutic doses of clobazam than after other benzodiazepines. Nevertheless, even when used as directed, the drug may alter reactivity to such an extent as to impair driving performance or the ability to operate machinery, especially when it is taken in conjunction with alcohol. As with other drugs of this type (benzodiazepines), the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use. Isolated cases of skin reactions such as rashes or urticaria have been observed. **DOSE AND ADMINISTRATION** As with other benzodiazepines, the possibility of a decrease in anticonvulsant efficacy in the course of treatment must be borne in mind. In patients with impaired liver and kidney function, Frisium (clobazam) should be used in reduced dosage. **Adults:** Small doses, 5-15 mg/day, should be used initially, gradually increasing to a maximum daily dose of 80 mg as necessary. **Children:** In infants (< 2 years), the initial daily dose is 0.5-1 mg/kg/day. The initial dose in children (2-16 years) should be 5 mg/day, which may be increased at 5-day intervals to a maximum of 40 mg/day. As with all benzodiazepines, abrupt withdrawal may precipitate seizures. It is therefore recommended that Frisium be gradually reduced in dose before treatment is discontinued. **Administration:** If the daily dose is divided, the higher portion should be taken at night. Daily doses up to 30 mg may be taken as a single dose at night. **AVAILABILITY** Frisium is available as white, uncoated, bevelled, round tablets of 7 mm diameter, marked with 'BGL' above and below the scorebreak on the obverse and the Hoechst 'Tower and Bridge' logo on the reverse. Frisium 10 mg tablets are packaged in blisters of PVC film and aluminium foil and are distributed in packs of 30 [3x10] tablets. Product Monograph available on request.

Reference: 1. Clobazam in the Treatment of Refractory Epilepsy - The Canadian Experience. A Retrospective Study, Canadian Clobazam Cooperative Group: Epilepsia, 1990;1-10.

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ELDEPRYL[®]

selegiline hydrochloride



FIRST LINE

Rx Summary
Antiparkinson Agent

Indications and clinical use:

As an adjunct to levodopa (with or without a decarboxylase inhibitor) in the management of the signs and symptoms of Parkinson's disease.

In newly diagnosed patients before symptoms begin to affect the patient's social or professional life, at which time more efficacious treatment becomes necessary.

Contraindications:

In patients with known hypersensitivity to Eldepryl, Eldepryl should not be used in patients with active peptic ulcer, extrapyramidal disorders such as excessive tremor or tardive dyskinesia, or patients with severe psychosis or profound dementia. Eldepryl should not be used with meperidine (Demerol or other trade names). This contraindication is often extended to other opioids.

Warnings (Selective vs non-selective inhibition of MAO-B):

Eldepryl should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. It is prudent, in general, to avoid the concomitant use of Eldepryl and fluoxetine (Prozac).

Warnings to patients:

Patients should be advised of the possible need to reduce levodopa dosage after the initiation of Eldepryl therapy. The patients should be advised not to exceed the daily dose of 10 mg. The risk of using higher doses of Eldepryl should be explained, and a brief description of the "hypertensive crisis" ("cheese reaction") provided.

Precautions:

Some patients given Eldepryl may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reacting with supersensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa by 10-30%.

NURSING MOTHERS: It is not known whether Eldepryl is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

PEDIATRIC USE: The effects of Eldepryl in children under 18 have not been evaluated.

Laboratory Tests:

No specific laboratory tests are essential for management of patients on Eldepryl. Transient or continuing abnormalities with tendency for elevated values in liver function tests have been described in long term therapy. Although serious hepatic toxicity has not been observed, caution is recommended in patients with a history of hepatic dysfunction. Periodic routine evaluation of all patients is however appropriate.

Drug Interactions:

The occurrence of stupor, muscular rigidity, severe agitation and elevated temperature has been reported in a man receiving selegiline and meperidine, as well as other medications. These symptoms were resolved over days when the combination was discontinued. This case is typical of the interaction of meperidine and MAOIs. Other than the possible exacerbation of side effects in patients receiving levodopa therapy, no interactions attributed to the combined use of ELDEPRYL and other drugs have been reported. It is also prudent to avoid the combination of ELDEPRYL and fluoxetine (Prozac).

Use during Pregnancy:

The use of Eldepryl during pregnancy has not been established. Therefore, Eldepryl should be given to a pregnant woman only if the potential benefits outweigh the potential risks.

Adverse reactions:

A) IN COMBINATION WITH LEVODOPA

THE SIDE EFFECTS OF ELDEPRYL ARE USUALLY THOSE ASSOCIATED WITH DOPAMINERGIC EXCESS. ELDEPRYL MAY POTENTIATE THE SIDE EFFECTS OF LEVODOPA, THEREFORE ADJUSTMENT OF THE DOSAGE OF LEVODOPA MAY BE REQUIRED. ONE OF THE MOST SERIOUS ADVERSE REACTIONS REPORTED WITH ELDEPRYL USED AS AN ADJUNCT TO LEVODOPA THERAPY ARE HALLUCINATIONS/CONFUSION, PARTICULARLY VISUAL HALLUCINATIONS.

Other reactions include nausea, dizziness, faintness, abdominal pain, dry mouth, vivid dreams, dyskinesias and headache.

B) IN MONOTHERAPY

The incidence of adverse reactions occurring in trials using Eldepryl as monotherapy has not been fully reported to date. Serious adverse reactions include depression, chest pain, myopathy and diarrhea. Other reported adverse reactions include insomnia, headache, nausea, dizziness and vertigo.

In prospective clinical trials, the following adverse effects (listed in decreasing order of frequency), led to the discontinuation of Eldepryl: Nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinesic involuntary movements, agitation, arrhythmia, bradykinesia chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only rarely as a cause of discontinuation

of treatment include anxiety, drowsiness/lethargy, nervousness, dystonia, increased episodes of freezing, increased tremor, weakness, excessive perspiration, constipation, weight loss, burning lips/mouth, ankle edema, gastrointestinal bleeding and hair loss.

Dosage:

The recommended dosage of Eldepryl as monotherapy in newly diagnosed patients, or as adjunct to levodopa (usually with a decarboxylase inhibitor) is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. When ELDEPRYL adjunctive therapy is added to the existing levodopa therapeutic regime, a reduction, usually of 10 to 30% in the dose of levodopa (in some instances a reduction in the dose of Eldepryl to 5 mg/day) may be required during the period of adjustment of therapy or in case of exacerbation of adverse effects. Doses higher than 10 mg per day should not be used. There is no evidence that additional benefit will be obtained from the administration of higher doses. Furthermore, higher doses will result in a loss of selectivity of Eldepryl towards MAO-B with an increase in the inhibition of type MAO-A.

There is an increased risk of adverse reactions with higher doses as well as an increased risk of hypertensive episode ("cheese reaction")

Supplied:

Eldepryl 5 mg tablets, available in bottles of 60 tablets.

References:

1. The Parkinson Study Group. Effect of Deprenyl on the Progression of Disability in Early Parkinson's Disease. *New Eng Journ* 321, 1364-1371, November 1989.
2. Eldepryl (selegiline hydrochloride) Product Monograph, December 1990.
3. Myllyla VV, Sotaniemi KA, Vuorinen JA, Heinonen EH. Selegiline as initial treatment in de novo parkinsonian patients. *Neurology* 1992; 42, 339-343.
4. Tetrud JW, Langston JW. The Effect of Deprenyl (Selegiline) on the Natural History of Parkinson's Disease. *Science*, August 1989, vol. 245, 519-522.
5. Myllyla VV, Sotaniemi KA, Vuorinen J, Heinonen EH. Selegiline (deprenyl) as primary treatment in Parkinson's disease. *Selegiline therapy in early Parkinson's disease*. July 1990, 19-24.
6. Langston JW in Lees A. *Deprenyl in Parkinson's Disease: Guidelines for Clinicians*. North American Round Table Series, No. 1, 1988, 1-26.
7. DuVoisin RC in Lees A. *Deprenyl in Parkinson's Disease: Guidelines for Clinicians*. North American Round Table Series, No. 1, 1988, 1-26.

Product Monograph available upon request.

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See page xiii.

ACADEMIC NEUROSURGEON – ONTARIO

Victoria Hospital Corporation, London, Ontario, an equal opportunity employer and an affiliated teaching hospital of the University of Western Ontario, invites applications for a full time position in the Division of Neurosurgery, Department of Clinical Neurological Sciences. Victoria Hospital is an 800 bed acute care teaching hospital affiliated with the University of Western Ontario and is the regional centre for critical care/trauma, oncology and paediatrics. Applicants must be Fellows of the Royal College of Physicians and Surgeons of Canada and eligible for licensure in the province of Ontario. The successful candidate must be an excellent surgeon with a demonstrated commitment to teaching and to collaborative clinical or basic research, preferably with a special interest in critical care/trauma, oncology, or paediatrics. Academic rank, salary and contractual arrangements will be commensurate with experience and qualifications. Competition will close within 90 days of this advertisement.

Submit curriculum vitae and the names of three referees to:

Dr. J. Gregory Cairncross
Search Committee Chairman
Department of Clinical Neurological Sciences
Victoria Hospital
375 South Street
London, Ontario, N6A 4G5 Canada.

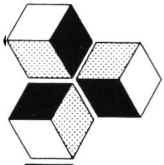
In accordance with Canadian immigration requirements, this advertisement is directed to Canadian Citizens and Permanent Residents of Canada. The University of Western Ontario is committed to employment equity, welcomes diversity in the workplace, and encourages applications from all qualified individuals including women, members of visible minorities, aboriginal persons and persons with disabilities.

NEUROLOGY RESIDENCY – McGILL UNIVERSITY: QUEBEC

Positions for July 1, 1994 for a three-year training program in neurology and the neurosciences leading to FRCP certification. Applicants must be Canadian graduates, currently residing outside Quebec, who have done either two years of training in internal medicine, one year of medicine and an internship year, OR two years of pediatrics. The core three-year program consists of 27 months of clinical training (adult and child neurology, epilepsy/EEG, neuromuscular disease/EMG), a six-month basic neuroscience research laboratory rotation and a three-month elective. The emphasis is on contemporary basic neuroscience and excellent clinical training.

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Montreal Neurological Institute
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Telephone (514) 398-1904



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Baycrest Centre for Geriatric Care is seeking a Board certified neurologist with experience in Behavioral Neurology to participate in an academic and clinical program in neurobehavior within the Division of Neurology, University of Toronto.

Salary commensurate with qualifications and experience.

Send CV and letter of intent to: **Dr. Morris Freedman, Director, Behavioral Neurology Program, Baycrest Centre for Geriatric Care, 3560 Bathurst Street, Toronto, Ontario M6A 2E1**

In accordance with its employment equity policy, the University of Toronto encourages applications from qualified women, men, members of visible minorities, aboriginal peoples and persons with disabilities. In accordance with Canadian Immigration requirements this advertisement is directed to Canadian citizens and permanent residents.

Neuroimaging Research Scientist

Sunnybrook Health Science Centre, a 1200-bed University of Toronto affiliated teaching hospital committed to high standards of excellence and a philosophy of caring, is seeking a qualified professional for –

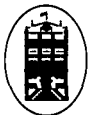
We are offering an exciting and challenging opportunity for an Imaging Neuroscientist to lead multi-disciplinary and multi-institutional research projects on brain-behaviour relationships using quantitative MR techniques in normal aging, dementia, focal brain injury and psychiatric illness. In addition to interactions with researchers in Aging, Behavioural Neurology, Neuropsychology and Psychiatry at Sunnybrook, the position offers research collaborations with a strong Imaging Research Program at Sunnybrook and with a well-known Cognitive Neuroscience Research Group at the Rotman Research Institute of Baycrest Centre. Collaborations with the PET Scan Unit at the Clarke Institute of Psychiatry will also be encouraged.

Applicants should have a PhD or MD with post-doctoral training and expertise in MR neuroimaging and should be eligible for cross-appointment at the University of Toronto at the Assistant Professor level or higher.

Sunnybrook Health Science Centre, located in Toronto, Ontario, Canada is an equal opportunity employer. In accordance with Canadian immigration requirements, this advertisement is directed initially to Canadian citizens and permanent residents. Applicants should submit a C.V. together with the names of three employment references to:



Dr. Geoff Fernie
Director, Research Program in Aging
Centre for Studies in Aging
Sunnybrook Health Science Centre
2075 Bayview Avenue, North York, Ontario M4N 3M5
Canada



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MOLECULAR-CELLULAR NEUROSCIENTISTS. The Neuroscience Program at the Loeb Research Institute and the Division of Neurology at the Ottawa Civic Hospital, a University of Ottawa teaching hospital, is seeking 2 qualified candidates, one at the assistant professor level (PhD and/or MD with at least 3 years postdoc training), and one at the level of established investigator (with an internationally competitive track record). Candidates must demonstrate excellence, originality and productivity in molecular and/or cellular neurobiology. You will join a program whose clinical foci in stroke/ischemia and degenerative/movement disorders are supported by neuroscience research group (8 PIs) who use cell and molecular biology and electrophysiology to study cell-cell communication and neurotransmission, membrane trafficking, mechanisms of neuron/glia response to ischemia, CNS regulation of hydromineral and cardiovascular homeostasis. Preference will be given to applicants using **molecular approaches directed to post-receptor signal transduction.** In accordance with Canadian immigration regulations, this advertisement is directed first, but not solely, to Canadian citizens and permanent residents.

Please forward a CV with names of 3 references and a statement of goals/interests by September 30, 1993 to: **Dr. Leo Renaud, Director, Neurology/Neurosciences, Ottawa Civic Hospital and Loeb Research Institute, 1053 Carling Ave., Ottawa, Ontario, CANADA K1Y 4E9.** We support equal opportunity and a smoke free environment.

ROTMAN RESEARCH INSTITUTE BAYCREST CENTRE FOR GERIATRIC CARE RESEARCH COGNITIVE NEUROSCIENTISTS

The Rotman Institute of Baycrest Centre, associated with the Department of Psychology and the Faculty of Medicine of the University of Toronto, invites applications for research positions in cognitive neuroscience. Present expertise at the Institute includes behavioural neurology, clinical neuropsychology, cognitive and experimental psychology, and neuroimaging.

The successful candidates will possess a Ph.D., M.D., or equivalent; be eligible for cross-appointment at the University of Toronto at the assistant or associate professor level; and have expertise and a track record in cognitive neuroscience research, particularly memory and frontal lobe functions. In addition to a base in human cognition, desired areas of expertise include electrophysiology, quantitative imaging, computational modelling and neuroimaging. Research goals will be broad based, with a focus on aging, focal lesions and dementia.

Baycrest Centre and the University of Toronto encourage applications from qualified women and men, members of visible minorities, aboriginal peoples and persons with disabilities. In accordance with Canadian immigration requirements, this advertisement is directed firstly to Canadian citizens and permanent residents.

Applicants should submit a C.V., relevant reprints and the names of three references to:

Dr. Donald T. Stuss
Vice President, Research
Baycrest Centre for Geriatric Care
3560 Bathurst Street
Toronto, Ontario, CANADA M6A 2E1
Tel: (416) 785-2522
Fax: (416) 785-2862



**“My husband is 55 years old.
And he’s been stolen from me.”**

Alzheimer Disease is a degenerative brain disorder that destroys vital brain cells. It affects over 300,000 Canadians. And that’s not including the people who love them.

Slowly, the disease steals away the ability to think, understand, remember, communicate, or perform the simplest tasks, leaving them completely dependent.

There is no known cause, nor is there a cure. Today.

The Alzheimer Society of Canada is a national organization dedicated to helping those affected by the disease, as well as their caregivers. We also conduct research into possible causes, treatments and a cure, so that we can put an end to the devastation of this killer disease. Tomorrow.

Alzheimer
CANADA

Help for Today. Hope for Tomorrow.

A well orchestrated approach



Rational therapy with Frisium is a well orchestrated approach to complete seizure control in patients of all ages, regardless of seizure type. Adverse events with Frisium are generally mild and transient.¹ Clinically significant drug interactions are uncommon, and impairment of alertness is less pronounced with Frisium than with other benzodiazepines. Help keep these patients in harmony with their surroundings.*

Add
Frisium[®] (clobazam)
To achieve seizure control.

PAAB FRI 2698/9053E

* Please consult precautions statement in Product Monograph.

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For brief prescribing information see page xx.



There are ways of telling when a young epilepsy patient is on Tegretol® CR.

Excellent Seizure Control.

☑ Tegretol® CR (controlled-release carbamazepine) controls seizures in many patients—with little impact on cognitive function.^{1,2} Tegretol CR can leave many patients free to think clearly and do their best.^{1,2}

Consistent Blood Levels.

Tegretol CR delivers fewer “peaks and valleys” in blood levels than conventional Tegretol. That means fewer side effects and a more stable pattern of cognitive functioning.^{3,4}

Convenient B.I.D. Dosing.

When initiating or switching therapy, consider Tegretol CR. It comes in easy-to-break 200mg and 400mg tablets for dosage flexibility, and offers B.I.D. dosing to enhance patient compliance.



TEGRETOL® CR.

*Helping epilepsy patients reach
their full potential.*

Geigy

Mississauga, Ontario L5N 2W5

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