

# 33rd Meeting of the Canadian Congress of Neurological Sciences

Montreal, June 16-20, 1998

## Preliminary Program

*Plenary Sessions • Platform sessions and debates • Meet the Expert Breakfasts: Neurology, Neurosurgery, Child Neurology • Comprehensive Exhibition of the most current pharmaceutical products and medical equipment • Industry Course • Forum on Fellowship Training Programs • Dedicated Poster Viewing Sessions & Interactive Posters • Welcome Reception • Neuroscience Challenge Boat Race*

### **Auxiliary Symposia**

Modern Epilepsy Management  
Unusual Movement Disorder Video Session  
Update on Cerebral Ischemia  
Tremors and Treatment  
Coma and Impaired Consciousness  
Malignant Brain Tumours

### **Child Neurology Day: Topics in Neonatal Neurology**

Neurobiology Review Course

### **Society Courses**

Surgical Management of Pediatric Epilepsy Syndromes  
Vascular Malformations  
Management of Disorders of the Thoracic Spine  
Motor Neuron Disorders and Sleep Disorders  
New Technologies Applied to Child Neurology  
Neurogenetics  
New Findings in Alzheimer's Disease  
New Issues and Treatment in Multiple Sclerosis  
Migraine Headaches

### **Special Feature**

Next year's meeting will highlight the 50th Anniversary of the Canadian Neurological Society founded by Wilder Penfield which consisted of members who were both neurologists and neurosurgeons. To commemorate this event, we are planning historical static displays in addition to the scientific posters and other anniversary events.

### **Special Guests**

<i>Child Neurology Lecturer</i>	<b>Joseph Volpe, Harvard University, Boston</b>
<i>Neurophysiology Lecturer</i>	<b>Alan J. Mc Comas, McMaster University, Hamilton</b>
<i>Penfield Lecturer</i>	<b>Robert Spetzler, Barrow Neurological Institute, Phoenix</b>
<i>Richardson Lecturer</i>	<b>Albert Aguayo, McGill University, Montreal</b>
<i>Royal College Neurology</i>	<b>Michael Moskowitz, Massachusetts General Hospital, Boston</b>
<i>Royal College Neurosurgery</i>	<b>Michael Scott, Boston Children's Hospital, Boston</b>

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# TEGRETOL®

Tablets  
(Carbamazepine)  
Suspension (100 mg/tsp)

## THERAPEUTIC CLASSIFICATION

- Anticonvulsant
- For Symptomatic Relief of Trigeminal Neuralgia
- 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, recourse to 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 mono-therapy or as an adjunct to lithium in the treatment of acute mania or prophylaxis of bipolar (manic-depressive) disorders in patients who are resistant to or are intolerant of conventional antimanic drugs. Carbamazepine may be a useful alternative to neuro-leptics 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. These 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 (MAO) 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. Then 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, to any of the components of the tablets or suspension, or to any of the tricyclic compounds, 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 LYLLE SYNDROME, TEGRETOL SHOULD BE WITHDRAWN AT ONCE.**

**LONG-TERM TOXICITY STUDIES IN RATS INDICATED A POTENTIAL CARCINOGENIC RISK. THEREFORE, THE POSSIBLE RISK OF THE DRUG MUST BE WEIGHED 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 anti-epileptic 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 from patients if required to prevent major seizures because of the risks posed, to both 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. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

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 K<sub>1</sub> administration to the mother during 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 Drug Interactions section under Precautions).

## 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 or 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. However, treatment with TEGRETOL 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 elderly patients 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 a 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. Such patients should be followed closely while taking the drug.

**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. Caution should also be exercised 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 heart 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, warn patients 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. Accordingly, patients should 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 therefore advisable to abstain from alcohol during treatment.

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

**ADVERSE REACTIONS**

The reactions which have been most frequently reported with TEGRETOL (carbamazepine) are CNS (e.g., drowsiness, headache, unsteadiness on the feet, diplopia, dizziness), gastrointestinal disturbances (nausea, vomiting), as well as 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 anemia, pure red cell aplasia, macrocytic anemia, megaloblastic anemia, acute intermittent porphyria, reticulocytosis, folic acid deficiency, thrombocytopenic purpura, and possibly hemolytic anemia. 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.

Rare: Elevated transaminases, jaundice, hepatitis of cholestatic, parenchymal (hepatocellular), or mixed type. Isolated cases: granulomatous hepatitis.

**Dermatologic:** Occasional or 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. Isolated cases of hirsutism have been reported, however the causal relationship is not clear.

**Neurologic:** Frequent: vertigo, somnolence, ataxia and fatigue. Occasional: 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, collapse, 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:** 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, conjunctivitis, retinal changes, tinnitus, hyperacusis, taste disturbances.

**Endocrine system and metabolism:** Occasional: 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: gynecomastia, galactorrhea, abnormal thyroid function tests (decreased L-thyroxine i.e. FT<sub>4</sub>, T<sub>4</sub>, T<sub>3</sub>, T<sub>3</sub>U) 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, 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. Treatment should be discontinued should such hypersensitivity reactions occur.

**DOSE 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 should be taken with meals whenever possible. TEGRETOL Tablets, CHEWTABS and Suspension should be taken in 2 to 4 divided doses daily.

TEGRETOL Suspension should be well shaken before use since improper re-suspension may lead to administering an incorrect dose. Since a given dose of TEGRETOL Suspension produces higher peak carbamazepine levels than the same dose in tablet form, it is advisable to start with low doses and to increase slowly to avoid adverse reactions. When switching a patient from TEGRETOL Tablets to TEGRETOL Suspension, the same number of mg per day should be given in smaller, more frequent doses (i.e., BID Tablets to TID Suspension). TEGRETOL CHEWTABS and the Suspension are particularly suitable for patients who have difficulty swallowing tablets or who need initial careful adjustment of dosage.

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. These 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 on the first day. Increase 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 anti-convulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except for phenytoin, which may be increased (see Drug Interactions section under Precautions and Pregnancy And Nursing section under Warnings).

**Use in Trigeminal Neuralgia:** Initial daily dosage should be small, 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 between 200-800 mg daily; but 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.

**AVAILABILITY OF DOSAGE FORM**

	Pr TEGRETOL® Tablets 200 mg	Pr TEGRETOL® CHEWTABS 100 mg	Pr TEGRETOL® CHEWTABS 200 mg	Pr TEGRETOL® CR 200 mg	Pr TEGRETOL® CR 400 mg	Pr TEGRETOL® Suspension 100 mg/tsp
Colour	White	White with red specks	White with red specks	Beige-orange	Brown-orange	Orange
Shape	Round, flat-faced, bevel-edged	Round, flat-faced, bevel-edged	Oval, biconvex	Oval, slightly biconvex	Oval, slightly biconvex	
Imprint	Engraved GEIGY on one side and quadrisectioned 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 HC on the other. Bisected on both sides	CG/CG engraved on one side and ENE/ENE on the other. Bisected on both sides	Not applicable
Availability	Bottles of 100 & 500	Bottles of 100	Bottles of 100	Bottles of 100	Bottles of 100	Bottles of 450 mL
Storage Conditions	Store below 30°C, protect from humidity	Store below 30°C, protect from humidity and light	Store below 30°C, protect from humidity and light	Store below 25°C, protect from humidity	Store below 25°C, protect from humidity	Store below 30°C, protect from humidity and light

Tegretol is a schedule F drug and can only be obtained by prescription from a licensed practitioner. Product Monograph available on request. December 7, 1995

**References:**

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**Geigy**

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# BETASERON®

Interferon beta-1b

## THERAPEUTIC CLASSIFICATION

Immunomodulator

### ACTION AND CLINICAL PHARMACOLOGY

**Description:** BETASERON® (interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques and formulated for use by injection. Interferon beta-1b is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human interferon beta<sub>1b</sub>. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17. Interferon beta-1b is a highly purified protein that has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural material.

The specific activity of BETASERON is approximately 32 million international units per mg (MIU/mg) interferon beta-1b. Each vial contains 0.3 mg (9.6 MIU) interferon beta-1b. The unit measurement is derived by comparing the antiviral activity of the product to the World Health Organization (WHO) reference standard of recombinant human interferon beta-1b. Dextrose and Albumin Human, USP (15 mg each/vial) are added as stabilizers. Prior to 1993, a different analytical standard was used to determine potency. It assigned 54 million IU to 0.3 mg interferon beta-1b.

Lyophilized BETASERON is a sterile, white to off-white powder intended for subcutaneous injection after reconstitution with the diluent supplied (Sodium Chloride, 0.54% Solution).

**General:** Interferons are a family of naturally occurring proteins, which have molecular weights ranging from 15,000 to 21,000 daltons. Three major classes of interferons have been identified: alpha, beta, and gamma. Interferon beta-1b, interferon alpha, and interferon gamma have overlapping yet distinct biologic activities. The activities of interferon beta-1b are species-restricted and, therefore, the most pertinent pharmacological information on BETASERON (interferon beta-1b) is derived from studies of human cells in culture and in vivo.

**Biologic Activities:** Interferon beta-1b has been shown to possess both antiviral and immunomodulatory activities. The mechanisms by which BETASERON exerts its actions in multiple sclerosis (MS) are not clearly understood. However, it is known that the biologic response-modifying properties of interferon beta-1b are mediated through its interactions with specific cell receptors found on the surface of human cells. The binding of interferon beta-1b to these receptors induces the expression of a number of interferon-induced gene products (e.g., 2',5'-oligoadenylate synthetase, protein kinase, and indoleamine 2,3-dioxygenase) that are believed to be the mediators of the biological actions of interferon beta-1b. A number of these interferon-induced products have been readily measured in the serum and cellular fractions of blood collected from patients treated with interferon beta-1b.

**Clinical Trials:** The effectiveness of BETASERON in relapsing-remitting MS was evaluated in a double-blind, multicentric (11 sites: 4 in Canada and 7 in the U.S.), randomized,

parallel, placebo-controlled clinical investigation of 2 years duration. The study included MS patients, aged 18 to 50, who were ambulatory (Kurtzke expanded disability status scale [EDSS] of  $\leq 5.5$ ), exhibited a relapsing-remitting clinical course, met Poser's criteria for clinically definite and/or laboratory supported definite MS and had experienced at least two exacerbations over 2 years preceding the trial without exacerbation in the preceding month. Patients who had received prior immunosuppressant therapy were excluded.

An exacerbation was defined, per protocol, as the appearance of a new clinical sign/symptom or the clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persisted for a minimum of 24 hours.

Patients selected for study were randomized to treatment with either placebo (n=123), 0.05 mg (1.6 MIU) BETASERON (n=125), or 0.25 mg (8 MIU) BETASERON (n=124) self-administered subcutaneously every other day. Outcome based on the first 372 randomized patients was evaluated after 2 years.

Patients who required more than three 28-day courses of corticosteroids were withdrawn from the study. Minor analgesics (e.g., acetaminophen), antidepressants, and oral antibiotics were allowed ad libitum but chronic nonsteroidal anti-inflammatory drug (NSAID) use was not allowed.

The primary, protocol defined, outcome assessment measures were 1) frequency of exacerbations per patient and 2) proportion of exacerbation free patients. A number of secondary outcome measures were also employed as described in Table 1.

In addition to clinical measures, annual magnetic resonance imaging (MRI) was performed and quantitated for extent of disease as determined by changes in total area of lesions.

In a substudy of patients (n=52) at one site, MRIs were performed every 6 weeks and quantitated for disease activity as determined by changes in size and number of lesions.

Results at the protocol designated endpoint of 2 years (see TABLE 1). In the 2-year analysis, there was a 31% reduction in annual exacerbation rate, from 1.31 in the placebo group to 0.9 in the 0.25 mg (8 MIU) group. The p-value for this difference was 0.0001. The proportion of patients free of exacerbations was 16% in the placebo group, compared with 25% in the BETASERON 0.25 mg (8 MIU) group.

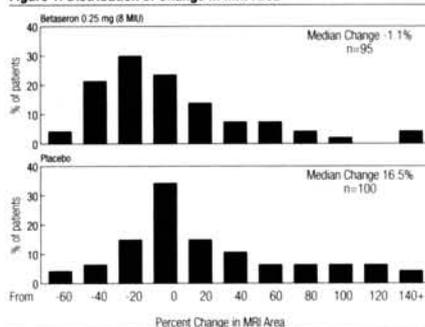
Of the first 372 patients randomized, 72 (19%) failed to complete 2 full years on their assigned treatments. The reasons given for withdrawal varied with treatment assignment. Excessive use of steroids accounted for 11 of the 26 placebo withdrawals. In contrast, among the 25 withdrawals from the 0.25 mg (8 MIU) assigned group, excessive steroid use accounted for only one withdrawal. Withdrawals for adverse events attributed to study article, however, were more common among BETASERON treated patients: 1 and 10 withdrew from the placebo and 0.25 mg (8 MIU) groups, respectively.

Over the 2-year period, there were 25 MS-related hospitalizations in the 0.25 mg (8 MIU) BETASERON-treated group compared to 48 hospitalizations in the placebo group. In comparison, non-MS hospitalizations were evenly distributed between the groups, with 16 in the 0.25 mg (8 MIU) BETASERON group and 15 in the placebo group. The average number of days of MS-related steroid use was 41 days in the 0.25 mg (8 MIU) BETASERON group and 55 days in the placebo group (p=0.004).

MRI data were also analyzed for patients in this study. A frequency distribution of the observed percent changes in MRI area at the end of 2 years was obtained by grouping the percentages in successive intervals of equal width. Figure 1 displays a histogram of the proportions of patients who fell into each of these intervals. The median percent change in MRI area for the 0.25 mg (8 MIU) group was -1.1% which was significantly smaller than the 16.5% observed for the placebo group (p=0.0001).

Fifty-two patients at one site had frequent MRI scans (every 6 weeks). The percentage of scans with new or expanding lesions was 29% in the placebo group and 6% in the 0.25 mg (8 MIU) treatment group (p=0.006).

Figure 1: Distribution of Change in MRI Area



MRI scanning is viewed as a useful means to visualize changes in white matter that are believed to be a reflection of the pathologic changes that, appropriately located within the central nervous system (CNS), account for some of the signs and symptoms that typify relapsing-remitting MS. The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in lesion area often do not correlate with clinical exacerbations probably because many of the lesions affect so-called "silent" regions of the CNS. Moreover, it is not clear what fraction of the lesions seen on MRI become foci of irreversible demyelination (i.e., classic white matter plaques). The prognostic significance of the MRI findings in this study has not been evaluated.

At the end of 2 years on assigned treatment, patients in the study had the option of continuing on treatment under blinded conditions. Approximately 80% of patients in each treatment group accepted. Although there was a trend toward patient benefit in the BETASERON groups during the third year, particularly in the 0.25 mg (8 MIU) group, there was no statistically significant difference between the BETASERON-treated vs. placebo-treated patients in exacerbation rate, or in any of the secondary endpoints described in Table 1. As noted above, in the 2-year analysis, there was a 31% reduction in exacerbation rate in the 0.25 mg (8 MIU) group, compared to placebo. The p-value for this difference was 0.0001. In the analysis of the third year alone, the difference between treatment groups was 28%. The p-value was 0.065. The lower number of patients may account for the loss of statistical significance, and lack of direct comparability among the patient groups in this extension study make the interpretation of these results difficult. The third year MRI data did not show a trend toward additional benefit in the BETASERON arm compared with the placebo arm.

Throughout the clinical trial, serum samples from patients were monitored for the development of antibodies to interferon beta-1b. In patients receiving 0.25 mg (8 MIU) BETASERON (n=124) every other day, 45% were found to have serum neutralizing activity on at least one occasion. One third had neutralizing activity confirmed by at least two consecutive positive titres. This development of neutralizing activity may be associated with a reduction in clinical efficacy, although the exact relationship between antibody formation and therapeutic efficacy is not yet known.

### INDICATIONS AND CLINICAL USE

BETASERON (interferon beta-1b) is indicated for use in ambulatory patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations. (See ACTION AND CLINICAL PHARMACOLOGY, Clinical Trials.) Relapsing-remitting MS is characterized by recurrent attacks of neurologic dysfunction followed by complete or incomplete recovery. The safety and efficacy of BETASERON in chronic-progressive MS has not been evaluated.

### CONTRAINDICATIONS

BETASERON (interferon beta-1b) is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, Albumin Human USP, or any other component of the formulation.

### WARNINGS

One suicide and four attempted suicides were observed among 372 study patients during a 3-year period. All five patients received BETASERON (interferon beta-1b) (three in the 0.05 mg [1.6 MIU] group and two in the 0.25 mg [8.0 MIU] group). There were no attempted suicides in patients on study who did not receive BETASERON. Depression and suicide have been reported to occur in patients receiving interferon alpha, a related compound. Patients treated with BETASERON should

be informed that depression and suicidal ideation may be a side effect of the treatment and should report these symptoms immediately to the prescribing physician. Patients exhibiting depression should be monitored closely and cessation of therapy should be considered.

### PRECAUTIONS

**General:** Patients should be instructed in injection techniques to assure the safe self-administration of BETASERON (interferon beta-1b). (See below and the BETASERON® [interferon beta-1b] INFORMATION FOR THE PATIENT sheet.)

### Information to be provided to the patient: Instruction on self-injection technique and procedures.

It is recommended that the first injection be administered by, or under the direct supervision of, a physician. Appropriate instructions for reconstitution of BETASERON and self-injection, using aseptic techniques, should be given to the patient. A careful review of the BETASERON® [interferon beta-1b] INFORMATION FOR THE PATIENT sheet is also recommended.

Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. Information on how to acquire a puncture resistant container for disposal of used needles and syringes should be given to the patient along with instructions for safe disposal of full containers.

Eighty-five percent of patients in the controlled MS trial reported injection site reactions at one or more times during therapy. Post-marketing experience has been

consistent with this finding, with infrequent reports of injection site necrosis. The onset of injection site necrosis usually appears early in therapy with most cases reported to have occurred in the first two to three months of therapy. The number of sites where necrosis has been observed was variable.

Rarely, the area of necrosis has extended to subcutaneous fat or fascia. Response to treatment of injection site necrosis with antibiotics and/or steroids has been variable. In some of these patients elective debridement and, less frequently, skin grafting took place to facilitate healing which could take from three to six months.

Some patients experienced healing of necrotic skin lesions while BETASERON therapy continued. In other cases new necrotic lesions developed even after therapy was discontinued.

The nature and severity of all reported reactions should be carefully assessed. Patient understanding and use of aseptic self-injection technique and procedures should be periodically reevaluated.

Flu-like symptoms are not uncommon following initiation of therapy with BETASERON. In the controlled MS clinical trial, acetaminophen was permitted for relief of fever or myalgia.

Patients should be cautioned not to change the dosage or the schedule of administration without medical consultation.

**Warnings of adverse reactions.** Patients should be advised about the common adverse events associated with the use of BETASERON, particularly, injection site reactions and the flu-like symptom complex (see ADVERSE REACTIONS).

Patients should be cautioned to report depression or suicidal ideation (see WARNINGS).

Patients should be advised about the abortifacient potential of BETASERON (see PRECAUTIONS, Use in Pregnancy).

**Laboratory Tests:** The following laboratory tests are recommended prior to initiating BETASERON therapy and at periodic intervals thereafter: thyroid function test, hemoglobin, complete and differential white blood cell counts, platelet counts and blood chemistries including liver function tests. A pregnancy test, chest roentgenogram and ECG should also be performed prior to initiating BETASERON therapy. In the controlled MS trial, patients were monitored every 3 months. The study protocol stipulated that BETASERON therapy be discontinued in the event the absolute neutrophil count fell below 750/mm<sup>3</sup>. When the absolute neutrophil count had returned to a value greater than 750/mm<sup>3</sup>, therapy could be restarted at a 50% reduced dose. No patients were withdrawn or dose-reduced for neutropenia or lymphopenia.

Similarly, if AST/ALT (SGOT/SGPT) levels exceeded 10 times the upper limit of normal, or if the serum bilirubin exceeded 5 times the upper limit of normal, therapy was discontinued. In each instance during the controlled MS trial, hepatic enzyme abnormalities returned to normal following discontinuation of therapy. When measurements had decreased to below these levels, therapy could be restarted at a 50% dose reduction, if clinically appropriate. Dose was reduced in two patients due to increased liver enzymes; one continued on treatment and one was ultimately withdrawn.

**Drug Interactions:** Interactions between BETASERON and other drugs have not been fully evaluated. Although studies designed to examine drug interactions have not been done, it was noted that BETASERON patients (n=180) had received corticosteroid or ACTH treatment of relapses for periods of up to 28 days.

BETASERON administered in three cancer patients over a dose range of 0.025 mg (0.8 MIU) to 2.2 mg (71 MIU) led to a dose-dependent inhibition of antipyrine elimination. The effect of alternate-day administration of 0.25 mg (8 MIU) BETASERON on drug metabolism in MS patients is unknown.

**Impairment of Fertility:** Studies in female rhesus monkeys

Table 1: 2-Year Study Results

### Primary and Secondary Endpoints

Efficacy Parameters	Treatment Groups			Statistical Comparisons		
	Placebo (n=123)	0.05 mg (1.6 MIU) (n=125)	0.25 mg (8 MIU) (n=124)	p-value		
Primary Clinical Endpoints				Placebo vs 0.05 mg (1.6 MIU)	0.05 mg (1.6 MIU) vs 0.25 mg (8 MIU)	Placebo vs 0.25 mg (8 MIU)
Annual exacerbation rate	1.31	1.14	0.90	0.005	0.113	0.0001
Proportion of exacerbation-free patients†	16%	18%	25%	0.609	0.288	0.094
Exacerbation frequency per patient	0 <sup>†</sup>	20	22	0.151	0.077	0.001
	1	32	31			
	2	20	28			
	3	15	15			
	4	15	7			
	≥5	21	16			
Secondary Endpoints <sup>‡</sup>						
Median number of months to first on-study exacerbation	5	6	9	0.299	0.097	0.010
Rate of moderate or severe exacerbations per year	0.47	0.29	0.23	0.020	0.257	0.001
Mean number of moderate or severe exacerbation days per patient	44.1	33.2	19.5	0.229	0.064	0.001
Mean change in EDSS score <sup>‡</sup> at endpoint	0.21	0.21	-0.07	0.995	0.108	0.144
Mean change in Scripps score <sup>‡‡</sup> at endpoint	-0.53	-0.50	0.66	0.641	0.051	0.126
Median duration per exacerbation (days)	36	33	35.5	ND	ND	ND
% change in mean MRI lesion area at endpoint	21.4%	9.8%	-0.9%	0.015	0.019	0.0001

ND: Not done.

† 14 exacerbation-free patients (0 from placebo, 6 from 0.05 mg, and 8 from 0.25 mg groups) dropped out of the study before completing 6 months of therapy. These patients are excluded from this analysis.

‡ Sequelae and Functional Neurologic Status, both required by protocol, were not analyzed individually but are included as a function of the EDSS.

‡ EDSS scores range from 0-10, with higher scores reflecting greater disability.

‡‡ Scripps neurologic rating scores range from 0-100, with smaller scores reflecting greater disability.

with normal menstrual cycles, at doses up to 0.33 mg (10.7 MIU/kg/day (equivalent to 32 times the recommended human dose based on body surface area comparison) showed no apparent adverse effects on the menstrual cycle or on associated hormonal profiles (progesterone and estradiol) when administered over 3 consecutive menstrual cycles. The extrapolability of animal doses to human doses is not known. Effects of BETASERON on women with normal menstrual cycles are not known.

**Use in Pregnancy:** BETASERON was not teratogenic at doses up to 0.42 mg (13.3 MIU/kg/day) in rhesus monkeys, but demonstrated a dose-related abortifacient activity when administered at doses ranging from 0.028 mg (0.89 MIU/kg/day (2.8 times the recommended human dose based on body surface area comparison) to 0.42 mg (13.3 MIU/kg/day (40 times the recommended human dose based on body surface area comparison). The extrapolability of animal doses to human doses is not known. Lower doses were not studied in monkeys. Spontaneous abortions while on treatment were reported in patients (n=4) who participated in the BETASERON MS clinical trial. BETASERON given to rhesus monkeys on gestation days 20 to 70 did not cause teratogenic effects; however, it is not known if teratogenic effects exist in humans. There are no adequate and well controlled studies in pregnant women. Women of childbearing potential should take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking BETASERON, the patient should discontinue therapy.

**Nursing Mothers:** It is not known whether BETASERON is excreted in human milk. Given that many drugs are excreted in human milk, there is a potential for serious adverse reactions in nursing infants, therefore a decision should be made whether to discontinue nursing or discontinue BETASERON treatment.

**Pediatric Use:** Safety and efficacy in children under 18 years of age have not been established.

**Dependence Liability:** No evidence or experience suggests that abuse or dependence occurs with BETASERON therapy; however, the risk of dependence has not been systematically evaluated.

**ADVERSE REACTIONS**

Experience with BETASERON (interferon beta-1b) in patients with MS is limited to a total of 147 patients at the recommended dose of 0.25 mg (8 MIU) or more, every other day. Consequently, adverse events that are associated with the use of BETASERON in MS patients at an incidence of 1% or less may not have been observed in pre-marketing studies. Clinical experience with BETASERON in non-MS patients (e.g., cancer patients, HIV positive patients) provides additional safety data; however, this experience may not be fully applicable to MS patients.

Injection site reactions (85%) and injection site necrosis (5%) occurred after administration of BETASERON. Inflammation, pain, hypersensitivity, necrosis, and non-specific reactions were significantly associated (p<0.05) with the 0.25 mg (8 MIU) BETASERON-treated group. Only inflammation, pain, and necrosis were reported as severe events. The incidence rate for injection site reactions was calculated over the course of 3 years. This incidence rate decreased over time, with 79% of patients experiencing the event during the first 3 months of treatment compared to 47% during the last 6 months. The median time to the first occurrence of an injection site reaction was 7 days. Patients with injection site reactions reported these events 183.7 days per year. Three patients withdrew from the 0.25 mg (8 MIU) BETASERON-treated group for injection site pain.

Flu-like symptom complex was reported in 76% of the patients treated with 0.25 mg (8 MIU) BETASERON. A patient was defined as having a flu-like symptom complex if flu-like syndrome or at least two of the following symptoms were concurrently reported: fever, chills, myalgia, malaise or sweating. Only myalgia, fever, and chills were reported as severe in more than 5% of the patients. The incidence rate for flu-like symptom complex was also calculated over the course of 3 years. The incidence rate of these events decreased over time, with 60% of patients experiencing the event during the first 3 months of treatment compared to 10% during the last 6 months. The median time to the first occurrence of flu-like symptom complex was 3.5 days and the median duration per patient was 7.5 days per year.

Laboratory abnormalities included:

- lymphocyte count < 1500/mm<sup>3</sup> (82%),
- ALT (SGPT) > 5 times baseline value (19%),
- absolute neutrophil count < 1500/mm<sup>3</sup> (18%) (no patients had absolute neutrophil counts < 500/mm<sup>3</sup>),
- WBC < 3000/mm<sup>3</sup> (16%), and
- total bilirubin > 2.5 times baseline value (6%).

Three patients were withdrawn from treatment with 0.25 mg (8 MIU) BETASERON for abnormal liver enzymes including one following dose reduction (see **PRECAUTIONS, Laboratory Tests**).

Twenty-one (28%) of the 76 females of childbearing age treated at 0.25 mg (8 MIU) BETASERON and 10 (13%) of the 76 females of child-bearing age treated with placebo reported menstrual disorders. All reports were of mild to moderate severity and included: intermenstrual bleeding and spotting, early or delayed menses, decreased days of menstrual flow, and clotting and spotting during menstruation.

Mental disorders such as depression, anxiety, emotional lability, depersonalization, suicide attempts and confusion were observed in this study. Two patients withdrew for confusion. One suicide and four attempted suicides were

also reported. It is not known whether these symptoms may be related to the underlying neurological basis of MS, to BETASERON treatment, or to a combination of both. Some similar symptoms have been noted in patients receiving interferon alpha and both interferons are thought to act through the same receptor. Patients who experience these symptoms should be monitored closely and cessation of therapy should be considered.

Additional common clinical and laboratory adverse events associated with the use of BETASERON are listed in the following paragraphs. These events occurred at an incidence of 5% or more in the 124 MS patients treated with 0.25 mg (8 MIU) BETASERON every other day for periods of up to 3 years in the controlled trial, and at an incidence that was at least twice that observed in the 123 placebo patients.

- Common adverse clinical and laboratory events associated with the use of BETASERON were:
- injection site reaction (85%),
  - lymphocyte count < 1500/mm<sup>3</sup> (82%),
  - ALT (SGPT) > 5 times baseline value (19%),
  - absolute neutrophil count < 1500/mm<sup>3</sup> (18%),
  - menstrual disorder (17%),
  - WBC < 3000/mm<sup>3</sup> (16%),
  - palpitation (8%),
  - dyspnea (8%),
  - cystitis (8%),
  - hypertension (7%),
  - breast pain (7%),
  - tachycardia (6%),
  - gastrointestinal disorders (6%),
  - total bilirubin > 2.5 times baseline value (6%),
  - somnolence (6%),
  - laryngitis (6%),
  - pelvic pain (6%),
  - menorrhagia (6%),
  - injection site necrosis (5%), and
  - peripheral vascular disorders (5%).

A total of 277 MS patients have been treated with BETASERON in doses ranging from 0.025 mg (0.8 MIU) to 0.5 mg (16 MIU). During the first 3 years of treatment, withdrawals due to clinical adverse events or laboratory abnormalities not mentioned above included:

- fatigue (2%, 6 patients),
- cardiac arrhythmia (< 1%, 1 patient),
- allergic urticarial skin reaction to injections (< 1%, 1 patient),
- headache (< 1%, 1 patient),
- unspecified adverse events (< 1%, 1 patient), and
- "felt sick" (< 1%, 1 patient).

The table that follows enumerates adverse events and laboratory abnormalities that occurred at an incidence of 2% or more among the 124 MS patients treated with 0.25 mg (8 MIU) BETASERON every other day for periods of up to 3 years in the controlled trial and at an incidence that was at least 2% more than that observed in the 123 placebo patients. Reported adverse events have been re-classified using the standard COSTART glossary to reduce the total number of terms employed in Table 2. In the following table, terms so general as to be uninformative, and those events where a drug cause was remote have been excluded.

**Table 2: Adverse Events and Laboratory Abnormalities**

Adverse Reaction	Placebo n=123	0.25 mg (8 MIU) n=124
<b>Body as a Whole</b>		
- Injection site reaction*	37%	85%
- Headache	77%	84%
- Fever*	41%	59%
- Flu-like symptom complex*	56%	76%
- Pain	48%	52%
- Asthenia*	35%	49%
- Chills*	19%	46%
- Abdominal pain	24%	32%
- Malaise*	3%	15%
- Generalized edema	6%	8%
- Pelvic pain	3%	6%
- Injection site necrosis*	0%	5%
- Cyst	2%	4%
- Necrosis	0%	2%
- Suicide attempt	0%	2%
<b>Cardiovascular System</b>		
- Migraine	7%	12%
- Palpitation*	2%	8%
- Hypertension	2%	7%
- Tachycardia	3%	6%
- Peripheral vascular disorder	2%	5%
- Hemorrhage	1%	3%
<b>Digestive System</b>		
- Diarrhea	29%	35%
- Constipation	18%	24%
- Vomiting	19%	21%
- Gastrointestinal disorder	3%	6%
<b>Endocrine System</b>		
- Goiter	0%	2%
<b>Hemic and Lymphatic System</b>		
- Lymphocytes < 1500/mm <sup>3</sup>	67%	82%
- ANC < 1500/mm <sup>3</sup> *	6%	18%
- WBC < 3000/mm <sup>3</sup> *	5%	16%
- Lymphadenopathy	11%	14%
<b>Metabolic and Nutritional Disorders</b>		
- ALT (SGPT) > 5 times baseline*	6%	19%

**Table 2: Adverse Events and Laboratory Abnormalities (cont'd)**

Adverse Reaction	Placebo n=123	0.25 mg (8 MIU) n=124
- Glucose < 55 mg/dL	13%	15%
- Total bilirubin > 2.5 times baseline	2%	6%
- Urine protein > 1+	3%	5%
- AST (SGOT) > 5 times baseline*	0%	4%
- Weight gain	0%	4%
- Weight loss	2%	4%
<b>Musculoskeletal System</b>		
- Myalgia*	28%	44%
- Myasthenia	10%	13%
<b>Nervous System</b>		
- Dizziness	28%	35%
- Hypertonia	24%	26%
- Depression	24%	25%
- Anxiety	13%	15%
- Nervousness	5%	8%
- Somnolence	3%	6%
- Confusion	2%	4%
- Speech disorder	1%	3%
- Convulsion	0%	2%
- Hyperkinesia	0%	2%
- Amnesia	0%	2%
<b>Respiratory System</b>		
- Sinusitis	26%	36%
- Dyspnea*	2%	8%
- Laryngitis	2%	6%
<b>Skin and Appendages</b>		
- Sweating*	11%	23%
- Alopecia	2%	4%
<b>Special Senses</b>		
- Conjunctivitis	10%	12%
- Abnormal vision	4%	7%
<b>Urogenital System</b>		
- Dysmenorrhea	11%	18%
- Menstrual disorder*	8%	17%
- Metrorrhagia	8%	15%
- Cystitis	4%	8%
- Breast pain	3%	7%
- Menorrhagia	3%	6%
- Urinary urgency	2%	4%
- Fibrocystic breast	1%	3%
- Breast neoplasm	0%	2%

\* Significantly associated with BETASERON treatment

It should be noted that the figures cited in Table 2 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. The cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Other events observed during pre-marketing evaluation of various doses of BETASERON in 1440 patients are listed in the paragraphs that follow. Given that most of the events were observed in open and uncontrolled studies, the role of BETASERON in their causation cannot be reliably determined.

**Body as a Whole:** abscess, adenoma, anaphylactoid reaction, ascites, cellulitis, hernia, hydrocephalus, hypothermia, infection, peritonitis, photosensitivity, sarcoma, sepsis, and shock;

**Cardiovascular System:** angina pectoris, arrhythmia, atrial fibrillation, cardiomegaly, cardiac arrest, cerebral hemorrhage, cerebral ischemia, endocarditis, heart failure, hypotension, myocardial infarct, pericardial effusion, postural hypotension, pulmonary embolus, spider angioma, subarachnoid vein, syncope, thrombophlebitis, thrombosis, varicose veins, vasospasm, venous pressure increased, ventricular extrasystoles, and ventricular fibrillation;

**Digestive System:** aphthous stomatitis, cardiopasm, cheilitis, cholecystitis, cholelithiasis, duodenal ulcer, dry mouth, enteritis, esophagitis, fecal impaction, fecal incontinence, flatulence, gastritis, gastrointestinal hemorrhage, gingivitis, glossitis, hematemesis, hepatic neoplasia, hepatitis, hepatomegaly, ileus, increased salivation, intestinal obstruction, melena, nausea, oral leukoplakia, oral moniliasis, pancreatitis, periorbital abscess, proctitis, rectal hemorrhage, salivary gland enlargement, stomach ache, and tenesmus;

**Endocrine System:** Cushing's Syndrome, diabetes insipidus, diabetes mellitus, hypothyroidism, and inappropriate ADH;

**Hemic and Lymphatic System:** chronic lymphocytic leukemia, hemoglobin less than 9.4 g/100 mL, petechia, platelets less than 75,000/mm<sup>3</sup>, and splenomegaly;

**Metabolic and Nutritional Disorders:** alcohol intolerance, alkaline phosphatase greater than 5 times baseline value, BUN greater than 40 mg/dL, calcium greater than 11.5 mg/dL, cyanosis, edema, glucose greater than 160 mg/dL, glycosuria, hypoglycemic reaction, hypoxia, ketosis, and thirst;

**Musculoskeletal System:** arthritis, arthrosis, bursitis, leg cramps, muscle atrophy, myopathy, myositis, ptosis, and tenosynovitis;

**Nervous System:** abnormal gait, acute brain syndrome, agitation, apathy, aphasia, ataxia, brain edema, chronic brain syndrome, coma, delirium, delusions, dementia, depersonalization, diplopia, dystonia, encephalopathy, euphoria, facial paralysis, foot drop, hallucinations, hemiplegia, hyperalgesia, hyperesthesia, incoordination, intracranial hypertension, libido decreased, manic reaction, meningitis, neuralgia, neuropathy, neurosis, nystagmus, oculogyric crisis,

ophthalmoplegia, papilledema, paralysis, paranoid reaction, psychosis, reflexes decreased, stupor, subdural hematoma, torticollis, tremor and urinary retention;

**Respiratory System:** apnea, asthma, atelectasis, carcinoma of the lung, hemoptysis, hiccup, hyperventilation, hyperventilation, interstitial pneumonia, lung edema, pleural effusion, pneumonia, and pneumothorax;

**Skin and Appendages:** contact dermatitis, erythema nodosum, exfoliative dermatitis, furunculosis, hirsutism, leukoderma, lichenoid dermatitis, maculopapular rash, psoriasis, seborrhea, skin benign neoplasm, skin carcinoma, skin hypertrophy, skin necrosis, skin ulcer, urticaria, and vesiculobullous rash;

**Special Senses:** blepharitis, blindness, deafness, dry eyes, ear pain, iritis, keratoconjunctivitis, mydriasis, otitis externa, otitis media, parosmia, photophobia, retinitis, taste loss, taste perversion, and visual field defect;

**Urogenital System:** anuria, balanitis, breast engorgement, cervicitis, epididymitis, gynecocystitis, hematuria, impotence, kidney calculus, kidney failure, kidney tubular disorder, leukorrhea, nephritis, nocturia, oliguria, polyuria, salpingitis, urethritis, urinary incontinence, uterine fibroids enlarged, uterine neoplasm, and vaginal hemorrhage.

**DOSAGE AND ADMINISTRATION**

**FOR SUBCUTANEOUS USE ONLY**

The recommended dose of BETASERON (interferon beta-1b) for the treatment of ambulatory relapsing-remitting MS is 0.25 mg (8 MIU) injected subcutaneously every other day. Limited data regarding the activity of a lower dose are presented above (see **ACTION AND CLINICAL PHARMACOLOGY, Clinical Trials**).

Evidence of efficacy beyond 2 years is not known since the primary evidence of efficacy derives from a 2-year, double-blind, placebo-controlled clinical trial (see **ACTION AND CLINICAL PHARMACOLOGY, Clinical Trials**). Safety data is not available beyond the third year. Some patients were discontinued from this trial due to unremitting disease progression of 6 months or greater.

To reconstitute lyophilized BETASERON for injection, use a sterile syringe and needle to inject 1.2 mL of the diluent supplied, Sodium Chloride, 0.54% Solution, into the BETASERON vial. Gently swirl the vial of BETASERON to dissolve the drug completely; do not shake. Inspect the reconstituted product visually and discard the product before use if it contains particulate matter or is discolored. After reconstitution with accompanying diluent, each mL of solution contains 0.25 mg (8 MIU) interferon beta-1b, 13 mg Albumin Human USP and 13 mg Dextrose USP.

Withdraw 1 mL of reconstituted solution from the vial into a sterile syringe fitted with a 27-gauge needle and inject the solution subcutaneously. Sites for self-injection include abdomen, buttocks and thighs. A vial is suitable for single use only; unused portions should be discarded 3 hours after reconstitution. (See the **BETASERON® [interferon beta-1b] INFORMATION FOR THE PATIENT** sheet for **SELF-INJECTION PROCEDURE**.)

**PHARMACEUTICAL INFORMATION**

**Common Name:** interferon beta-1b (USAN)  
**Molecular Weight:** approximately 18,500 daltons  
**Physical Form:** sterile, lyophilized powder  
**Composition**  
 (each vial contains): 0.3 mg (9.6 MIU) interferon beta-1b, 15 mg Albumin Human, USP  
 15 mg Dextrose, USP

**Stability**  
 (before reconstitution): Store under refrigeration at 2° to 8°C (36° to 46°F). Avoid freezing. If refrigeration is not possible, vials of BETASERON and diluent should be kept as cool as possible, below 30°C (86°F), away from heat and light, and used within 7 days.

**Stability**  
 (after reconstitution): The reconstituted product contains no preservative. If not used immediately, store under refrigeration at 2° to 8°C (36° to 46°F) and use within 3 hours of reconstitution. Avoid freezing.

**AVAILABILITY OF DOSAGE FORMS**

BETASERON (interferon beta-1b) is presented as a 3 mL single-use vial of lyophilized powder containing 0.3 mg (9.6 MIU) interferon beta-1b, 15 mg Albumin Human USP, and 15 mg Dextrose, USP. BETASERON is supplied in cartons containing 15 vials of medication and 15 vials of diluent (2 mL of Sodium Chloride 0.54% solution, per vial). Store under refrigeration at 2° to 8°C (36° to 46°F).

Product Monograph available upon request.

1. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; 43: 655-661.

2. Paly DW, Li DK, the UBC MS/MRI Study Group, et al. The IFNB Depersonalization Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; 43: 662-667.

3. Data on File, Heeck confirmations, June 1997.

(FAAB)  
(PMAC)

# Lamictal<sup>®</sup>

Lamotrigine Tablets (25, 100 and 150 mg)  
THERAPEUTIC CLASS

Antiepileptic

## ACTION AND CLINICAL PHARMACOLOGY

LAMICTAL (lamotrigine) is a drug of the phenyltriazine class chemically unrelated to existing antiepileptic drugs (AEDs). Lamotrigine is thought to act at voltage-sensitive sodium channels to stabilize neuronal membranes and inhibit the release of excitatory amino acid neurotransmitters (e.g. glutamate, aspartate) that are thought to play a role in the generation and spread of epileptic seizures.

## Clinical Trials

In placebo-controlled clinical studies, LAMICTAL has been shown to be effective in reducing seizure frequency and the number of days with seizures when added to existing antiepileptic drug therapy in adult patients with partial seizures, with or without generalized tonic-clonic seizures, that are not satisfactorily controlled. Studies have also been conducted using lamotrigine monotherapy in patients (n=443) newly diagnosed with epilepsy (partial seizures, with or without secondary generalization or primary generalized tonic clonic). Results have shown comparable efficacy (time to first seizure, seizure frequency, percentage of patients seizure-free) with fewer side effects than currently approved therapies. Clinical trials have also demonstrated that patients (any seizure type) can be converted to lamotrigine monotherapy from polytherapy with significant numbers of patients maintaining or improving seizure control. Efficacy was maintained during long-term treatment (up to 152 weeks).

**Pharmacokinetics: Adults:** LAMICTAL is rapidly and completely absorbed following oral administration, reaching peak plasma concentrations 1.4 to 4.8 hours ( $T_{max}$ ) post-dosing. When administered with food, the rate of absorption is slightly reduced, but the extent remains unchanged. Following single LAMICTAL doses of 50-400 mg, peak plasma concentration ( $C_{max}$ )=0.6-4.6 µg/mL and the area under the plasma concentration-versus-time curve (AUC=29.9-2111 ngµg/mL) increase linearly with dose. The time-to-peak concentration, elimination half-life ( $t_{1/2}$ ) and volume of distribution (Vd/F) are independent of dose. The  $t_{1/2}$  averages 33 hours after single doses and Vd/F ranges from 0.9 to 1.4 L/kg. Following repeated dosing in healthy volunteers for 14 days, the  $t_{1/2}$  decreased by an average of 26% (mean steady state  $t_{1/2}$  of 26.4 hours) and plasma clearance increased by an average of 33%. In a single-dose study where healthy volunteers were administered both oral and intravenous doses of lamotrigine, the absolute bioavailability of oral lamotrigine was 98%. Lamotrigine is approximately 55% bound to human plasma proteins. This binding is unaffected by therapeutic concentrations of phenytoin, phenobarbital or valproic acid. Lamotrigine does not displace other antiepileptic drugs (carbamazepine, phenytoin, phenobarbital) from protein binding sites. Lamotrigine is metabolized predominantly in the liver by glucuronic acid conjugation. The major metabolite is an inactive 2-N-glucuronide conjugate that can be hydrolyzed by β-glucuronidase. Approximately 70% of an oral LAMICTAL dose is recovered in urine as this metabolite. **Elderly:** The pharmacokinetics of lamotrigine in 12 healthy elderly volunteers (≥ 65 years) who each received a single oral dose of LAMICTAL (150 mg) were not different from those in healthy young volunteers. (However, see PRECAUTIONS, Use in the Elderly, and DOSAGE AND ADMINISTRATION.) **Renal Impairment:** The pharmacokinetics of a single oral dose of LAMICTAL (100 mg) were evaluated in 12 individuals with chronic renal failure (with mean creatinine clearance of 13 mL/min) who were not receiving other antiepileptic drugs. In this study, the elimination half-life of unchanged lamotrigine was prolonged (by an average of 63%) relative to individuals with normal renal function (see PRECAUTIONS, Renal Failure and DOSAGE AND ADMINISTRATION). **Hemodialysis:** In six hemodialysis patients, the elimination half-life of unchanged lamotrigine was doubled off dialysis, and reduced by 50% on dialysis, relative to individuals with normal renal function. **Hepatic Impairment:** The pharmacokinetics of lamotrigine in patients with impaired liver function have not been evaluated. **Gilbert's Syndrome:** Gilbert's syndrome (idiopathic unconjugated hyperbilirubinemia) does not appear to affect the pharmacokinetic profile of lamotrigine. **Concomitant Antiepileptic Drugs:** In patients with epilepsy, concomitant administration of LAMICTAL with enzyme-inducing AEDs (phenytoin, carbamazepine, primidone or phenobarbital) decreases the mean lamotrigine  $t_{1/2}$  to 13 hours. Concomitant administration of LAMICTAL with valproic acid significantly increases  $t_{1/2}$  and decreases the clearance of lamotrigine, whereas concomitant administration of LAMICTAL with valproic acid plus enzyme-inducing AEDs can prolong  $t_{1/2}$  up to approximately 27 hours. Acetaminophen was shown to slightly decrease the  $t_{1/2}$  and increase the clearance of lamotrigine. The key lamotrigine parameters for adult patients and healthy volunteers are summarized in Table 1.

Table 1: Mean Pharmacokinetic Parameters in Adult Patients with Epilepsy or Healthy Volunteers

LAMICTAL Administered	Healthy Young Volunteers		Patients with Epilepsy			
	LAMICTAL	LAMICTAL + Valproic Acid <sup>2</sup>	LAMICTAL + Enzyme-Inducing AEDs	LAMICTAL + Valproic Acid	LAMICTAL + Valproic Acid + Enzyme-Inducing AEDs	
$T_{max}$ (hrs)	Single Dose	2.2 (0.25-12.0) <sup>1</sup>	1.8 (1.0-4.0)	2.3 (0.5-5.0)	4.8 (1.8-8.4)	3.8 (1.0-10.0)
	Multiple Dose	1.7 (0.5-4.0)	1.9 (0.5-3.5)	2.0 (0.75-5.93)	ND	ND
$t_{1/2}$	Single Dose	32.8 (14.0-103.0)	48.3 (31.5-88.6)	14.4 (6.4-30.4)	58.8 (30.5-88.8)	27.2 (11.2-51.6)
	Multiple Dose	25.4 (11.6-61.6)	70.3 (41.9-113.5)	12.6 (7.5-23.1)	ND	ND
Plasma Clearance (mL/min/kg)	Single Dose	0.44 (0.12-1.10)	0.30 (0.14-0.42)	1.10 (0.51-2.22)	0.28 (0.16-0.40)	0.53 (0.27-1.04)
	Multiple Dose	0.58 (0.24-1.15)	0.18 (0.12-0.33)	1.21 (0.66-1.82)	ND	ND

ND=Not done

1 Range of individual values across studies

2 Valproic acid administered chronically (Multiple Dose Study) or for 2 days (Single Dose Study)

## INDICATIONS AND CLINICAL USE

LAMICTAL (lamotrigine) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy. LAMICTAL is also indicated for use as monotherapy following withdrawal of concomitant antiepileptic drugs.

## CONTRAINDICATIONS

LAMICTAL (lamotrigine) is contraindicated in patients with known hypersensitivity to lamotrigine or to any components of the formulation.

## WARNINGS

SEVERE, POTENTIALLY LIFE-THREATENING RASHES HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF LAMICTAL. THESE REPORTS, OCCURRING IN APPROXIMATELY ONE IN EVERY THOUSAND ADULTS, HAVE INCLUDED STEVENS JOHNSON SYNDROME AND, RARELY, TOXIC EPIDERMAL NECROLYSIS. RARE DEATHS HAVE BEEN REPORTED. THE INCIDENCE OF SEVERE, POTENTIALLY LIFE-THREATENING RASH IN PEDIATRIC PATIENTS APPEARS HIGHER THAN THAT REPORTED IN ADULTS USING LAMICTAL. SPECIFICALLY, REPORTS FROM CLINICAL TRIALS SUGGEST THAT AS MANY AS 1 IN 50 TO 1 IN 100 PEDIATRIC PATIENTS MAY DEVELOP A POTENTIALLY LIFE-THREATENING RASH. IT BEARS EMPHASIS, THAT LAMICTAL IS NOT CURRENTLY APPROVED FOR USE IN PATIENTS BELOW THE AGE OF 18 (see PRECAUTIONS). A HIGHER INCIDENCE OF SERIOUS DERMATOLOGIC EVENTS (see PRECAUTIONS, Skin-related events, TABLES 2 AND 3; see also DOSAGE AND ADMINISTRATION) HAS BEEN ASSOCIATED WITH MORE RAPID INITIAL TITRATION DOSING (EXCEEDING THE RECOMMENDED INITIAL DOSE OR EXCEEDING THE RECOMMENDED DOSE ESCALATION), AND USE OF CONCOMITANT VALPROIC ACID. NEARLY ALL CASES OF SERIOUS RASHES ASSOCIATED WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (E.G., 6 MONTHS). ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE POTENTIAL RISK SIGNALED BY THE FIRST APPEARANCE OF A RASH. ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE LIFE-THREATENING. ACCORDINGLY, ALL PATIENTS WHO DEVELOP RASH SHOULD BE PROMPTLY EVALUATED AND LAMICTAL WITHDRAWN IMMEDIATELY, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED.

**Hypersensitivity Reactions:** Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial edema and abnormalities of the blood and liver. The syndrome

shows a wide spectrum of clinical severity and may rarely lead to disseminated intravascular coagulation (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and LAMICTAL discontinued if an alternative aetiology cannot be established.

**Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.**

## PRECAUTIONS

**Drug Discontinuation:** Abrupt discontinuation of any antiepileptic drug (AED) in a responsive patient with epilepsy may provoke rebound seizures. In general, withdrawal of an AED should be gradual to minimize this risk. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL (lamotrigine) should be tapered over a period of at least two weeks (see DOSAGE AND ADMINISTRATION). **Occupational Hazards:** Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials common adverse effects included dizziness, ataxia, drowsiness, diplopia, and blurred vision. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that LAMICTAL does not affect them adversely. **Skin-Related Events:** In controlled studies of adjunctive lamotrigine therapy, the incidence of rash (usually maculopapular and/or erythematous) in patients receiving LAMICTAL was 10% compared with 5% in placebo patients. The rash usually occurred within the first six weeks of therapy and resolved during continued administration of LAMICTAL. LAMICTAL was discontinued because of rash in 1.1% of patients in controlled studies and 3.8% of all patients in all studies. The rate of rash-related withdrawal in clinical studies was higher with more rapid initial titration dosing, and in patients receiving concomitant valproic acid (VPA), particularly in the absence of enzyme-inducing AEDs. (See Tables 2 and 3; see also WARNINGS, and DOSAGE AND ADMINISTRATION.)

Table 2: Effect of Concomitant AEDs on Rash Associated with LAMICTAL in All Controlled and Uncontrolled Clinical Trials Regardless of Dosing Escalation Scheme

AED Group	Total Patient Number	All Rashes	Withdrawal Due to Rash	Hospitalization in Association with Rash
Enzyme-Inducing AEDs <sup>1</sup>	1,788	9.2%	1.8%	0.1%
Enzyme-Inducing AEDs <sup>1</sup> + VPA	318	8.8%	3.5%	0.9%
VPA + Non-Enzyme-Inducing AEDs <sup>2</sup>	159	20.8%	11.9%	2.5%
Non-Enzyme-Inducing AEDs <sup>2</sup>	27	18.5%	0.0%	0.0%

1 Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone

2 Non-enzyme-inducing AEDs include clobazepam, clobazam, ethosuximide, methsuximide, vigabatrin, and gabapentin

Table 3: Effect of the Initial Daily Dose<sup>1</sup> of LAMICTAL in the Presence of Concomitant AEDs, on the Incidence of Rash Leading to Withdrawal of Treatment in Add-On Clinical Trials

AED Group	Enzyme-Inducing AEDs <sup>2</sup>	Enzyme-Inducing AEDs + VPA	VPA ± Non-Enzyme-Inducing AEDs <sup>3</sup>			
LAMICTAL Average Daily Dose (mg)	Total Patient Number	Percentage of Patients Withdrawn	Total Patient Number	Percentage of Patients Withdrawn	Total Patient Number	Percentage of Patients Withdrawn
12.5	9	0.0	10	0.0	51	7.8
25	3	0.0	7	0.0	58	12.1
50	182	1.1	111	0.9	35	5.7
100	993	1.4	179	4.5	15	40.0
≥125	601	2.8	11	18.2	0	0.0

1 Average daily dose in week 1

2 Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone

3 Non-enzyme-inducing AEDs include clobazepam, clobazam, ethosuximide, methsuximide, vigabatrin, and gabapentin

Increased incidence of rash-related withdrawal was seen when initial doses were higher and titration more rapid than recommended under DOSAGE AND ADMINISTRATION.

**Drug Interactions: Antiepileptic Drugs (AEDs):** Lamotrigine does not affect the plasma concentrations of concomitantly administered enzyme-inducing AEDs. Antiepileptic drugs that induce hepatic drug-metabolizing enzymes (phenytoin, carbamazepine, phenobarbital, primidone) increase the plasma clearance and reduce the elimination half-life of lamotrigine (see ACTION AND CLINICAL PHARMACOLOGY). Valproic acid reduces the plasma clearance and prolongs the elimination half-life of lamotrigine (see ACTION AND CLINICAL PHARMACOLOGY). When LAMICTAL was administered to 18 healthy volunteers already receiving valproic acid, a modest decrease (25% on average) in the trough steady-state valproic acid plasma concentrations was observed over a 3-week period, followed by stabilization. However, the addition of LAMICTAL did not affect the plasma concentration of valproic acid in patients receiving enzyme-inducing AEDs in combination with valproic acid. (See also PRECAUTIONS, Skin-Related Events.) **Oral Contraceptives:** In a study of 12 female volunteers, LAMICTAL did not affect plasma concentrations of ethinylestradiol and levonorgestrel following administration of the oral contraceptive pill. However, as with the introduction of other chronic therapy in patients taking oral contraceptives, the patient should be asked to report any change in the menstrual bleeding pattern. **Drugs Depressing Cardiac Conduction:** (See Patients with Special Diseases and Conditions.) **Drug/Laboratory Test Interactions:** LAMICTAL has not been associated with any assay interferences in clinical laboratory tests. **Use in the Elderly:** The safety and efficacy of LAMICTAL in elderly patients with epilepsy have not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions and limited experience with LAMICTAL in this population. **Use in Children:** The safety and efficacy of LAMICTAL in children under 18 years of age have not yet been established (see WARNINGS). **Use in Obstetrics: Pregnancy:** Studies in mice, rats and rabbits given lamotrigine orally or intravenously revealed no evidence of teratogenicity; however, maternal and secondary fetal toxicity were observed. Studies in rats and rabbits indicate that lamotrigine crosses the placenta; placental and fetal levels of lamotrigine were low and comparable to levels in maternal plasma. Because animal reproduction studies are not always predictive of human response, LAMICTAL should only be used during pregnancy if the benefits of therapy outweigh the risks associated with it. Clinical trials data indicate that lamotrigine has no effect on blood folate concentrations in adults; however, its effects during human fetal development are unknown. **Labor and Delivery:** The effect of LAMICTAL on labor and delivery in humans is unknown. **Nursing Mothers:** LAMICTAL is excreted in human milk. Because of the potential for adverse reactions from LAMICTAL in nursing infants, breast-feeding while taking this medication is not recommended. **Patients with Special Diseases and Conditions:** Clinical experience with LAMICTAL in patients with concomitant illness is limited. Caution is advised when using LAMICTAL in patients with diseases or conditions that could affect the metabolism or elimination of the drug. **Renal Failure:** A study in individuals with chronic renal failure (not receiving other AEDs) indicated that the elimination half-life of unchanged lamotrigine is prolonged relative to individuals with normal renal function (see ACTION AND CLINICAL PHARMACOLOGY). Use of LAMICTAL in patients with severe renal impairment should proceed with caution. **Impaired Liver Function:** There is no experience with the use of LAMICTAL in patients with impaired liver function. Caution should be exercised in dose selection for patients with this condition. **Cardiac Conduction Abnormalities:** One placebo-controlled trial that compared electrocardiograms at baseline and during treatment, demonstrated a mild prolongation of the P-R interval associated with LAMICTAL administration. The prolongation was statistically significant but clinically insignificant. Patients with significant cardiovascular disease or electrocardiographic abnormalities were, however, systematically excluded from clinical trials. Thus, LAMICTAL should be used with caution in patients with cardiac conduction abnormalities, and in patients taking concomitant medications which depress AV conduction. **Dependence Liability:** No evidence of abuse potential has been associated with LAMICTAL, nor is there evidence of psychological or physical dependence in humans. **Laboratory Tests:** The use of LAMICTAL does not require routine monitoring of any clinical laboratory parameters or plasma levels of concomitant AEDs.

**ADVERSE REACTIONS**

RARELY, SERIOUS SKIN RASHES, INCLUDING STEVENS JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS (LYELL SYNDROME) HAVE BEEN REPORTED. THE LATTER CONDITION CARRIES A HIGH MORTALITY (see WARNINGS). Adverse experiences in patients receiving LAMICTAL (lamotrigine) were generally mild, occurred within the first two weeks of therapy, and resolved without discontinuation of the drug. **Commonly Observed:** The most commonly observed adverse experiences associated with the use of adjunctive therapy with LAMICTAL (incidence of at least 10%) were dizziness, headache, diplopia, somnolence, ataxia, nausea, and asthenia. Dizziness, diplopia, ataxia, and blurred vision were dose-related and occurred more commonly in patients receiving carbamazepine in combination with LAMICTAL than in patients receiving other enzyme-inducing AEDs with LAMICTAL. Reduction of the daily dose and/or alteration of the timing of doses of concomitant antiepileptic drugs and/or LAMICTAL may reduce or eliminate these symptoms. Clinical data suggest a higher incidence of rash in patients who are receiving concomitant valproic

acid, or non-inducing AEDs (see **WARNINGS**; see also **PRECAUTIONS, Skin-Related Events**, Table 2). **Adverse Events Associated with Discontinuation of Treatment:** Across all add-on studies, the most common adverse experiences associated with discontinuation of LAMICTAL were rash, dizziness, headache, ataxia, nausea, diplopia, somnolence, seizure exacerbation, asthenia, and blurred vision. In controlled clinical trials, 6.9% of the 711 patients receiving LAMICTAL discontinued therapy due to an adverse experience, versus 2.9% of the 419 patients receiving placebo. Of 3,501 patients and volunteers who received LAMICTAL in premarketing clinical studies, 358 (10.2%) discontinued therapy due to an adverse experience. **Serious Adverse Events Associated with Discontinuation of Treatment:** Discontinuation due to an adverse experience classified as serious occurred in 2.3% of patients and volunteers who received LAMICTAL in the premarketing studies. Rash accounted for almost half of the discontinuations due to serious adverse experiences. More rapid initial titration dosing of LAMICTAL, and concomitant use of valproic acid were associated with higher incidences of rash-related withdrawal in clinical studies (see **WARNINGS**; see also **PRECAUTIONS, Skin-Related Events**, Table 3). **Controlled Add-on Clinical Studies:** Table 4 enumerates adverse experiences that occurred with an incidence of 2% or greater among refractory patients with epilepsy treated with LAMICTAL. **Other Events Observed During Clinical Studies:** During clinical testing, multiple doses of LAMICTAL were administered to 3,501 patients and volunteers. The conditions and duration of exposure to LAMICTAL during these clinical studies varied greatly. Studies included monotherapy and pediatric trials. A substantial proportion of the exposure was gained in open, uncontrolled clinical studies. Adverse experiences associated with exposure to LAMICTAL were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of adverse experiences into a smaller number of standardized event categories. Since the adverse experiences reported occurred during treatment with LAMICTAL in combination with other antiepileptic drugs, they were not necessarily caused by LAMICTAL. The following adverse events have been reported on one or more occasions by at least 1% of patients and volunteers exposed to LAMICTAL: anorexia, weight gain, amnesia, concentration disturbance, confusion, emotional lability, nervousness, nystagmus, paresthesia, thinking abnormality and vertigo. (All types of events are included except those already listed in Table 4.)

**Table 4: Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Studies<sup>1</sup>**

Body System/ Adverse Experience <sup>2</sup>	Percent of Patients Receiving LAMICTAL (and other AEDs) (n=711)	Percent of Patients Receiving Placebo (and other AEDs) (n=419)	Percent of Patients Receiving LAMICTAL (and other AEDs) Who Were Discontinued (n=711)
<b>BODY AS A WHOLE</b>			
Headache	29.1	19.1	1.3
Accidental injury	9.1	8.6	0.1
Asthenia	8.6	8.8	0.3
Flu Syndrome	7.0	5.5	0.0
Pain	6.2	2.9	0.1
Back Pain	5.8	6.2	0.0
Fever	5.5	3.6	0.1
Abdominal Pain	5.2	3.6	0.1
Infection	4.4	4.1	0.0
Neck Pain	2.4	1.2	0.0
Malaise	2.3	1.9	0.3
Seizure Exacerbation	2.3	0.5	0.3
<b>DIGESTIVE</b>			
Nausea	18.6	9.5	1.3
Vomiting	9.4	4.3	0.3
Diarrhea	6.3	4.1	0.3
Dyspepsia	5.3	2.1	0.1
Constipation	4.1	3.1	0.0
Tooth Disorder	3.2	1.7	0.0
<b>MUSCULOSKELETAL</b>			
Myalgia	2.8	3.1	0.0
Arthralgia	2.0	0.2	0.0
<b>NERVOUS</b>			
Dizziness	38.4	13.4	2.4
Ataxia	21.7	5.5	0.6
Somnolence	14.2	6.9	0.0
Incoordination	6.0	2.1	0.3
Insomnia	5.6	1.9	0.4
Tremor	4.4	1.4	0.0
Depression	4.2	2.6	0.0
Anxiety	3.8	2.6	0.0
Convulsion	3.2	1.2	0.3
Irritability	3.0	1.9	0.1
Speech Disorder	2.5	0.2	0.1
Memory Decreased	2.4	1.9	0.0
<b>RESPIRATORY</b>			
Rhinitis	13.6	9.3	0.0
Pharyngitis	9.8	8.8	0.0
Cough Increased	7.5	5.7	0.0
Respiratory Disorder	5.3	5.5	0.1
<b>SKIN AND APPENDAGES</b>			
Rash	10.0	5.0	1.1
Pruritus	3.1	1.7	0.3
<b>SPECIAL SENSES</b>			
Diplopia	27.6	6.7	0.7
Blurred Vision	15.5	4.5	1.1
Vision Abnormality	3.4	1.0	0.0
<b>UROGENITAL</b>			
Female Patients (n=365)		(n=207)	
Dysmenorrhea	6.6	6.3	0.0
Menstrual Disorder	5.2	5.8	0.0
Vaginitis	4.1	0.5	0.0

<sup>1</sup> Patients in these studies were receiving 1 to 3 concomitant enzyme-inducing antiepileptic drugs in addition to LAMICTAL or placebo. Patients may have reported multiple adverse experiences during the study or at discontinuation. Thus, patients may be included in more than one category.

<sup>2</sup> Adverse Experiences reported by at least 2% of patients treated with LAMICTAL are included.

**Monotherapy Clinical Studies:** Withdrawals due to adverse events were reported in 42 (9.5%) of newly diagnosed patients treated with LAMICTAL monotherapy. The most common adverse experiences associated with discontinuation of LAMICTAL were rash (6.1%), asthenia (1.1%), headache (1.1%), nausea (0.7%) and vomiting (0.7%). **Other Events Observed During Clinical Practice and from "Compassionate Plea" Patients:** In addition to the adverse experiences reported during clinical testing of LAMICTAL, the following adverse experiences have been reported in patients receiving LAMICTAL marketed in other countries and from worldwide "compassionate plea" patients. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: apnea, erythema multiforme, esophagitis, hematemesia, hemolytic anemia, pancreatitis, pancytopenia and progressive immunosuppression.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**

During the clinical development program, the highest known overdose of LAMICTAL (lamotrigine) occurred in a 33-year old female who ingested between 4,000 and 5,000 mg LAMICTAL that corresponded to a plasma level of 52 µg/mL four hours after the ingestion. The patient presented to the emergency room comatose and remained comatose for 8 to 12 hours, returned to almost normal over the next 24 hours, and completely recovered by the third day. There are no specific antidotes for LAMICTAL. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced or gastric lavage should be performed. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In six renal failure patients, about 20% of the amount of lamotrigine in the body was removed during 4 hours of hemodialysis.

**DOSAGE AND ADMINISTRATION**

**Adults:** LAMICTAL (lamotrigine) is intended for oral administration and may be taken with or without food. LAMICTAL should be added to the patient's current antiepileptic therapy. Valproic acid more than doubles the elimination half-life of lamotrigine and reduces the plasma clearance by 50%; conversely, hepatic enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, and primidone reduce the elimination half-life of lamotrigine by 50% and double the plasma clearance (see **ACTION AND CLINICAL PHARMACOLOGY**). These clinically important interactions require dosage schedules of LAMICTAL as summarized in Table 5. LAMICTAL does not alter plasma concentrations of concomitantly administered enzyme-inducing AEDs and therefore they do not usually require dose adjustment to maintain therapeutic plasma concentrations. For patients receiving LAMICTAL in combination with other AEDs, an evaluation of all AEDs in the regimen should be considered if a change in seizure control or an appearance or worsening of adverse experiences is observed. If there is a need to discontinue therapy with LAMICTAL, a step-wise reduction of dose over at least two weeks (approximately 50% per week) is recommended unless safety concerns require a more rapid withdrawal (see **PRECAUTIONS**). The relationship of plasma concentration to clinical response has not been established for lamotrigine. Dosing of LAMICTAL should be based on therapeutic response. In controlled clinical studies, doses of LAMICTAL that were efficacious generally produced steady-state trough plasma lamotrigine concentrations of 1 to 4 µg/mL in patients receiving one or more concomitant AEDs. Doses of LAMICTAL producing this plasma concentration range were well tolerated. As with any antiepileptic drug, the oral dose of LAMICTAL should be adjusted to the needs of the individual patient, taking into consideration the concomitant AED therapy the patient is receiving.

**Table 5: LAMICTAL Recommended Dosage Schedule for Adults**

Treatment Week	Patients Taking		For Information*
	Enzyme-Inducing AEDs <sup>1</sup> With Valproic Acid	Enzyme-Inducing AEDs <sup>1</sup> Without Valproic Acid	
Weeks 1 + 2	25 mg once a day	50 mg once a day	25 mg every other day
Weeks 3 + 4	25 mg twice a day	50 mg twice a day	25 mg once a day
Usual Maintenance	50-100 mg twice a day To achieve maintenance, doses may be increased by 25-50 mg every 1 to 2 weeks.	150-250 mg twice a day To achieve maintenance, doses may be increased by 100 mg every 1 to 2 weeks.	50-100 mg twice a day To achieve maintenance, doses may be increased by 25-50 mg every 1 to 2 weeks.

<sup>1</sup> Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone

\* Column reflects dosage recommendations in the United Kingdom and is provided for information.

**Because of an increased risk of rash, the recommended initial dose and subsequent dose escalations of LAMICTAL should not be exceeded (see **WARNINGS**).**

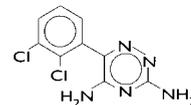
**There have been no controlled studies to establish the effectiveness or optimal dosing regimen of add-on LAMICTAL therapy in patients receiving only non-enzyme-inducing AEDs or valproic acid. However, available data from open clinical trials indicate that the addition of LAMICTAL under these conditions is associated with a higher incidence of serious rash or rash-related withdrawal, even at an initial titration dose of 12.5 mg daily (see **PRECAUTIONS, Skin Related Events**, Table 3; see also **WARNINGS**).** The potential medical benefits of addition of LAMICTAL under these conditions must be weighed against the increased risk of serious rash. If use of LAMICTAL under these conditions is considered clinically indicated, titration dosing should proceed with extreme caution, especially during the first six weeks of treatment.

**Withdrawal of Concomitant AEDs:** Concomitant AEDs may be decreased over a 5-week period, by approximately 20% of the original dose every week. However, a slower taper may be used if clinically indicated. During this period, the dose of LAMICTAL administered will be dependent upon the effect of the drug being withdrawn on the pharmacokinetics of lamotrigine, together with the overall clinical response of the patient. The withdrawal of enzyme-inducing AEDs (i.e. phenytoin, phenobarbital, primidone, and carbamazepine) will result in an approximate doubling of the t<sub>1/2</sub> of lamotrigine. Under these conditions, it may be necessary to reduce the dose of LAMICTAL. In contrast, the withdrawal of enzyme-inhibiting AEDs (i.e. valproic acid) will result in a decrease in the t<sub>1/2</sub> of lamotrigine and may require an increase in the dose of LAMICTAL. **Geriatric Patients:** There is little experience with the use of LAMICTAL in elderly patients. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions. **Patients with Impaired Renal Function:** The elimination half-life of lamotrigine is prolonged in patients with impaired renal function (see **ACTION AND CLINICAL PHARMACOLOGY**). Caution should be exercised in dose selection for patients with impaired renal function. **Patients with Impaired Hepatic Function:** There is no experience with the use of LAMICTAL in patients with impaired liver function. Because lamotrigine is metabolized by the liver, caution should be exercised in dose selection for patients with this condition. **Children:** Dosage recommendations for children under 18 years of age are not yet established.

**PHARMACEUTICAL INFORMATION**

**Drug Substance**

**Brand Name:** LAMICTAL  
**Common Name:** Lamotrigine  
**Chemical Name:** 1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl)-[USAN]  
**Chemical Name:** 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine [Chem. Abstr.]  
**Structural Formula:**  
 [USAN]



**Molecular Formula:** C<sub>9</sub>H<sub>7</sub>Cl<sub>2</sub>N<sub>5</sub> **Molecular Weight:** 256.09

**Description:** Lamotrigine is a white to pale cream powder. The pKa at 25°C is 5.7. It is practically insoluble in water (0.017% w/v); slightly soluble in ethanol (0.41% w/v), chloroform (0.11% w/v) and octanol (0.28% w/v).

**Composition**

LAMICTAL Tablets contain lamotrigine and the following non-medical ingredients: cellulose, lactose, magnesium stearate, povidone, sodium starch glycolate, and coloring agents:

- 25 mg (white tablets) - None
- 100 mg (peach tablets) - Sunset Yellow FCF Lake
- 150 mg (cream tablets) - Ferric Oxide, Yellow

**Stability and Storage Recommendations**

LAMICTAL Tablets should be stored at controlled room temperature (15°C to 30°C) in a dry place and protected from light.

**AVAILABILITY OF DOSAGE FORMS**

LAMICTAL Tablets are available in three different strengths:

- LAMICTAL Tablets 25 mg: White, scored, shield-shaped tablets engraved with "LAMICTAL" and "25". Bottles of 100.
- LAMICTAL Tablets 100 mg: Peach, scored, shield-shaped tablets engraved with "LAMICTAL" and "100". Bottles of 100.
- LAMICTAL Tablets 150 mg: Cream, scored, shield-shaped tablets engraved with "LAMICTAL" and "150". Bottles of 60.

Product Monograph available to healthcare professionals on request.

Date of revision: April 16, 1997

**References:** 1. Schmidt D & Gram L. Monotherapy versus polytherapy in epilepsy. *CNS Drugs* 1995; 3:194-208. 2. Brodie MJ. Lamotrigine - An update. *Can J Neurol Sci* 1996; 23(Suppl. 2):S6-S9. 3. Product Monograph of LAMICTAL (lamotrigine). Glaxo Wellcome Inc. 1997. 4. Fought E. Lamotrigine monotherapy in patients with refractory partial-onset seizures. *In: Loiseau P (ed.) Lamotrigine - A Brighter Future. International Congress and Symposium Series 214*. London: The Royal Society of Medicine Press; 1996:37-42. 5. Perucca E. Add-on trial of lamotrigine followed by withdrawal of concomitant medication and stabilization on monotherapy. *In: Loiseau P (ed.) Lamotrigine - A Brighter Future. International Congress and Symposium Series 214*. London: The Royal Society of Medicine Press; 1996:23-30. 6. Brodie MJ. Lamotrigine monotherapy: an overview. *In: Loiseau P (ed.) Lamotrigine - A Brighter Future. International Congress and Symposium Series 214*. London: The Royal Society of Medicine Press; 1996:43-49.

**GlaxoWellcome**

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ropinirole (as ropinirole hydrochloride)

0.25 mg, 1.0 mg, 2.0 mg, 5.0 mg

Therapeutic Classification: Anti-Parkinsonian Agent / Dopamine Agonist

Action and Clinical Pharmacology

REQUIP (ropinirole hydrochloride) is a non-ergoline dopamine agonist, which activates post-synaptic dopamine receptors.

In vitro studies have shown that ropinirole binds with high affinity to cloned human D2, D3, and D4 receptors. The antiparkinsonian activity of ropinirole is believed to be due to its stimulatory effects on central post-synaptic dopamine D2 receptors within the caudate-putamen.

Ropinirole is a potent agonist both in vitro and in vivo and restores motor function in animal models of Parkinson's disease. Ropinirole has been shown to reverse the motor deficits induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in primates.

Neither ropinirole nor its metabolites bind with high affinity to dopamine D1 receptors. Ropinirole also has very low affinity for 5-HT1, 5-HT2, benzodiazepine, GABA, muscarinic, alpha- or beta-adrenoreceptors. Ropinirole binds to opiate receptors with low affinity, however, studies show that this weak opiate activity has no consequences at pharmacological doses in vivo.

In rats, ropinirole binds to melanin-containing tissues (e.g., the eye) to a greater degree than non-pigmented tissues, and tissue levels decline with a half-life of 16-20 days. It is unknown whether or not ropinirole accumulates in these tissues over time.

In healthy normotensive subjects, single oral doses of REQUIP, in the range of 0.01 to 2.5 mg, had little or no effect on supine blood pressure and pulse rate. Upon standing, REQUIP caused decreases in systolic and mainly diastolic blood pressure at doses above 0.25 mg. In some subjects, these changes were associated with the emergence of orthostatic symptoms, bradycardia and, in one case, transient sinus arrest in the context of a severe vasovagal syncope. The effect of repeat dosing and slow titration of REQUIP was not studied in healthy volunteers. The mechanism of REQUIP-induced orthostatic symptoms probably relates to its dopamine D2-mediated blunting of the noradrenergic response to standing and subsequent decrease in peripheral vascular resistance. Orthostatic signs and symptoms were often accompanied by nausea. REQUIP had no dose-related effect on ECG wave form and rhythm in young healthy male volunteers.

At doses >0.8 mg REQUIP suppressed serum prolactin concentrations in healthy male volunteers.

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Pharmacokinetics

Absorption, Bioavailability, and Distribution

Ropinirole is rapidly absorbed with median peak concentrations occurring within 1.5 hours after oral dosing. Despite complete absorption, absolute bioavailability of ropinirole is reduced to approximately 50% as a result of first-pass metabolism. Relative bioavailability from a tablet compared to an oral solution is 85%. Over the therapeutic dose range, Cmax and AUC values increase in proportion to the increase in dose (see Table 1).

The average oral clearance is approximately 47 L/h (range 17-113 L/h) and is constant over the entire dosage range. The terminal elimination half-life is approximately 6 h (range 2-27 h) and the volume of distribution at steady state is approximately 480 L (range 216-891 L) or 7.0 L/kg (range 3.1-12.9 L/kg).

Table 1. Steady state pharmacokinetic parameters (mean and range) of ropinirole in patients with Parkinson's disease administered ropinirole in a t.i.d. regimen

Table with 5 columns: Unit Dose mg, Cmax ng/mL, Cmax ng/mL, Tmax h, AUC0-24 ng.h/mL. Rows show data for 1, 2, and 4 mg doses.

\*median

Steady state concentrations are expected to be achieved within 2 days of dosing. There is, on average, a two-fold higher steady-state plasma concentration of ropinirole following the recommended t.i.d. regimen compared to those observed following a single oral dose.

Food delayed the rate of absorption of ropinirole (median Tmax was increased by 2.6 hours and Cmax was decreased by 25%) in Parkinsonian patients. However, there was no marked change in the overall systemic availability of the drug. Ropinirole may be given with or without food. While administration of the drug with food may improve gastrointestinal tolerance, in severely fluctuating patients, the morning dose may be given without food in order to avoid a delay in time to switch "ON".

Population pharmacokinetic analyses have shown that frequently co-administered medications, such as levodopa, selegiline, amantadine, anticholinergic drugs, ibuprofen, benzodiazepines and antidepressants did not alter the pharmacokinetics of ropinirole.

Plasma protein binding is low (10 to 40%).

Ropinirole has a blood to plasma ratio of 1.2.

Metabolism

Ropinirole is extensively metabolized by the liver. The N-despropyl metabolite is the major metabolite circulating in the plasma. Based on AUC data, the plasma levels of the metabolite were consistently higher than those of the parent drug suggesting a nonsaturable conversion of ropinirole to the N-despropyl metabolite. The affinity of the N-despropyl metabolite for human cloned D2 receptors is lower than the affinity of ropinirole. In addition the metabolite does not cross the blood-brain barrier. Thus, it is unlikely to contribute to the therapeutic effects of ropinirole. The plasma concentrations of the hydroxylated metabolite are low and account for about 1-5% of the ropinirole concentrations. Although the hydroxylated metabolite was more active than ropinirole in in vitro D2 receptor binding studies, at therapeutic doses it is not expected to contribute to the activity of ropinirole.

In vitro studies indicate that the major cytochrome P450 isozyme involved in the metabolism of ropinirole is CYP1A2. In patients with Parkinson's disease, ciprofloxacin, an inhibitor of CYP1A2, significantly increased the systemic availability of ropinirole, while theophylline, a substrate of CYP1A2, was devoid of such activity (see PRECAUTIONS, Drug Interactions).

Elimination

Recovery of radioactivity after oral and intravenous administration of 14C-ropinirole was approximately 88% and 90% of the dose, respectively. Urinary excretion of unchanged ropinirole is low and represents approximately 5 to 10% of the dose. N-despropyl ropinirole is the predominant metabolite found in the urine (40%), followed by the glucuronide of the hydroxy metabolite (10%), and the carboxylic acid metabolite (10%) formed from N-despropyl ropinirole.

Population Subgroups

Renal and Hepatic Impairment

Based on population pharmacokinetics, no clinically significant differences were observed in the pharmacokinetics of REQUIP in Parkinsonian patients with moderate renal impairment (creatinine clearance between 30 to 50 mL/min; n=18; mean age 74 years) compared to age-matched patients with creatinine clearance above 50 mL/min (n=44; mean age 70 years). Therefore, no dosage adjustment is necessary in Parkinsonian patients with mild to moderate renal impairment (see PRECAUTIONS AND DOSAGE AND ADMINISTRATION).

The use of REQUIP in patients with severe renal impairment or hepatic impairment has not been studied. Administration of REQUIP to such patients is not recommended (see PRECAUTIONS AND DOSAGE AND ADMINISTRATION).

Gender

Population pharmacokinetic analysis indicated that the oral clearance and volume of distribution of REQUIP at steady state were similar in male patients (n=99; mean age 60 years) and female patients who were not taking concomitant estrogens (n=56; mean age 65 years).

Estrogen Replacement Therapy

In women, on long-term treatment with conjugated estrogens (n=16; mean age 63

years), the oral clearance of REQUIP was decreased by an average of 36% compared to the oral clearance in women not receiving supplemental estrogens (n=56; mean age 65 years). The average terminal elimination half-life was 9.0 hours in the estrogen group and 6.5 hours in patients not taking estrogens (see PRECAUTIONS AND DOSAGE AND ADMINISTRATION).

Age

Population pharmacokinetic analysis revealed that the oral clearance of REQUIP seen in patients under the age of 65 years (n=97), was reduced from 62.1 L/h to 45.5 L/h in patients between the ages of 65 and 75 years (n=83). In patients older than 75 years (n=11), oral clearance was similar to that seen in the 65 to 75 year age group (41.7 L/h). However, since the dose of REQUIP is to be individually titrated to clinical response, dosage adjustment is not necessary in the elderly (above 65 years).

Clinical Trials

Up to May 31, 1996, 1599 patients have been exposed to REQUIP, with 481 patients being exposed for over one year and 241 patients being exposed for over two years. Evidence to support the efficacy of REQUIP in treating the signs and symptoms of Parkinson's disease was obtained in multicentre, double-blind studies. These studies included either patients who had minimal or no prior dopaminergic therapy, or patients who were not optimally controlled with current levodopa-decarboxylase inhibitor therapy. In patients with early disease, REQUIP improved motor function (assessed by the motor component of the UPDRS [Unified Parkinson's Disease Rating Scale]) and delayed the need to initiate treatment with levodopa. In patients with more advanced disease, REQUIP reduced "off" time (based upon patient diaries recording time "on" of REQUIP) and permitted a reduction in levodopa dose. The subsequent severity described some of the studies in which REQUIP was titrated (see DOSAGE AND ADMINISTRATION) to the maximal dose of 8 mg t.i.d.

In clinical trials where dosing was titrated to optimal clinical effect, the mean daily dose of REQUIP at 24 weeks was 9.5 mg in early therapy (n=282) and was 13.5 mg in adjunct therapy (n=303).

In the pivotal clinical trials, including studies where the dose was titrated to the target maximum of 24 mg per day, the mean daily dose of REQUIP at endpoint was 10.7 mg in early therapy (n=458) and 12.5 mg in adjunct therapy (n=456).

In the total patient database (n=1599) over 50% of patients were dosed between 6 and 15 mg of REQUIP per day in both early and adjunct therapy. Less than 22% of patients exceeded a total daily dose of 15 mg.

During the clinical trials, the dose of REQUIP was titrated to optimal clinical response and tolerance. Retrospective analysis showed that female patients required lower doses than male patients but were exposed to REQUIP for similar periods of time.

Early Therapy

In a double-blind, randomized, placebo-controlled, 6-month study, REQUIP-treated patients (n=116) demonstrated a 24% improvement in UPDRS motor scores from baseline, compared to placebo-treated patients (n=125), who demonstrated a 3% worsening in motor scores. On the Clinical Global Impression (CGI) scale, 33% of REQUIP-treated patients and 12% of placebo-treated patients were rated as "very much improved" and "much improved." "Rescue levodopa" was needed by 11% of REQUIP-treated and 29% of placebo-treated patients. All differences were statistically significant.

In a double-blind, randomized, 5-year study, at the 6-month interim analysis, REQUIP (n=179) was compared to levodopa-benserazide (n=89). The decrease in UPDRS motor scores versus baseline was greater with levodopa than with REQUIP. However, the proportion of "responders" (UPDRS improvement of at least 30%) did not differ between levodopa and REQUIP. Results on the CGI indicated that there was no difference between REQUIP and levodopa in less severely afflicted patients (Hoehn and Yahr stage I to II) but levodopa was more efficacious in patients with more severe disease.

Adjunct Therapy

In a double-blind, randomized, clinical trial of 6-month duration, REQUIP (n=94) was compared to placebo (n=54) as adjunct therapy to levodopa. The primary efficacy parameter, defined as both a 20% or greater reduction in levodopa dose and a 20% or greater reduction in "off" time, was achieved by 28% of REQUIP-treated patients and 11% of placebo-treated patients. This difference was statistically significant. The daily dose of levodopa was reduced by 19% and 2.8% in the REQUIP and placebo-treated patients, respectively.

The relationship between efficacy and plasma concentrations of REQUIP was assessed from population pharmacokinetic data obtained in 141 male and female patients who participated in two prospective studies.

In general, the average plasma concentrations of REQUIP at steady state (Css) were higher in patients classified as responders versus non-responders, although considerable overlap in the range of Cmax between the two groups was noted. Mean (±SD) REQUIP Cmax for responders and non-responders were 22.8±10.8 ng/mL and 15.1±9.7 ng/mL, respectively.

INDICATIONS AND CLINICAL USE

REQUIP (ropinirole hydrochloride) is indicated in the treatment of the signs and symptoms of idiopathic Parkinson's disease.

REQUIP can be used both as early therapy, without concomitant levodopa and as an adjunct to levodopa.

CONTRAINDICATIONS

REQUIP (ropinirole hydrochloride) is contraindicated in patients with a known hypersensitivity to ropinirole hydrochloride or the excipients of the drug product.

WARNINGS

Orthostatic Symptoms

Dopamine agonists appear to impair the systemic regulation of blood pressure with resulting orthostatic symptoms of dizziness or lightheadedness, with or without documented hypotension. These symptoms appear to occur especially during dose escalation. Therefore, patients treated with dopamine agonists should be carefully monitored for signs and symptoms of orthostatic hypotension, especially during dose escalation (see DOSAGE AND ADMINISTRATION) and should be informed of this risk.

Hallucinations

In controlled trials, REQUIP (ropinirole hydrochloride) caused hallucination in 5.1% of patients during early therapy (1.4% in the placebo group) and in 10.1% of patients receiving REQUIP and levodopa (4.2% receiving placebo and levodopa). Hallucination was of sufficient severity that it led to discontinuation in 1.3% and 1.9% of patients during early and adjunct therapy, respectively. The incidence of hallucination was dose-dependent both in early and adjunct therapy studies.

PRECAUTIONS

Cardiovascular

Since REQUIP (ropinirole hydrochloride) has not been studied in patients with a history or evidence of significant cardiovascular disease including myocardial infarction, unstable angina, cardiac decompensation, cardiac arrhythmias, vaso-occlusive disease (including cerebral) or cardiomyopathy, it should be used with caution in such patients.

There is limited experience with REQUIP in patients treated with antihypertensive and antiarrhythmic agents. Consequently, in such patients, the dose of REQUIP should be titrated with caution.

Neuroleptic Malignant Syndrome

A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy.

A single spontaneous report of a symptom complex resembling the neuroleptic malignant syndrome has been observed in a 66 year old diabetic male patient with Parkinson's disease, who developed fever, muscle stiffness, and drowsiness 8 days after beginning REQUIP treatment. The patient also experienced acute bronchitis, which did not respond to antibiotic treatment. REQUIP was discontinued three days before the patient died. The reporting physician considered these events to be possibly related to REQUIP treatment (see DOSAGE AND ADMINISTRATION).

A single spontaneous report of severe muscle pain has been reported in a 66 year old male patient around his thigh. The reporting physician considered the event to be probably related to REQUIP treatment.

Retinal, Vestibular, and Taste

In a two year carcinogenicity study in albino Sprague-Dawley rats, retinal atrophy was observed at incidences of 0%, 1.4%, 1.4% and 10% of male rats and 0%, 4.4%, 2.9% and 12.9% of female rats dosed at 0, 1.5, 15 and 50 mg/kg/day respectively. The incidence was significantly higher in both male and female animals dosed at 50 mg/kg/day. The 50 mg/kg/day dose represents a 2.8 fold greater exposure (AUC) and a 13.1 fold greater exposure (Cmax) to ropinirole in rats than the exposure would be in humans at the maximum recommended dose of 24 mg/day. The relevance of this finding to humans is not known.

Pregnancy

The use of REQUIP during pregnancy is not recommended.

REQUIP given to pregnant rats during organogenesis (gestation days 8 through 15) resulted in decreased fetal body weight at 60 mg/kg/day (approximately 3 - 4 times the AUC at the maximal human dose of 8 mg t.i.d.), increased fetal death at 90 mg/kg/day (approximately 5 times the AUC at the maximal human dose of 8 mg t.i.d.) and digital malformations at 150 mg/kg/day (approximately 8-9 times the AUC at the maximal human dose of 8 mg t.i.d.). These effects occurred at maternally toxic doses. There was no indication of an effect on development of the conceptus at a maternally toxic dose of 20 mg/kg/day in the rabbit. In a perinatal-postnatal study in rats, 10 mg/kg/day of REQUIP (approximately 0.5 - 0.6 times the AUC at the maximal human dose of 8 mg t.i.d.) impaired growth and development of nursing offspring and altered neurological development of female offspring.

Nursing Mothers

Since REQUIP suppresses lactation, it should not be administered to mothers who wish to breast-feed infants.

Studies in rats have shown that REQUIP and/or its metabolites cross the placenta and are excreted in breast milk. Consequently, the human fetus and/or neonate may be exposed to dopamine agonist activity.

Use in Women receiving Estrogen Replacement Therapy

In female patients on long-term treatment with conjugated estrogens, oral clearance was reduced and elimination half-life prolonged compared to patients not receiving estrogens (see Pharmacokinetics). In patients already receiving estrogen replacement therapy, REQUIP may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or introduced during treatment with REQUIP, adjustment of the REQUIP dosage may be required.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Renal and Hepatic Impairment

No dosage adjustment is needed in patients with mild to moderate renal impairment (creatinine clearance of 30 to 50 mL/min; see Pharmacokinetics).

Because the use of REQUIP in patients with severe renal impairment or hepatic impairment has not been studied, administration of REQUIP to such patients is not recommended.

Drug Interactions

Psychotropic Drugs

Neuroleptics and other centrally active dopamine antagonists may diminish the effectiveness of REQUIP. Therefore, concomitant use of these products is not recommended.

Based on population pharmacokinetic assessment, no interaction was seen between REQUIP and tricyclic antidepressants or benzodiazepines.

Anti-Parkinson Drugs

Based on population pharmacokinetic assessment, there were no interactions between REQUIP and drugs commonly used to treat Parkinson's disease, i.e., selegiline, amantadine, and anticholinergics.

Levodopa

The potential pharmacokinetic interaction of levodopa/carbidopa (100 mg/100 mg b.i.d.) and REQUIP (2 mg t.i.d.) was assessed in levodopa naive (de novo) male and female patients with Parkinson's disease (n=30; mean age 64 years). The rate and extent of availability of REQUIP at steady state were essentially the same with or without levodopa. Similarly, the rate and extent of availability of levodopa, as well as its elimination half-life, were essentially the same in the presence and absence of REQUIP.

Inhibitors of CYP1A2: Ciprofloxacin

The effect of ciprofloxacin (500 mg b.i.d.) on the pharmacokinetics of REQUIP (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12; mean age 55 years). The extent of systemic availability of REQUIP was significantly increased when coadministered with ciprofloxacin (AUC increased by 1.84 fold). Thus, in patients already receiving CYP1A2 inhibitors such as ciprofloxacin, REQUIP therapy may be instituted in the recommended manner and the dose titrated according to clinical response. However, if therapy with a drug known to be an inhibitor of CYP1A2 is stopped or introduced during treatment with REQUIP, adjustment of the REQUIP dosage may be required.

Substrates of CYP1A2: Theophylline

The effect of oral theophylline (300 mg b.i.d.) on the pharmacokinetics of REQUIP (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12; mean age 59 years). There was no marked change in the rate or extent of availability of REQUIP when coadministered with theophylline. Similarly, coadministration of REQUIP with intravenous theophylline (5 mg/kg) did not result in any marked change in the pharmacokinetics of theophylline. It is therefore unlikely that substrates of CYP1A2 would significantly alter the pharmacokinetics of REQUIP and vice-versa.

Digoxin

The effect of REQUIP (2 mg t.i.d.) on the pharmacokinetics of digoxin (0.125-0.25 mg o.d.) was studied in male and female patients with Parkinson's disease (n=10; mean age 72 years). Coadministration at steady state with REQUIP resulted in a 10% decrease in digoxin AUC although mean trough digoxin plasma concentrations were unaltered. However, the effect of higher recommended doses of REQUIP on the pharmacokinetics of digoxin is not known.

Alcohol

No information is available on the potential for interaction between REQUIP and alcohol. As with other centrally active medications, patients should be cautioned against taking REQUIP with alcohol.

Psycho-Motor Performance

As orthostatic symptoms of dizziness or lightheadedness as well as somnolence may occur during REQUIP therapy, patients should be cautioned not to drive a motor vehicle or operate potentially hazardous machinery until they are reasonably certain that REQUIP therapy does not affect their ability to engage in such activities.

ADVERSE REACTIONS

Adverse Reactions Associated with Discontinuation of Treatment

Of 1599 patients who received REQUIP (ropinirole hydrochloride) during the premarketing clinical trials, 17.1% in early-therapy studies and 17.3% in adjunct-therapy studies discontinued treatment due to adverse reactions. The events resulting in discontinuation of REQUIP in 1% or more of patients were as follows: Early therapy: nausea (6.4%), dizziness (3.8%), aggravated Parkinson's disease (1.3%), hallucination (1.3%), headache (1.3%), somnolence (1.3%) and vomiting (1.3%). Adjunct therapy: dizziness (2.9%), dyskinesia (2.4%), confusion (2.4%), vomiting (2.4%), hallucination (1.9%), nausea (1.9%), anxiety (1.9%), and increased sweating (1.4%). Patients over 75 years of age (n=130) showed slightly higher incidences of withdrawal due to hallucination, confusion and dizziness than patients less than 75 years of age.

Most Frequent Adverse Events

Adverse events occurring with an incidence of greater than, or equal to, 10% were as follows: Early therapy: nausea, dizziness, somnolence, headache, peripheral edema, vomiting, syncope, fatigue and viral infection. Adjunct therapy: dyskinesia, nausea, dizziness, somnolence and headache.

Dopamine agonists, with an ergoline chemical structure have been associated with adverse experiences such as retroperitoneal fibrosis, erythromelalgia and pulmonary reactions. REQUIP has a novel, non-ergoline chemical structure and no reports of such events have been observed in clinical trials.

Incidence of Adverse Events in Placebo Controlled Trials

The incidence of postural hypotension, an event commonly associated with initiation of dopamine agonist therapy, was not notably different from placebo in clinical trials. However, decreases in systolic blood pressure to < 90 mmHg have been observed in 13% (<65 years), 16% (65-75 years) and 7.6% (>75 years) of patients treated with REQUIP.

The following table lists adverse events that occurred at an incidence of 1% or more among REQUIP-treated patients who participated in placebo-controlled trials for up to one year. Patients were dosed in a range of 0.75 mg to 24 mg/day. Reported adverse events were classified using a standard World Health Organization (WHO)-based dictionary terminology.

The occurrence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies can not be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse events incidence rate in the population studied.

**TABLE 2**  
Adverse events with incidence  $\geq 1\%$  from all placebo-controlled early and adjunct therapy studies

	Early Therapy		Adjunct Therapy	
	REQUIP N = 157 % occurrence	Placebo N = 147 % occurrence	REQUIP N = 208 % occurrence	Placebo N = 120 % occurrence
<b>Autonomic Nervous System</b>				
Sweating increased	6.4	4.1	7.2	1.7
Mouth Dry	5.1	3.4	5.3	0.8
Flushing	3.2	0.7	1.4	0.8
<b>Body as a Whole General</b>				
Peripheral Edema	13.4	4.1	3.9	2.5
Fatigue	10.8	4.1	10.6	9.2
Injury	7.6	4.1	5.3	3.3
Pain	6.4	1.4	—	—
Asthma	4.5	2.7	6.7	3.3
Drug Level Increased	3.8	2.0	—	—
Chest Pain	4.2	0.7	1.4	0.8
Malaise	1.9	0.0	—	—
Therapeutic Response Decreased	1.9	0.0	—	—
Cellulitis	1.3	0.0	—	—
Influenza-Like Symptoms	3.8	2.0	1.0	0.0
Fever	—	—	1.4	0.0
<b>Cardiovascular General</b>				
Syncope	11.5	1.4	2.9	1.7
Hypotension Postural	6.4	4.8	—	—
Hypertension	4.5	3.4	3.4	3.3
Hypotension	1.9	0.0	2.4	0.8
Cardiac Failure	—	—	1.0	0.0
<b>Central and Peripheral Nervous System</b>				
Dizziness	40.1	21.8	26.0	15.8
Dyskinesia	—	—	33.7	12.5
Headache	17.2	17.0	16.8	11.7
Ataxia (Falls)	—	—	9.6	6.7
Tremor	—	—	6.3	2.5
Parosmia	—	—	3.3	2.5
Hyperesthesia	3.8	2.0	—	—
Dystonia	—	—	4.3	4.2
Hypokinesia	—	—	5.3	4.2
Paresis	—	—	2.9	0.0
Speech disorder	—	—	1.0	0.0
Vertigo	1.9	0.0	—	—
Carpal Tunnel Syndrome	1.3	0.7	—	—
<b>Gastrointestinal System</b>				
Nausea	59.9	21.8	29.8	18.3
Vomiting	12.1	6.8	7.2	4.2
Dyspepsia	9.6	4.8	—	—
Constipation	8.3	7.5	5.8	3.3
Abdominal Pain	6.4	2.7	8.7	7.5
Diarrhea	—	—	8.8	2.5
Anorexia	3.8	1.4	—	—
Flatulence	2.5	1.4	1.9	0.8
Tooth Disorder	1.9	0.7	1.0	0.8
Saliva increased	—	—	2.4	0.8
Colitis	1.3	0.0	—	—
Dysphagia	1.3	0.0	2.4	0.8
Periodontitis	1.3	0.0	1.4	0.8
Eruetion	—	—	1.4	0.0
Fecal Incontinence	—	—	1.0	0.0
Hemorrhoids	—	—	1.0	0.0
Gastroesophageal Reflux	—	—	1.0	0.0
Gastrointestinal Disorder (NOS)	—	—	1.0	0.0
Toothache	—	—	1.0	0.0
<b>Hearing and Vestibular</b>				
Tinnitus	1.3	0.0	—	—
<b>Heart Rate and Rhythm</b>				
Palpitation	3.2	2.0	2.9	2.5
Extrasystoles	1.9	0.7	—	—
Tachycardia	1.9	0.0	—	—
Fibrillation Atrial	1.3	0.0	—	—
Tachycardia Supraventricular	1.3	0.0	—	—
Bradycardia	—	—	1.0	0.0
<b>Liver and Biliary System</b>				
Gamma-GT Increased	1.3	0.7	1.0	0.0
Hepatic Enzymes Increased	1.3	0.0	—	—
<b>Metabolic and Nutritional</b>				
Alkaline Phosphate Increased	2.5	1.4	1.0	0.0
Weight Decrease	—	—	2.4	0.8
Hypoglycemia	1.3	0.0	—	—
<b>Musculoskeletal System</b>				
Arthralgia	—	—	6.7	5.0
Arthritis	—	—	2.9	0.8
Arthritis Aggravated	1.3	0.0	1.4	0.0
<b>Myocardial, Endocardial, Pericardial Valve</b>				
Myocardial Ischemia	1.3	0.7	—	—
<b>Psychiatric</b>				
Somnolence	40.1	6.1	20.2	8.3
Anxiety	5.1	1.4	6.3	3.3
Confusion	5.1	1.4	8.7	1.7
Hallucination	5.1	1.4	10.1	4.2
Nervousness	—	—	4.8	2.5
Yawning	3.2	0.0	—	—
Amnesia	2.5	1.4	4.8	0.8
Dreaming Abnormal	—	—	2.9	1.7
Depersonalization	—	—	1.4	0.0
Paranoid Reaction	—	—	1.4	0.0
Agitation	1.3	0.7	1.0	0.0
Concentration Impaired	1.3	0.0	—	—
Illusion	—	—	1.4	0.8
Thinking Abnormal	—	—	1.0	0.0
Apathy	—	—	1.0	0.0
Increased Libido	—	—	1.0	0.0
Personality Disorder	—	—	1.0	0.0
<b>Red Blood Cell</b>				
Anemia	—	—	2.4	0.0
<b>Reproductive Male</b>				
Impotence	2.5	1.4	—	—
Prostatic Disorder	—	—	1.0	0.0
Penis Disorder	—	—	1.3	0.0
<b>Resistance Mechanism</b>				
Upper Respiratory Tract Infection	—	—	8.7	8.3
Infection Viral	10.8	3.4	7.2	6.7
<b>Respiratory System</b>				
Pharyngitis	6.4	4.1	—	—
Rhinitis	3.8	2.7	—	—
Sinusitis	3.8	2.7	—	—
Dyspnea	3.2	0.0	2.9	1.7
Bronchitis	2.5	1.4	—	—
Respiratory Disorder	1.9	1.4	1.9	0.0
Pneumonia	1.3	0.7	1.0	0.8
Coughing	—	—	1.4	0.8
<b>Skin/Appendages</b>				
Furunculitis	—	—	1.0	0.0
<b>Urinary System</b>				
Urinary Tract Infection	5.1	4.1	6.3	2.5
Cystitis	1.3	0.7	—	—
Micturition Frequency	—	—	1.4	0.0
Pyuria	—	—	1.9	0.8
Urinary Incontinence	—	—	1.9	0.8
Urinary Retention	1.3	0.7	—	—
Dysuria	—	—	1.0	0.0
<b>Vascular Extracardiac</b>				
Peripheral Ischemia	2.5	0.0	—	—
<b>Vision</b>				
Vision Abnormal	5.7	3.4	—	—
Eye Abnormality	3.2	1.4	—	—
Diplopia	1.9	0.0	1.9	0.8
Xerophthalmia	—	—	1.4	0.8
Cataract	—	—	1.4	0.8
Lacrimation Abnormal	—	—	1.4	0.8
<b>White Cell and Reticuloendothelial System</b>				
Eosinophilia	—	—	1.4	0.0

\* Incidence of adverse event <1%.

In addition to the events listed in Table 2, the following adverse events were recorded with rates equal to, or more common in, placebo-treated patients:

**Early Therapy:** fever, hot flushes, injury, rigors, ataxia, dyskinesia, dystonia, hyperkinesia, involuntary muscle contractions, paresthesia, aggravated Parkinsonism, tremor, diarrhea, gingivitis, increased saliva, bradycardia, gout, hyperglycemia, decreased weight, arthralgia, arthritis, back pain, myalgia, basal cell carcinoma, anxiety, depression, abnormal dreaming, insomnia, nervousness, prostatic disorder, upper respiratory tract infection, coughing, rash, hematuria and leg cramps.

**Adjunct Therapy:** asthma, chest pain, fatigue, hot flushes, postural hypotension, abnormal gait, hyperkinesia, aggravated Parkinsonism, vertigo, abdominal pain, constipation, back pain, myalgia, depression, insomnia, parosmia (WHO dictionary term for nightmares), viral infection, upper respiratory tract infection, pharyngitis, rhinitis, rash, rash erythematous, taste perversion, hematuria, leg cramps and diplopia, myocardial infarction, extrasystoles/supraventricular.

**Events Observed During the Premarketing Evaluation of REQUIP:** Of the 1599 patients who received REQUIP in therapeutic studies, the following adverse events, which are not included in Table 2 or in the listing above, have been noted up to May 1996. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with REQUIP cannot be determined.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse events are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1,000 patients; *rare* events are those occurring in fewer than 1/1,000 patients.

**Autonomic Nervous System:** rare, cold clammy skin.

**Body as a Whole:** *infrequent*, pallor, allergy, peripheral edema, enlarged abdomen, substernal chest pain, edema, allergic reaction, ascites, precordial chest pain, therapeutic response increased, ischemic necrosis, edema generalised, rare, periorbital edema, face edema, halitosis.

**Cardiovascular System:** *frequent*, cardiac failure, heart disorder, specific abnormal ECG, aneurysm, cardiomegaly, abnormal ECG, aggravated hypertension, rare, cyanosis, fluid overload, heart valve disorder.

**Central and Peripheral Nervous System:** *frequent*, neuralgia, *infrequent*, hypertonias, speech disorder, choreoathetosis, abnormal coordination, dysphonia, extrapyramidal disorder, migraine, aphasia, coma, convulsions, hypotonia, nerve root lesion, peripheral neuropathy, paralysis, stupor, rare, cerebral atrophy, grand mal convulsions, hemiparesis, hemiplegia, hyperreflexia, neuropathy, ptosis, sensory disturbance, hydrocephaly.

**Collagen:** rare, rheumatoid arthritis.

**Endocrine System:** *infrequent*, gonormastia, hypothyroidism, rare, SIADH (syndrome of inappropriate anti-diuretic hormone secretion), increased thyroxine, goitre, hyperthyroid.

**Gastrointestinal System:** *frequent*, gastrointestinal disorder (NOS), *infrequent*, gastritis, gastroenteritis, gastroesophageal reflux, increased appetite, esophagitis, peptic ulcer, diverticulitis, hemorrhoids, hiccup, tooth caries, increased amylose, duodenal ulcer, duodenitis, fecal incontinence, GI hemorrhage, glossitis, rectal hemorrhage, melena, pancreatitis, rectal disorder, altered saliva, stomatitis, ulcerative stomatitis, tongue edema, gastric ulcer, tooth disorder, rare, esophageal stricture, esophageal ulceration, hemorrhagic gastritis, gingival bleeding, hematemesis, lactose intolerance, salivary duct obstruction, tenesmus, tongue disorder, hemorrhagic duodenal ulcer, aggravated tooth caries.

**Hearing:** *infrequent*, earache, decreased hearing, vestibular disorder, ear disorder (NOS), rare, hyperacusis, deafness.

**Heart Rate and Rhythm:** *infrequent*, arrhythmia, bundle branch block, cardiac arrest, supraventricular extrasystoles, ventricular tachycardia, rare, atrioventricular block.

**Liver and Biliary System:** *infrequent*, abnormal hepatic function, increased SGPT, bilirubinemia, cholecystitis, cholelithiasis, hepatocellular damage, increased SGOT, rare, biliary pain, aggravated bilirubinemia, gall bladder disorder.

**Metabolic and Nutritional Systems:** *frequent*, increased blood urea nitrogen, *infrequent*, increased LDH, increased NPN, hyperuricemia, increased weight, hyperphosphatemia, diabetes mellitus, glycosuria, hypercholesterolemia, acidosis, hypokalemia, hyponatremia, thirst, increased creatine phosphokinase, dehydration, aggravated diabetes mellitus, hyperkalemia, rare, electrolyte abnormality, enzyme abnormality, hypochloremia, obesity, increased phosphatase acid, decreased serum iron.

**Musculoskeletal System:** *frequent*, arthrosis, *infrequent*, arthropathy, osteoporosis, tendinitis, bone disorder, bursitis, muscle weakness, polymyalgia rheumatica, skeletal pain, torticollis, rare, muscle atrophy, myositis, Dupuytren's contracture, spine malformation.

**Myocardial, Endocardial, Pericardial Valve:** *frequent*, angina pectoris, *infrequent*, myocardial infarction, aggravated angina pectoris, rare, mitral insufficiency.

**Neoplasia:** *infrequent*, carcinoma, malignant female breast neoplasm, dermoid cyst, malignant skin neoplasm, prostate adenocarcinoma, adenocarcinoma, neoplasm (NOS), rare, bladder carcinoma, benign brain neoplasm, breast fibroadenosis, malignant endometrial neoplasm, esophageal carcinoma, malignant larynx neoplasm, malignant lymphoma, malignant neoplasm, neuroma, lipoma, rectal carcinoma, uterine neoplasm.

**Platelet Bleeding and Clotting:** *infrequent*, purpura, thrombocytopenia, hematoma.

**Psychiatric:** *frequent*, aggravated depression, agitation, *infrequent*, increased libido, sleep disorder, apathy, dementia, delirium, emotional lability, psychosis, aggressive reaction, delusion, psychotic depression, euphoria, decreased libido, manic reaction, neuritis, personality disorder, somnambulism, rare, suicide attempt.

**Red Blood Cell:** *infrequent*, hypochromic anemia, anemia B<sub>12</sub> deficiency, rare, polycythemia.

**Female Reproductive:** *infrequent*, amenorrhea, menstrual disorder, vaginal hemorrhage, uterine disorders (NOS), rare, female breast enlargement, intermenstrual bleeding, mastitis, uterine hemorrhage, dysmenorrhea.

**Male Reproductive:** *infrequent*, epididymitis, balanoposthitis, ejaculation failure, penis disorder, perineal pain male, rare, Peyronie's disease, ejaculation disorder, testis disorder.

**Resistance mechanism:** *frequent*, *infrequent*, herpes zoster, moniliasis, otitis media, sepsis, herpes simplex, fungal infection, abscess, bacterial infection, genital moniliasis, rare, poliomyelitis.

**Respiratory:** *frequent*, pneumonia, *infrequent*, asthma, epistaxis, laryngitis, pleurisy, increased sputum, pulmonary edema, rare, hypoxia, respiratory insufficiency, vocal cord paralysis.

**Skin and Appendages:** *infrequent*, dermatitis, alopecia, skin discoloration, dry skin, skin hypertrophy, skin ulceration, fungal dermatitis, eczema, hyperkeratosis, photosensitivity reaction, psoriasis, maculopapular rash, psoriasisform rash, seborrhea, skin disorder, urticaria, furunculosis, rare, bulous eruption, nail disorder, nevus, photosensitivity allergic reaction, aggravated psoriasis, skin exfoliation, abnormal skin odor.

**Other Special Senses:** rare, parosmia.

**Urinary:** *infrequent*, albuminuria, dysuria, nocturia, polyuria, renal calculus, abnormal urine, micturition disorder, rare, oliguria, pyelonephritis, renal cyst, acute renal failure, renal pain, uremia, urethral disorder, urinary casts, bladder calculus, nephritis.

**Vascular Extracardiac:** *infrequent*, cerebrovascular disorder, vein disorder, varicose vein, peripheral gangrene, phlebitis, vascular disorder, rare, atherosclerosis, limb embolism, pulmonary embolism, gangrene, superficial phlebitis, subarachnoid hemorrhage, deep thrombophlebitis, leg thrombophlebitis, thrombosis, arteritis.

**Vision:** *infrequent*, conjunctivitis, blepharitis, abnormal accommodation, bi-photospasm, eye pain, glaucoma, photophobia, scotoma, rare, blindness, blindness temporary, hemianopia, keratitis, photopsia, macula lutea degeneration, vitreous detachment, retinal disorder.

**White Cell and Reticuloendothelial System:** *infrequent*, leukocytosis, leukopenia, lymphopenia, lymphedema, lymphocytosis, rare, lymphadenopathy, granulocytopenia.

**SYMPTOMS AND TREATMENT OF OVERDOSEAGE**

There were no reports of intentional overdose of REQUIP (ropinirole hydrochloride) in the premarketing clinical trials. A total of 27 patients accidentally took more than their prescribed dose of REQUIP, with 10 patients ingesting more than 24 mg/day. The largest overdose reported in premarketing clinical trials was 435 mg taken over a 7-day period (62.1 mg/day). Of patients who received a dose greater than 24 mg/day, one experienced mild oro-facial dyskinesia, another patient experienced intermittent nausea. Other symptoms reported with accidental overdoses were: agitation, increased dyskinesia, gressiveness, sedation, orthostatic hypotension, chest pain, confusion, vomiting and nausea.

It is anticipated that the symptoms of REQUIP overdose will be related to its dopaminergic activity. General supportive measures are recommended. Vital signs should be maintained, if necessary. Removal of any unabsorbed material (e.g., by gastric lavage) should be considered.

**DOSEAGE AND ADMINISTRATION**

REQUIP (ropinirole hydrochloride) should be taken three times daily. While administration of REQUIP with meals may improve gastrointestinal tolerance, REQUIP may be taken with or without food (see "Pharmacokinetics" section).

The recommended starting dosage is 0.25 mg three times daily. Based on individual patient response, dosage should then be titrated by weekly increments of 0.25 mg per dose as described in the table below. After week 4, daily dosage may be increased by 0.5 to 1.0 mg per dose on a weekly basis up to 24 mg per day. Doses greater than 24 mg/day have not been tested in clinical trials. Smaller dose increments are recommended for patients who may be at risk for orthostatic symptoms. In clinical trials, initial benefits were observed with 3 mg/day and higher doses.

	Week			
	1	2	3	4
Unit Dose (mg)	0.25	0.5	0.75	1.0
Total Daily Dose (mg)	0.75	1.5	2.25	3.0

When REQUIP is administered as adjunct therapy to levodopa, the dose of levodopa may be decreased gradually as tolerated once a therapeutic effect with REQUIP has been observed (see "Clinical Trials" section).

REQUIP should be discontinued gradually over a 7-day period. The frequency of administration should be reduced from three times daily to twice daily for 4 days. For the remaining 3 days, the frequency should be reduced to once daily prior to complete withdrawal of REQUIP.

**Renal and Hepatic Impairment**  
In patients with mild to moderate renal impairment, REQUIP may be titrated in the recommended manner according to clinical response. Patients with severe renal impairment or on hemodialysis have not been studied and administration of REQUIP to such patients is not recommended.

Patients with hepatic impairment have not been studied and administration of REQUIP to such patients is not recommended.

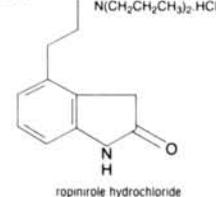
**Estrogen Replacement Therapy**  
In patients already receiving estrogen replacement therapy, REQUIP may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or started during treatment with REQUIP, adjustment of the REQUIP dosage may be required.

**PHARMACEUTICAL INFORMATION**

**Drug Substance:**  
Proper Name: Ropinirole Hydrochloride

**USAN and Chemical Name:**  
4-[2-(Dipropylamino)ethyl]-2-indolinone monohydrochloride

**Molecular Formula:** C<sub>16</sub>H<sub>25</sub>N<sub>2</sub>OCl  
**Structural Formula:**



ropinirole hydrochloride

**Molecular Weight:** 296.84 (260.38 as the free base)  
**Description:** Ropinirole hydrochloride is a white to pale greenish-yellow powder.

**Physico-Chemical Properties:** Ropinirole hydrochloride has a melting range of 243° to 250°C and a solubility of 133 mg/mL in water. The pKa of the protonated tertiary amino group was found to be 9.68 at 25°C and that of the indol-2-one group was found to be 12.43 at 37°C. The distribution coefficients between n-octanol/water and cyclohexane/water at pH 8.4 and 37°C are given by log D values of +2.33 and -0.07 respectively.

**Composition:** Ropinirole hydrochloride is the active ingredient. Non-medical ingredients include: Hydrox

# Once-a-day Aricept<sup>®</sup>

donepezil HCl 5 & 10 mg tablets

## PHARMACOLOGIC CLASSIFICATION

Cholinesterase Inhibitor

## ACTION AND CLINICAL PHARMACOLOGY

ARICEPT (donepezil hydrochloride) is a piperidine-based, reversible inhibitor of the enzyme acetylcholinesterase.

A consistent pathological change in Alzheimer's Disease is the degeneration of cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. The resulting hypofunction of these pathways is thought to account for some of the clinical manifestations of dementia. Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine (ACh) through reversible inhibition of its hydrolysis by acetylcholinesterase (AChE). If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact.

There is no evidence that donepezil alters the course of the underlying dementing process.

## Clinical Pharmacokinetics and Metabolism

**Absorption:** Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations ( $C_{max}$ ) approximately 3 to 4 hours after dose administration. Plasma concentrations and area under the curve (AUC) were found to rise in proportion to the dose administered within the 1- to 10 mg dose range studied. The terminal disposition half-life ( $t_{1/2}$ ) is approximately 70 hours and the mean apparent plasma clearance (CLF) is 0.13 L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold and steady state is reached within 15 days. The minimum, maximum and steady-state plasma concentrations ( $C_{min}$  and  $C_{max}$ ) and pharmacodynamic effect (i.e., percent inhibition of acetylcholinesterase in erythrocyte membranes) of donepezil hydrochloride in healthy adult male and female volunteers are given in Table 1.

**Table 1. Plasma Concentrations and Pharmacodynamic Effect of Donepezil Hydrochloride at Steady-State (Mean ± S.D.)**

Dose (mg/day)	$C_{min}$ (ng/mL)	$C_{max}$ (ng/mL)	$C_{50}$ (ng/mL)	$E_{50}$ %	$E_{max}$ %	$E_{50}$ %
5	21.4 ± 3.8	34.1 ± 7.3	26.5 ± 3.9	62.2 ± 5.8	71.8 ± 4.3	65.3 ± 5.2
10	38.5 ± 8.6	60.5 ± 10.0	47.0 ± 8.2	74.7 ± 4.4	83.6 ± 1.9	77.8 ± 3.0

$C_{50}$  Plasma concentration at 50% effect  
 $E_{50}$  Inhibition of erythrocyte membrane acetylcholinesterase at 50% effect

The range of inhibition of erythrocyte membrane acetylcholinesterase noted in Alzheimer's Disease patients in controlled clinical trials was 40- to 80% and 60- to 90% for the 5 mg/day and 10 mg/day doses, respectively.

Pharmacokinetic parameters from healthy adult male and female volunteers participating in a multiple-dose study where single daily doses of 5 mg or 10 mg of donepezil hydrochloride were administered each evening are summarized in Table 2. Treatment duration was one month. However, volunteers randomized to the 10 mg/day dose group initially received 5 mg daily doses of donepezil for one week before receiving the 10 mg daily dose for the next three weeks in order to avoid acute cholinergic effects.

**Table 2. Pharmacokinetic Parameters of Donepezil Hydrochloride at Steady-State (Mean ± S.D.)**

Dose (mg/day)	$t_{max}$ (hr)	AUC <sub>0-24</sub> (ng·hr/mL)	CL <sub>F</sub> (L/hr/kg)	V <sub>d</sub> /F (L/kg)	$t_{1/2}$ (hr)
5	3.0 ± 1.4	634.8 ± 92.2	0.110 ± 0.02	11.8 ± 1.7	72.7 ± 10.6
10	3.9 ± 1.0	1127.8 ± 195.9	0.110 ± 0.02	11.6 ± 1.9	73.5 ± 11.8

$t_{max}$  Time to maximal plasma concentration  
AUC<sub>0-24</sub> Area under the plasma concentration versus time curve from 0- to 24 hours  
CL<sub>F</sub> Mean apparent plasma clearance  
V<sub>d</sub>/F Apparent volume of distribution  
 $t_{1/2}$  Elimination half-life

Neither food nor time of dose administration (i.e., morning versus evening dose) have an influence on the rate and extent of donepezil hydrochloride absorption.

The effect of achlorhydria on the absorption of donepezil hydrochloride is unknown.

**Distribution:** Donepezil hydrochloride is about 96% bound to human plasma proteins, mainly to albumins (~75%) and  $\alpha_1$ -acid glycoprotein (~21%) over the concentration range of 2- to 1000 ng/mL.

**Metabolism/Excretion:** Donepezil hydrochloride is extensively metabolized and is also excreted in the urine as parent drug. The rate of metabolism of donepezil hydrochloride is slow and does not appear to be saturable. There are four major metabolites - two of which are known to be active - and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of a single 5 mg dose of <sup>14</sup>C-labeled donepezil hydrochloride, plasma radioactivity expressed as a percent of the administered dose, was present primarily as unchanged donepezil hydrochloride (53%), and as 6-O-desmethyl donepezil (11%) which has been reported to inhibit AChE to the same extent as donepezil *in vitro* and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% of the total administered radioactivity was recovered from the urine and 15% was recovered from the feces (total recovery of 72%) over a period of 10 days. Approximately 28% of the labeled donepezil remained unrecovered, with about 17% of the donepezil dose recovered in the urine as parent drug.

**Age and Gender:** No formal pharmacokinetic study was conducted to examine age and gender-related differences in the pharmacokinetic profile of donepezil. However, mean plasma donepezil concentrations measured during therapeutic drug monitoring of elderly male and female patients with Alzheimer's Disease are comparable to those observed in young healthy volunteers.

**Renal:** In a study of four patients with moderate-to-severe renal impairment ( $Cl_{CR} < 22$  mL/min/1.73 m<sup>2</sup>), the clearance of donepezil did not differ from that of four age and sex-matched healthy subjects.

**Hepatic:** In a study of 10 patients with stable alcoholic cirrhosis, the clearance of donepezil was decreased by 20% relative to 10 healthy age and sex-matched subjects.

**Race:** No specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of donepezil. However, retrospective pharmacokinetic analysis indicates that gender and race (Japanese and Caucasians) did not affect the clearance of donepezil.

**Clinical Trial Data:** Two randomized, double-blind, placebo-controlled, clinical trials in patients with Alzheimer's Disease (diagnosed by DSM-III-R and NINCDS criteria; Mini-Mental State Examination  $\geq 10$  and  $\leq 26$  as well as the Clinical Dementia Rating of 1 or 2) provided efficacy data for donepezil in this patient population. In these studies, the mean age of patients was 73 years with a range of 50 to 94 years. Approximately 64% of the patients were women and 38% were men. The racial distribution was as follows: white 95%, black 3% and other races 2%.

In each study, the effectiveness of treatment with donepezil was evaluated using a dual outcome assessment strategy. The ability of donepezil to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a widely used and well validated multi-item instrument which samples cognitive domains affected by the disease.

The ability of donepezil to produce an overall clinical effect was assessed using the semi-structured CIBIC plus (Clinician's Interview Based Impression of Change that required the use of caregiver information). The CIBIC plus evaluates four major areas of functioning - general cognition, behavior and activities of daily living.

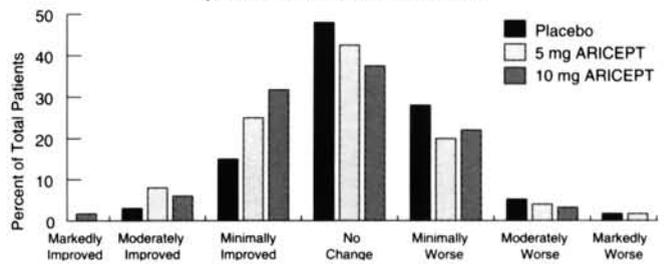
The data shown below for the two primary outcome measures in donepezil clinical trials were obtained from the intent-to-treat population (ITT analysis), i.e., all patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete the study, their last observation while on treatment was carried forward and used at endpoint.

**Fifteen-Week Study (12 weeks of treatment + 3-week placebo washout):** In this study, 468 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of donepezil for 12 weeks, followed by a 3-week placebo washout period. To reduce the likelihood of cholinergic effects, the 10 mg/day treatment group received 5 mg/day for the first week prior to receiving their first 10 mg daily dose.

**Effects on ADAS-cog:** Patients treated with donepezil showed significant improvements in ADAS-cog score from baseline, and when compared with placebo. The mean differences in mean ADAS-cog change scores for the donepezil-treated patients compared to the patients on placebo, for the intent-to-treat population, at week 12 were 2.44 ± 0.43 and 3.07 ± 0.43 units each, for the 5 mg/day and 10 mg/day donepezil treatment groups, respectively. These differences were statistically significant. The difference between active treatments was not statistically significant. Following a 3-week placebo washout period, the ADAS-cog scores for both donepezil treatment groups increased, indicating that discontinuation of donepezil resulted in a loss of its treatment effect. The duration of this placebo washout period was not sufficient to characterize the rate of loss of the treatment effect, but the 30-week study (see below) demonstrated that treatment effects associated with the use of donepezil abate within 6 weeks of treatment discontinuation.

**Effects on The CIBIC plus:** The CIBIC plus showed significant improvement with donepezil treatment versus placebo. The differences in mean scores for donepezil-treated patients compared to those on placebo for the intent-to-treat population at Week 12 were 0.29 ± 0.06 and 0.34 ± 0.06 units for the 5 mg/day and 10 mg/day treatment groups, respectively. These differences from placebo were statistically significant. There was no significant difference between the two active treatments. Figure 1 is a histogram of the frequency distribution of CIBIC plus scores achieved at Week 12 by patients assigned to each of the three treatment groups.

**Fig. 1. FREQUENCY DISTRIBUTION OF CIBIC PLUS SCORES AT WEEK 12**

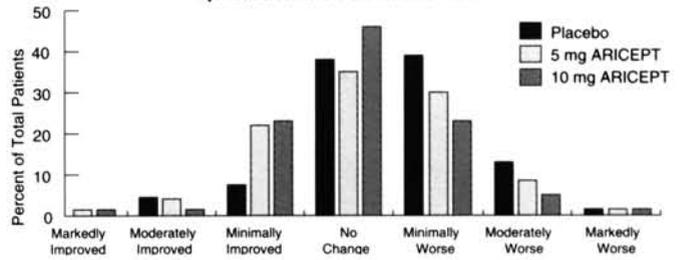


**Thirty-Week Study (24 weeks of treatment + 6-week placebo washout):** In this study, 473 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of donepezil for 24 weeks of double-blind active treatment followed by a 6-week single-blind placebo washout period. As in the 15-week study to avoid acute cholinergic effects, the 10 mg/day treatment group received 5 mg/day for the first week prior to receiving their first 10 mg daily dose.

**Effects on The ADAS-cog:** Patients treated with donepezil showed significant improvements in ADAS-cog score from baseline, and when compared with placebo. The mean differences in the ADAS-cog change scores for donepezil-treated patients compared to the patients on placebo for the intent-to-treat population at Week 24 were 2.49 ± 0.51 and 2.88 ± 0.51 units for the 5 mg/day and 10 mg/day treatments, respectively. These differences were statistically significant. The difference between the two active treatments was not statistically significant. Over the 24-week treatment period, 80% (5 mg) and 81% (10 mg) of donepezil-treated patients versus 58% placebo-treated patients showed no evidence of deterioration or an improvement. A 4-point improvement in ADAS-cog was observed in 38% (5 mg) and 54% (10 mg) of donepezil-treated patients versus 27% for placebo. A 7-point improvement was observed in 15% (5 mg) and 25% (10 mg) of donepezil-treated patients versus 8% for placebo. Following 6 weeks of placebo washout, scores on the ADAS-cog for both the ARICEPT-treatment groups were indistinguishable from those patients who had received only placebo for 30 weeks. This suggests that the beneficial effects of donepezil abate over 6 weeks following discontinuation of treatment and therefore do not represent a change in the underlying disease. There was no evidence of a rebound effect 6 weeks after abrupt discontinuation of therapy. This is in line with the pharmacokinetics of donepezil (i.e., ~70 hour half-life) which preclude an abrupt reduction in drug plasma levels.

**Effects on The CIBIC plus:** After 24 weeks of treatment, the mean drug-placebo differences were 0.36 ± 0.09 and 0.44 ± 0.07 units for 5 mg/day and 10 mg/day of donepezil, respectively. These differences were statistically significant. There was no statistically significant difference between the two active treatments. Figure 2 is a histogram of the frequency distribution of CIBIC plus scores achieved at Week 24 by patients assigned to each of the three treatment groups.

**Fig. 2. FREQUENCY DISTRIBUTION OF CIBIC PLUS SCORES AT WEEK 24**



Data from these controlled clinical trials showed that the beneficial symptomatic effects of ARICEPT versus placebo were more consistently apparent after 12 weeks of continuous treatment. Once treatment is discontinued, the effects of ARICEPT were shown to abate within 6 weeks of treatment discontinuation.

## INDICATIONS AND CLINICAL USE

ARICEPT (donepezil hydrochloride) is indicated for the symptomatic treatment of patients with mild-to-moderate dementia of the Alzheimer's type. ARICEPT has not been studied in controlled clinical trials for longer than 6 months.

ARICEPT tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's Disease.

## CONTRAINDICATIONS

ARICEPT (donepezil hydrochloride) is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives.

## WARNINGS

**Anesthesia:** ARICEPT (donepezil hydrochloride), as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

**Neurological Conditions: Seizures:** Some cases of seizures have been reported with the use of ARICEPT in clinical trials and from spontaneous Adverse Reaction reporting. Cholinomimetics can cause a reduction of seizure threshold, increasing the risk of seizures. However, seizure activity may also be a manifestation of Alzheimer's Disease. The risk/benefit of ARICEPT treatment for patients with a history of seizure disorder must therefore be carefully evaluated.

ARICEPT has not been studied in patients with moderately severe or severe Alzheimer's Disease, non-Alzheimer dementias or individuals with Parkinsonian features. The efficacy and safety of ARICEPT in these patient populations is unknown.

**Pulmonary Conditions:** Because of their cholinomimetic action, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. ARICEPT has not been studied in patients under treatment for these conditions and should therefore be used with particular caution in such patients.

**Cardiovascular:** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, most patients with significant cardiovascular conditions were excluded, except for patients with controlled hypertension (DBP  $\leq 95$  mmHg), right bundle branch blockage, and pacemakers. Therefore, caution should be taken in treating patients with active coronary artery disease and congestive heart failure. Syncope episodes have been reported in association with the use of ARICEPT. It is recommended that ARICEPT should not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncope episodes.

**Gastrointestinal:** Through their primary action, cholinesterase inhibitors may be expected to increase gastric secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent non-steroidal anti-inflammatory drugs (NSAIDs) including high doses of acetylsalicylic acid (ASA), should be monitored closely for symptoms of active or occult gastrointestinal bleeding. Clinical studies of ARICEPT have shown no increase, relative to placebo in the incidence of either peptic ulcer disease or gastrointestinal bleeding. (See ADVERSE REACTIONS Section.)

ARICEPT, as a predictable consequence of its pharmacological properties, has been shown to produce, in controlled clinical trials in patients with Alzheimer's Disease, diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have usually been mild and transient, sometimes lasting one- to- three weeks and have resolved during continued use of ARICEPT. (See ADVERSE REACTIONS Section.) A treatment with the 5 mg/day dose for over 6 weeks prior to initiating treatment with the 10 mg/day dose is associated with a lower incidence of gastrointestinal intolerance.

**Genitourinary:** Although not observed in clinical trials of ARICEPT, cholinomimetics may cause bladder outflow obstruction.

## PRECAUTIONS

### Concomitant Use with Other Drugs:

**Use with Anticholinergics:** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

**Use with Cholinomimetics and Other Cholinesterase Inhibitors:** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

**Use with Other Psychoactive Drugs:** Few patients in controlled clinical trials received neuroleptics, antidepressants or anticonvulsants; there is thus limited information concerning the interaction of ARICEPT with these drugs.

**Use in Patients  $\geq 65$  Years Old:** In controlled clinical studies with 5 and 10 mg of ARICEPT, 536 patients were between the ages of 65 to 84, and 37 patients were aged 85 years or older. In Alzheimer's Disease patients, nausea, diarrhea, vomiting, insomnia, fatigue and anorexia increased with dose and age and the incidence appeared to be greater in female patients. Since cholinesterase inhibitors as well as Alzheimer's Disease can be associated with significant weight loss, caution is advised regarding the use of ARICEPT in low body-weight elderly patients, especially in those  $\geq 85$  years old.

**Use in Elderly Patients with Comorbid Disease:** There is limited safety information for ARICEPT in patients with mild-to-moderate Alzheimer's Disease and significant comorbidity. The use of ARICEPT in Alzheimer's Disease patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Caution is advised regarding the use of ARICEPT doses above 5 mg in this patient population.

**Renally and Hepatically Impaired:** There is limited information regarding the pharmacokinetics of ARICEPT in renally and hepatically impaired Alzheimer's Disease patients (see **Clinical Pharmacokinetics and Metabolism** Section). Close monitoring for adverse effects in Alzheimer's Disease patients with renal or hepatic disease being treated with ARICEPT is therefore recommended.

**Drug-Drug Interactions:**

Pharmacokinetic studies limited to short-term, single-dose studies in young subjects evaluated the potential of ARICEPT for interaction with theophylline, cimetidine, warfarin and digoxin administration. No significant effects on the pharmacokinetics of these drugs were observed. Similar studies in elderly patients were not done.

**Drugs Highly Bound to Plasma Proteins:** Drug displacement studies have been performed *in vitro* between donepezil, a highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil at concentrations of 0.3–10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL) and warfarin (3 µg/mL) to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin.

**Effect of ARICEPT on the Metabolism of Other Drugs:** No *in vivo* clinical trials have been conducted to investigate the effect of ARICEPT on the clearance of drugs metabolized by CYP 3A4 (e.g., cisapride, terfenadine) or by CYP 2D6 (e.g., imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean  $K_a$  about 50–130 µM), that given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

It is not known whether ARICEPT has any potential for enzyme induction.

**Effect of Other Drugs on the Metabolism of ARICEPT:** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of these inhibitors is not known. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin and phenobarbital) could increase the rate of elimination of ARICEPT.

Pharmacokinetic studies demonstrated that the metabolism of ARICEPT is not significantly affected by concurrent administration of digoxin or cimetidine.

**Use in Pregnancy and Nursing Mothers:** The safety of ARICEPT during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or in nursing mothers unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus or the infant.

Teratology studies conducted in pregnant rats at doses of up to 16 mg/kg/day and in pregnant rabbits at doses of up to 10 mg/kg/day did not disclose any evidence for a teratogenic potential of ARICEPT.

**Pediatric Use:** There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT in any illness occurring in children. Therefore, ARICEPT is not recommended for use in children.

**ADVERSE REACTIONS**

A total of 747 patients with mild-to-moderate Alzheimer's Disease were treated in controlled clinical studies with ARICEPT (donepezil hydrochloride). Of these patients, 613 (82%) completed the studies. The mean duration of treatment for all ARICEPT groups was 132 days (range 1–356 days).

**Adverse Events Leading to Discontinuation:** The rates of discontinuation from controlled clinical trials of ARICEPT due to adverse events for the ARICEPT 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received the 10 mg/day dose after only a 1-week initial treatment with 5 mg/day ARICEPT was higher at 13%.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

**Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group**

Dose Group	Placebo	5 mg/day ARICEPT	10 mg/day ARICEPT
<b>Number of Patients Randomized</b>	355	350	315
<b>Events/Discontinuing</b>			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

**Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT:** The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT's cholinergic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common adverse events may be affected by the duration of treatment with an initial 5 mg (daily dose) increasing the dose to 10 mg/day. An open-label study was conducted with 269 patients who received placebo in the 15 and 30-week studies. These patients received a 5 mg/day dose for 6 weeks prior to initiating treatment with 10 mg/day. The rates of common adverse events were lower than those seen in controlled clinical trials who received 10 mg/day after only a one-week initial treatment period with a 5 mg daily dose, and were comparable to the rates noted in patients treated only with 5 mg/day.

See Table 2 for a comparison of the most common adverse events following one and six-week initial treatment periods with 5 mg/day ARICEPT.

**Table 2. Comparison of Rates of Adverse Events in Patients Treated with 10 mg/day after 1 and 6 Weeks of Initial Treatment with 5 mg/day**

Adverse Event	No Initial Treatment		One-Week Initial Treatment with 5 mg/day		Six-Week Initial Treatment with 5 mg/day	
	Placebo (n = 315)	5 mg/day (n = 311)	10 mg/day (n = 315)	10 mg/day (n = 269)	10 mg/day (n = 315)	10 mg/day (n = 269)
Nausea	6%	5%	19%	6%	19%	6%
Diarrhea	5%	8%	15%	9%	15%	9%
Insomnia	6%	6%	14%	6%	14%	6%
Fatigue	3%	4%	8%	3%	8%	3%
Vomiting	3%	3%	8%	5%	8%	5%
Muscle Cramps	2%	6%	8%	3%	8%	3%
Anorexia	2%	3%	7%	3%	7%	3%

**Adverse Events Reported in Controlled Trials:** The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment-emergent signs and symptoms (TESS) that were reported in at least 2% of patients from placebo-controlled clinical trials who received ARICEPT and for which the rate of occurrence was greater for ARICEPT than placebo-assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

**Table 3. Adverse Events Reported in Controlled Clinical Trials in At Least 2% of Patients Receiving ARICEPT and at a Higher Frequency than Placebo-Treated Patients**

Body System/ Adverse Events	Placebo n = 355	ARICEPT n = 747	Body System/ Adverse Events	Placebo n = 355	ARICEPT n = 747
Percent of Patients with any Adverse Event	72	74	<b>Metabolic and Nutritional</b>		
<b>Body as a Whole</b>			Weight Decrease	1	3
Headache	9	10	<b>Musculoskeletal System</b>		
Pain, Various Locations	8	9	Muscle Cramps	2	6
Accident	6	7	Arthritis	1	2
Fatigue	3	5	<b>Nervous System</b>		
<b>Cardiovascular System</b>			Insomnia	6	9
Syncope	1	2	Dizziness	6	8
<b>Digestive System</b>			Depression	<1	3
Nausea	6	11	Abnormal Dreams	0	3
Diarrhea	5	10	Somnolence	<1	2
Vomiting	3	5	<b>Urogenital</b>		
Anorexia	2	4	Frequent Urination	1	2
<b>Hemic and Lymphatic Systems</b>					
Echymosis	3	4			

**Other Adverse Events Observed During Clinical Trials:** ARICEPT has been administered to over 1700 individuals for various lengths of time during clinical trials worldwide. Approximately 1200 patients have been treated for at least 3 months, and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 115 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days.

Treatment-emergent signs and symptoms that occurred during three controlled clinical trials and two open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the studies were integrated and the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT. All adverse events occurring at least twice are included. Adverse events already listed in Tables 2 and 3 are not repeated here (i.e., events occurring at an incidence >2%). Also excluded are COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed as occurring in ≥1% and <2% of patients (i.e., in 1/100 to 2/1000 patients), frequent or in <1% of patients (i.e., in 1/100 to 1/1000 patients), infrequent. These adverse events are not necessarily related to ARICEPT treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

**Adverse Events Occurring in ≥1% and <2% or <1% of Patients Receiving ARICEPT**

**Body as a Whole:** (≥1% and <2%) influenza, chest pain, toothache, (<1%) fever, edema face, periorbital edema, hema. haital, abscess, cellulitis, chills, generalized coldness, head fullness, head pressure, chest pain.

**Cardiovascular System:** (≥1% and <2%) hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension, (<1%) angina pectoris, postural hypotension, myocardial infarction, premature ventricular contraction, arrhythmia, AV Block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thromboses.

**Digestive System:** (≥1% and <2%) fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain, (<1%) eructation, gingivitis, increased appetite, flatulence, periorbital abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever, sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, haemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer.

**Endocrine System:** (<1%) diabetes mellitus, goiter.

**Hemic & Lymphatic System:** (<1%) anaemia, thrombocytopenia, thrombocytopenia, eosinophilia, erythrocytopenia.

**Metabolic and Nutritional Disorders:** (≥1% and <2%) dehydration, (<1%) gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase.

**Musculoskeletal System:** (≥1% and <2%) bone fracture, (<1%) muscle weakness, muscle fasciculation.

**Nervous System:** (≥1% and <2%) delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, libido increased, restlessness, abnormal crying, nervousness, aphasia, (<1%) cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonía, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing, seizures.

**Respiratory System:** (≥1% and <2%) dyspnea, sore throat, bronchitis, (<1%) epistaxis, postnasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring.

**Skin and Appendages:** (≥1% and <2%) abrasion, pruritus, diaphoresis, urticaria, (<1%) dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, herpes simplex, skin striae, night sweats, skin ulcer.

**Special Senses:** (≥1% and <2%) cataract eye irritation, blurred vision, (<1%) dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes.

**Urogenital System:** (≥1% and <2%) urinary incontinence, nocturia, (<1%) dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

**SYMPTOMS AND TREATMENT OF OVERDOSEAGE**

**Symptoms:** Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

**Treatment:** The elimination half-life of ARICEPT at recommended doses is approximately 70 hours; thus, in the case of overdose, it is anticipated that prolonged treatment and monitoring of adverse and toxic reactions will be necessary. As in any case of overdose, general supportive measures should be utilized.

Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT (donepezil hydrochloride) overdose. Intravenous atropine sulfate titrated to effect is recommended. An initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

Dose-related signs of toxicity observed in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, fasciculation, and lower body surface temperature.

**DOSAGE AND ADMINISTRATION**

ARICEPT (donepezil hydrochloride) tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's Disease.

The recommended initial dose of ARICEPT is 5 mg taken once daily. Therapy with the 5 mg dose should be maintained for 4-6 weeks before considering a dose increase, in order to avoid or decrease the incidence of the most common adverse reactions to the drug (see **ADVERSE REACTIONS** Section) and to allow plasma levels to reach steady state.

For those patients who do not respond adequately to the 5 mg daily dose after 4- to 6-weeks of treatment, the 10 mg daily dose may then be considered.

The maximum recommended dose is 10 mg taken once daily.

Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects. Adverse events are more common in individuals of low body weight, in patients ≥ 85 years old and in females. It is recommended that ARICEPT be used with caution in elderly women of low body weight and that the dose should not exceed 5 mg/day.

ARICEPT should be taken once daily in the evening, before retiring. It may be taken with or without food.

In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

**Composition:**

Each 5 and 10 mg, film-coated tablet contains 5.00 and 10.00 mg of donepezil HCl respectively, equivalent to 4.56 and 9.12 mg of donepezil free base. Inactive ingredients are lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropylcellulose, and magnesium stearate. The film coating contains talc, polyethylene glycol, hydroxypropyl methylcellulose and titanium dioxide. Additionally, the 10 mg tablet contains iron oxide as a coloring agent.

**Stability and Storage Recommendations:**

Store at controlled room temperature, 15°C to 30°C and away from moisture.

**AVAILABILITY OF DOSAGE FORMS**

ARICEPT is supplied as film-coated tablets containing 5 mg (white tablets) or 10 mg (yellow tablets) of donepezil hydrochloride. The name ARICEPT and the strength are embossed on each tablet.

ARICEPT is available in high density polyethylene (HDPE) bottles of 30.

**REFERENCES:**

- Ashford JW. Diagnosis of Alzheimer's disease. *Psychiatr Annals*. 1996 May 126(5):262-268.
- ARICEPT Product Monograph. Pfizer Canada Inc.

Full Product Monograph available upon request.



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See pages A-22, A-23

# Epival<sup>®</sup>

(divalproex sodium)

## PRESCRIBING INFORMATION

**NAME OF DRUG:** EPIVAL<sup>®</sup> (divalproex sodium)  
Enteric-Coated Tablets

**THERAPEUTIC CLASSIFICATION:** Anticonvulsant

**ACTION AND CLINICAL PHARMACOLOGY:** EPIVAL (divalproex sodium) has anticonvulsant properties, and is chemically related to valproic acid. EPIVAL dissociates to the valproate ion in the gastrointestinal tract. Although its mechanism of action has not yet been established, it has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA). The effect on the neuronal membrane is unknown. Peak serum levels of valproic acid occur in 3 to 4 hours.

The serum half-life ( $t_{1/2}$ ) of valproic acid is typically in the range of 6 to 16 hours. Half-lives in the lower part of the above range are usually found in patients taking other drugs capable of enzyme induction. Enzyme induction may result in enhanced clearance of valproic acid by glucuronidation and microsomal oxidation. Because of these changes in valproic acid clearance, monitoring of valproate and concomitant drug concentrations should be intensified whenever enzyme-inducing drugs are introduced or withdrawn. A slight delay in absorption occurs when the drug is administered with meals but this does not affect the total absorption. Valproic acid is rapidly distributed throughout the body and the drug is strongly bound (90%) to human plasma proteins. Increases in doses may result in decreases in the extent of protein binding and variable changes in valproic acid clearance and elimination.

A good correlation has not been established between daily dose, serum level and therapeutic effect. In epilepsy, the therapeutic plasma concentration range is believed to be from 50 to 100 µg/mL (350 to 700 µmol/L) of total valproate. Occasional patients may be controlled with serum levels lower or higher than this range (see DOSAGE AND ADMINISTRATION).

In placebo-controlled clinical studies in acute mania, 79% of patients were dosed to a plasma concentration between 50 µg/mL and 125 µg/mL. Protein binding of valproate is saturable ranging from 90% at 50 µg/mL to 82% at 125 µg/mL.

Valproate is primarily metabolized in the liver. The principal metabolite formed in the liver is the glucuronide conjugate. Other metabolites in the urine are products of C-3, C-4 and C-5 oxidation. The major oxidative metabolite in the urine is 2-propyl-3-keto-pentanoic acid; minor metabolites are 2-propyl-glutaric acid, 2-propyl-5-hydroxy-pentanoic acid, 2-propyl-3-hydroxy-pentanoic acid and 2-propyl-4-hydroxy-pentanoic acid. Elimination of valproic acid and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little un-metabolized parent drug is excreted in the urine. (See WARNINGS for statement regarding fatal hepatic dysfunction.)

## INDICATIONS AND CLINICAL USE:

**Epilepsy:** EPIVAL (divalproex sodium) is indicated for use as sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal and is useful in primary generalized seizures with tonic-clonic manifestations. Divalproex sodium may also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

**Acute Mania:** EPIVAL (divalproex sodium) is indicated in the treatment of the manic episodes associated with bipolar disorder (DSM-III-R).

The effectiveness of EPIVAL in long-term use, that is for more than 3 weeks, has not been systematically evaluated in controlled trials. EPIVAL is not indicated for use as a mood stabilizer in patients under 18 years of age.

**CONTRAINDICATIONS:** EPIVAL (divalproex sodium) should not be administered to patients with hepatic disease or significant hepatic dysfunction; it is contraindicated in patients with known hypersensitivity to the drug.

**WARNINGS:** Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. These incidences usually occurred during the first six months of treatment with valproic acid. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease.

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.

If EPIVAL is to be used for the control of seizures in children two years old or younger, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks.

Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as, malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. 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 when administering divalproex sodium products to 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 decreases in concentration and serum ammonia for increases in concentration. If changes occur, divalproex sodium 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 drug. The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may increase with increasing dose. The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.

**Use in Pregnancy:** According to recent reports in the medical literature, valproic acid may produce teratogenic effects, such as neural tube defects (e.g., spina bifida) in the offspring of human females 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 antiepileptic drugs and an elevated 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 and/or palate, craniofacial abnormalities 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 antiepileptics. Some reports indicate a possible similar association with the use of other antiepileptic 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.

Other congenital anomalies (e.g., craniofacial defects, cardiovascular malformations and anomalies involving various body systems), compatible and incompatible with life, have been reported. Sufficient data to determine the incidence of these congenital anomalies is not available.

Patients taking valproate may develop clotting abnormalities. A patient who had low fibrinogen when taking multiple anticonvulsants including valproate gave birth to an infant with afibrinogenemia who subsequently died of hemorrhage. If valproic acid is used in pregnancy, the clotting parameters should be monitored carefully. Hepatic failure, resulting in the death of a newborn and of an infant have been reported following the use of valproate during pregnancy. Antiepileptic drugs should not be abruptly 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 childbearing 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 antiepileptic medication is in doubt, appropriate consultation is indicated.

Risk-benefit must be carefully considered when treating or counselling women of childbearing age for bipolar disorder. If EPIVAL is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

**Use in 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). It is not known what effect this may have on a nursing infant.

**Fertility:** The effect of valproate on testicular development and on sperm production and fertility in humans is unknown.

Long-term animal toxicity studies indicate that valproic acid is a weak carcinogen or promoter in rats and mice. The significance of these findings for humans is unknown at present.

## PRECAUTIONS:

**Hepatic dysfunction:** See CONTRAINDICATIONS AND WARNINGS.

**General:** Because of reports of thrombocytopenia, inhibition of the second phase of platelet aggregation, and abnormal coagulation parameters (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before instituting therapy and at periodic intervals. It is recommended that patients receiving EPIVAL (divalproex sodium) be monitored for platelet count and coagulation parameters prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of EPIVAL (divalproex sodium) 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. Asymptomatic elevations of ammonia are more common than symptomatic elevations and when present required more frequent monitoring. If clinically significant symptoms occur, divalproex sodium therapy should be modified or discontinued.

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. Suicidal ideation may be a manifestation of preexisting psychiatric disorders, and close supervision of high risk patients should accompany initial drug therapy.

**Renal Impairment:** Renal impairment is associated with an increase in the unbound fraction of valproate. In several studies, the unbound fraction of valproate in plasma from renally impaired patients was approximately double that for subjects with normal renal function. Hemodialysis in renally impaired patients may remove up to 20% of the circulating valproate.

**Use in Pediatric Patients:** Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions (See WARNINGS). When EPIVAL is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

Younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations. The variability in free fraction limits the clinical usefulness of monitoring total serum valproic concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.

The safety and effectiveness of divalproex sodium for the treatment of acute mania has not been studied in individuals below the age of 18 years.

**Use in the Elderly:** The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26 years). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly (see DOSAGE AND ADMINISTRATION).

The safety and efficacy of EPIVAL in elderly patients with epilepsy and mania has not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic and renal dysfunctions, and limited experience with EPIVAL in this population.

**Use in Pregnancy:** See WARNINGS.

**Driving and Hazardous Occupations:** EPIVAL (divalproex sodium) 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:** Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronyl transferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on valproate monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.

In contrast, drugs that are inhibitors of cytochrome P<sub>450</sub> isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P<sub>450</sub> microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

The concomitant administration of valproic acid with drugs that exhibit extensive protein binding (e.g., aspirin, carbamazepine, dicumarol, warfarin, tolbutamide, and phenytoin) may result in alteration of serum drug levels.

Caution is recommended when EPIVAL is administered with drugs affecting coagulation, (e.g., aspirin and warfarin). (See ADVERSE REACTIONS).

Since divalproex sodium may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy and whenever enzyme-inducing drugs are introduced or withdrawn.

The following list provides information about the potential for drug interactions between several commonly prescribed medications and valproate. The list is not exhaustive nor could it be, since new interactions are continuously being reported. Please note that drugs may be listed under specific name, family or pharmacologic class. Reading the entire section is recommended.

**Alcohol:** EPIVAL (divalproex sodium) may potentiate the CNS depressant action of alcohol.

**Aspirin:** A study involving the co-administration of aspirin at antipyretic doses with valproate to pediatric patients revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased four-fold in the presence of aspirin compared to valproate alone. Caution is recommended when EPIVAL is administered with drugs affecting coagulation, (e.g., aspirin and warfarin). (See ADVERSE REACTIONS).

**Benzodiazepines:** Valproic acid may decrease oxidative liver metabolism of some benzodiazepines, resulting in increased serum concentrations (see *Diazepam* and *Lorazepam*). The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

**Carbamazepine/carbamazepine-10,11-Epoxyde:** Concomitant use of carbamazepine with valproic acid may result in decreased serum concentrations and half-life of valproate due to increased metabolism induced by hepatic microsomal enzyme activity. Serum levels of carbamazepine decreased 17% while that of carbamazepine-10, 11 -epoxyde increased by 45% upon co-administration of valproate and carbamazepine to patients with epilepsy. Monitoring of serum concentrations is recommended when either medication is added to or withdrawn from an existing regimen. Changes in the serum concentration of the 10, 11 -epoxyde metabolite of carbamazepine, however, will not be detected by routine serum carbamazepine assay.

**Chlorpromazine:** A single study has shown that the concomitant use of chlorpromazine with valproic acid may result in a decrease in valproic acid clearance. Valproic acid serum concentrations and effects should be monitored when valproic acid is co-administered with chlorpromazine due to possible inhibition of valproic acid metabolism. In addition to enhancing central nervous system (CNS) depression when used concurrently with valproic acid, antipsychotics may lower the seizure threshold. Dosage adjustments may be necessary to control seizures.

**Cimetidine:** Cimetidine may decrease the clearance and increase the half-life of valproic acid by altering its metabolism. In patients receiving valproic acid, serum valproic acid levels should be monitored when treatment with cimetidine is instituted, increased, decreased, or discontinued. The valproic acid dose should be adjusted accordingly.

**Clonazepam:** The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.

**Diazepam:** Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n = 6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20% respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate. Valproic acid may decrease oxidative liver metabolism of some benzodiazepines, resulting in increased serum concentrations.

**Ethosuximide:** Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

**Felbamate:** Increases in average steady state valproate concentrations of 28 to 54% may occur when felbamate is administered to epileptic patients stabilized on valproate. A decrease in valproate dosage may be necessary when felbamate therapy is initiated. Lower doses of valproate may be necessary when used concomitantly with felbamate.

**Lamotrigine:** The effects of sodium valproate on lamotrigine were investigated in six healthy male subjects. Each subject received a single oral dose of lamotrigine alone and with valproic acid 200 mg every 8 hours for six doses starting 1 hour before the lamotrigine dose was given. Valproic acid administration reduced the total clearance of lamotrigine by 21% and increased the plasma elimination half-life from 37.4 hours to 48.3 hours ( $p < 0.005$ ). Renal clearance of lamotrigine was unchanged. In a study involving 16 epileptic patients, valproic acid doubled the elimination half-life of lamotrigine. In an open-labelled study, patients receiving enzyme-inducing antiepileptic drugs (e.g. carbamazepine, phenytoin, phenobarbital, or primidone) demonstrated a mean lamotrigine plasma elimination half-life of 14 hours while the elimination half-life was 30 hours in patients taking sodium valproate plus an enzyme-inducing antiepileptic agent. The latter value is similar to the lamotrigine half-life during monotherapy indicating that valproic acid may counteract the effect of the enzyme inducer. If valproic acid is discontinued in a patient receiving lamotrigine and an enzyme-inducing antiepileptic serum lamotrigine concentrations may decrease. Patients receiving combined antiepileptic therapy require careful monitoring when another agent is started, stopped or when the dose is altered.

**Lorazepam:** Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers (n = 9) was accompanied by a 17% decrease in the plasma clearance of lorazepam. Valproic acid may decrease oxidative liver metabolism of some benzodiazepines, resulting in increased serum concentrations.

**Lithium:** In a double-blind placebo-controlled multiple dose crossover study in 16 healthy male volunteers, pharmacokinetic parameters of lithium were not altered by the presence or absence of EPIVAL. The presence of lithium, however, resulted in an 11-12% increase in the AUC and  $C_{max}$  of valproate.  $T_{max}$  was also reduced. Although these changes were statistically significant, they are not likely to have clinical importance.

**Oral contraceptives:** Evidence suggests that there is an association between the use of certain antiepileptic drugs capable of enzyme induction and failure of oral contraceptives. One explanation for this interaction is that enzyme-inducing drugs effectively lower plasma concentrations of the relevant steroid hormones, resulting in unpaired ovulation. However, other mechanisms, not related to enzyme induction, may contribute to the failure of oral contraceptives. Valproic acid is not a significant enzyme inducer and would not be expected to decrease concentrations of steroid hormones. However, clinical data about the interaction of valproic acid with oral contraceptives are minimal.

**Phenobarbital:** There is evidence that valproic acid may cause a decrease in nonrenal clearance (50% increase in half-life and 30% decrease in plasma clearance of phenobarbital [60 mg single dose]). 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 concentrations. 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.

**Phenytoin:** Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%. In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

**Primidone:** Primidone is metabolized into a barbiturate, and therefore, may also be involved in a similar or identical interaction with valproate as phenobarbital.

**Selective serotonin re-uptake inhibitors (SSRI's):** Some evidence suggests that SSRI's inhibit the metabolism of valproate, resulting in higher than expected levels of valproate.

**Tricyclic antidepressants:** The metabolism of amitriptyline and nortriptyline after a single dose of amitriptyline (50 mg) was inhibited by multiple dosing with valproic acid (500 mg twice daily) in sixteen healthy male and female volunteers. For the sum of amitriptyline and nortriptyline plasma concentrations, in the presence of valproic acid, the mean  $C_{max}$  and AUC were increased by 19% and 42%, respectively.

In addition to enhancing CNS depression when used concurrently with valproic acid, tricyclic antidepressants may lower the seizure threshold. Dosage adjustments may be necessary to control seizures.

**Warfarin:** The potential exists for valproate to displace warfarin from protein binding sites. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if divalproex sodium therapy is instituted in patients taking anticoagulants.

**Others - Antipsychotics and MAO Inhibitors:** In addition to enhancing central nervous system (CNS) depression when used concurrently with valproic acid antipsychotics and MAO Inhibitors may lower the seizure threshold. Dosage adjustments may be necessary to control seizures.

#### ADVERSE REACTIONS:

**Epilepsy:** Adverse events that have been reported with valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

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

**Gastrointestinal:** The most commonly reported side effects at the initiation of therapy are nausea, vomiting and indigestion. 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 reported. The administration of delayed-release divalproex sodium may result in reduction of gastrointestinal side effects in some patients.

**CNS Effects:** Sedative effects have been noted in patients receiving valproic acid alone but occur most often in patients on combination therapy. Sedation usually disappears upon reduction of other antiepileptic medication. Hallucination, ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes", tremor (may be dose-related), confusion, dysarthria, dizziness, hyposthesia, vertigo and incoordination have rarely been noted. Rare cases of coma have been reported in patients receiving valproic acid alone or in conjunction with phenobarbital. Encephalopathy, with or without fever or hyperammonemia, has been reported without evidence of hepatic dysfunction or inappropriate valproate plasma levels. Most patients recovered, with noted improvement of symptoms, upon discontinuation of the drug.

Reversible cerebral atrophy and dementia have been reported in association with valproate therapy.

**Dermatologic:** Transient increases in hair loss have been observed. Skin rash, photosensitivity, generalized pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), and petechiae have rarely been noted.

**Endocrine:** There have been reports of irregular menses and secondary amenorrhea, breast enlargement, galactorrhea and parotid gland swelling 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-General). This may be reflected in altered bleeding time. Petechiae, bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis, macrocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported. Anemia, including macrocytic with or without folate deficiency, bone marrow suppression and acute intermittent porphyria have been reported.

**Hepatic:** Minor elevations of transaminases (e.g., 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), hyponatremia and inappropriate ADH secretion. There have been rare reports of Fanconi's syndrome occurring primarily in children. Hyperglycemia has been reported and associated with a fatal outcome in a patient with preexisting non-ketotic hyperglycemia.

**Genitourinary:** Enuresis

**Pancreatic:** There have been reports of acute pancreatitis, including rare fatal cases, occurring in patients receiving valproate therapy.

**Special Senses:** Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established.

**Other:** Edema of the extremities has been reported. A lupus erythematosus-like syndrome has been reported rarely.

**Bipolar Disorder:** The incidence of adverse events has been ascertained based on data from two short-term (21 day) placebo-controlled clinical trials of divalproex sodium in the treatment of acute mania, and from two long-term (up to 3 years) retrospective open trials.

**Most Commonly Observed:** During the short-term placebo-controlled trials, the six most commonly reported adverse events in patients (N = 89) exposed to divalproex sodium were nausea (22%), headache (21%), somnolence (19%), pain (15%), vomiting (12%), and dizziness (12%).

In the long-term retrospective trials (634 patients exposed to divalproex sodium), the six most commonly reported adverse events were somnolence (31%), tremor (29%), headache (24%), asthenia (23%), diarrhea (22%), and nausea (20%).

**Associated With Discontinuation of Treatment:** In the placebo-controlled trials, adverse events which resulted in valproate discontinuation in at least one percent of patients were nausea (4%), abdominal pain (3%), somnolence (2%), and rash (2%).

In the long-term retrospective trials, adverse events which resulted in valproate discontinuation in at least one percent of patients were alopecia (2.4%), somnolence (1.9%), nausea (1.7%), and tremor (1.4%). The time to onset of these events was generally within the first two months of initial exposure to valproate. A notable exception was alopecia, which was first experienced after 3-6 months of exposure by 8 of the 15 patients who discontinued valproate in response to the event.

**Controlled Trials:** Table 1 summarizes those treatment emergent adverse events reported for patients in the placebo-controlled trials when the incidence rate in the divalproex sodium group was at least 5%. (Maximum treatment duration was 21 days; maximum dose in 83% of patients was between 1000 mg-2500 mg per day).

Table 1  
Treatment-Emergent Adverse Event Incidence  
(≥ 5%) in Short-Term Placebo-Controlled Trials

Body System/Event	Percentage of Patients	
	divalproex sodium (N = 89)	placebo (N = 97)
<i>Body as a Whole</i>		
Headache	21.3	30.9
Pain	14.6	15.5
Accidental injury	11.2	5.2
Asthenia	10.1	7.2
Abdominal Pain	9.0	8.2
Back Pain	5.6	6.2
<i>Digestive System</i>		
Nausea	22.5	15.5
Vomiting	12.4*	3.1
Diarrhea	10.1	13.4
Dyspepsia	9.0	8.2
Constipation	7.9	8.2
<i>Nervous System</i>		
Somnolence	19.1	12.4
Dizziness	12.4	4.1
Tremor	5.6	6.2
<i>Respiratory System</i>		
Pharyngitis	6.7	9.3
<i>Skin and Appendages</i>		
Rash	5.6	3.1

\* Statistically significant at  $p < 0.05$  level.

**Adverse Events in Elderly Patients:** In elderly patients (above 65 years of age), there were more frequent reports of accidental injury, infection, pain, and to a lesser degree, somnolence and tremor, when compared to patients 18-65 years of age. Somnolence and tremor tended to be associated with the discontinuation of valproate.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE:** Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported, however, patients have recovered from valproate levels as high as 2120 µg/mL.

(continued on page A-44)



## THERAPEUTIC CLASSIFICATION

Antiparkinsonian Agent/COMT-Inhibitor

## ACTIONS AND CLINICAL PHARMACOLOGY

Tasmar (tolcapone) is a selective and reversible inhibitor of catechol-O-methyltransferase (COMT). COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include dopa, catecholamines (dopamine, norepinephrine, epinephrine) and their hydroxylated metabolites. The function of COMT is the elimination of biologically active catechols and some other hydroxylated metabolites. In the presence of a decarboxylase inhibitor, COMT becomes the major enzyme which is responsible for the metabolism of levodopa to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD). The mechanism of action of tolcapone is believed to be related to its ability to inhibit COMT and thereby alter the plasma pharmacokinetics of levodopa. When tolcapone is given in conjunction with levodopa and an aromatic amino acid decarboxylase inhibitor (AADC-I), such as carbidopa or benserazide, plasma levels of levodopa are more sustained than after the administration of levodopa and an AADC-I alone. The sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease as well as increased levodopa adverse effects, requiring a decrease in the daily dose of levodopa. There is some evidence that high levels of plasma 3-OMD are associated with poor response to levodopa in patients with Parkinson's disease. Tolcapone markedly reduces the plasma levels of 3-OMD.

## PHARMACODYNAMICS

Effect of tolcapone on erythrocyte COMT activity: Studies in healthy volunteers have shown that tolcapone reversibly inhibits human erythrocyte COMT activity after oral administration. The inhibition is dose-related and tolerance does not develop to this effect. With a 200 mg single dose of tolcapone, maximum inhibition of erythrocyte COMT activity was approximately 80%. During repeated dosing with tolcapone (200 mg t.i.d.), erythrocyte COMT inhibition was 30% to 45% at trough tolcapone plasma concentrations. Effect of tolcapone on the pharmacokinetics of levodopa and 3-OMD: When tolcapone is administered together with levodopa/AADC-I (carbidopa or benserazide), it increases the relative bioavailability (AUC) of levodopa by approximately twofold. This is due to a decrease in levodopa clearance resulting in a prolongation of its terminal elimination half-life ( $t_{1/2\beta}$ ). In healthy, elderly volunteers (n=36, age: 55 to 75 years), the terminal elimination half-life of levodopa increased from 1.9 hours in placebo-treated subjects to 3.2 hours in subjects treated with tolcapone, 200 mg t.i.d. Average peak levodopa plasma concentration (C<sub>max</sub>) and the time of its occurrence (t<sub>max</sub>) were unaffected. The onset of effect of tolcapone occurred after its first administration. Population pharmacokinetic analyses in patients with Parkinson's disease have corroborated the effects of tolcapone on the pharmacokinetics of levodopa shown in healthy volunteers. During long-term clinical trials, tolcapone increased the relative bioavailability of levodopa, prolonged its elimination half-life, and thus, reduced the fluctuations in levodopa plasma concentrations (C<sub>max</sub>-C<sub>min</sub>). Studies in healthy volunteers and in patients with Parkinson's disease have confirmed that (a) maximal effects occur with the 100 and 200 mg doses of tolcapone, given t.i.d., and (b) tolcapone given in combination with levodopa/AADC-I, decreases markedly and dose-dependently the plasma levels of 3-OMD. The effect of tolcapone, on the pharmacokinetics of levodopa, was similar with all pharmaceutical formulations of levodopa/carbidopa and levodopa/benserazide, and was independent of the dose of levodopa.

## PHARMACOKINETICS AND METABOLISM OF TOLCAPONE

**VOLUNTEERS** The pharmacokinetics of tolcapone were linear in young volunteers over the single dose range of 50 to 400 mg and in elderly volunteers at the therapeutic doses (100 and 200 mg t.i.d.), and were independent of levodopa/AADC-I (carbidopa or benserazide) coadministration. The elimination half-life was 2-3 hours. Accumulation was not seen during t.i.d. dosing. Patients with Parkinson's disease: Population pharmacokinetic analyses indicated that the pharmacokinetics of tolcapone in patients with Parkinson's disease were in agreement with those observed in healthy volunteers. In a dose range of 50 to 400 mg t.i.d., the exposure to tolcapone was dose proportional. The mean C<sub>max</sub> and AUC values at the 200 mg t.i.d. dose were 6 µg/ml and 25.1 µg·h/ml, respectively. The pharmacokinetic behaviour of tolcapone was stable during long-term treatment. AUC values were similar in 'fluctuating' and 'non-fluctuating' patients. The elimination half-life of tolcapone was somewhat longer in patients than in volunteers, i.e., approximately 4-8 hours. Gender and age did not seem to affect the pharmacokinetics of tolcapone.

**ABSORPTION** Tolcapone is rapidly absorbed with a t<sub>max</sub> of approximately 2 hours. The absolute bioavailability following oral administration is about 65%. In clinical trials, there were no restrictions as to how the drug was taken in relation to meals. Population pharmacokinetic studies indicated that while food delayed the absorption of tolcapone, its relative bioavailability was still 80% to 90% when the drug was taken within one hour before and two hours after meals.

**DISTRIBUTION AND PROTEIN BINDING** The volume of distribution (V<sub>ss</sub>) of tolcapone in healthy volunteers after iv administration was small (9 L). In patients, a higher volume of distribution (15-35 L) was estimated after oral dosing. Tolcapone does not distribute widely into tissues due to its high plasma protein binding. The plasma protein binding of tolcapone is >99% over the concentration range of 0.32 to 30 µg/ml. At clinical doses, mean C<sub>max</sub> values were <10 µg/ml at the 200 mg dose. In vitro experiments have shown that tolcapone binds mainly to serum albumin.

**METABOLISM/ELIMINATION** Tolcapone is almost completely metabolised prior to excretion, with only a very small amount (0.5% of dose) found unchanged in urine. The main metabolic pathway of tolcapone is conjugation to its inactive glucuronide. In addition, the compound is methylated by COMT to 3-O-methyl-tolcapone and metabolised by cytochromes P450 3A4 and P450 2A6 to a primary alcohol (hydroxylation of the 4' methyl group), which is subsequently oxidised to the carboxylic acid. Reduction to a putative amine, as well as the subsequent N-acetylation, occur to a minor extent. After oral administration of <sup>14</sup>C-labelled tolcapone, 60% of the labelled material is excreted in urine, and 40% in feces. More than 50% of the labelled dose of tolcapone is identified as 8 metabolites. Numerous additional metabolites account for the rest, none of them exceeding 5% of dose. Tolcapone is a low-extraction-ratio drug (extraction ratio = 0.15), with a moderate systemic clearance of about 7 L/h.

**HEPATIC IMPAIRMENT** A study in patients with hepatic impairment has shown that moderate non-cirrhotic liver disease did not affect the pharmacokinetics of tolcapone. However, in patients with moderate cirrhotic liver disease, clearance and volume of distribution of unbound tolcapone were reduced by 44% and 35%, respectively, when compared to values seen in demographically-matched healthy volunteers. Since the reduction in clearance may increase the average concentration of unbound tolcapone approximately twofold, special dosing recommendations are given for patients with moderate cirrhotic liver disease (see DOSAGE AND ADMINISTRATION). In patients with moderate liver cirrhosis, the C<sub>max</sub> and AUC of tolcapone glucuronide increased substantially (AUC values were 7.4 µg·h/ml in healthy volunteers, 20 µg·h/ml in subjects with non-cirrhotic liver disease, and 52 µg·h/ml in subjects with cirrhotic liver disease). However, since tolcapone glucuronide is inactive and since this metabolic pathway is irreversible, it is unlikely that the changes will be clinically significant.

**RENAL IMPAIRMENT** A specific study to evaluate the pharmacokinetics of tolcapone in patients with renal impairment has not been carried out. However, population pharmacokinetic analysis has shown in more than 400 patients that the clearance of tolcapone was not affected in a clinically meaningful way when creatinine clearance was >30 ml/min. This could be explained by the fact that only a negligible amount of unchanged tolcapone is excreted in the urine, and the main metabolite, tolcapone-glucuronide, is excreted both in urine and bile (feces).

## STUDIES ASSESSING POTENTIAL DRUG INTERACTIONS

Effect of tolcapone on the pharmacokinetics of other drugs: Protein Binding: Although tolcapone is highly protein-bound, in vitro studies have shown that tolcapone, at 50 µg/ml (approximately 5 fold higher than therapeutic concentrations) did not displace other highly protein-bound drugs at therapeutic concentrations, like warfarin (0.5-7.2 µg/ml), phenytoin (7.9-38.7 µg/ml), tolbutamide (24.5-96.1 µg/ml), or digoxin (9.0-27.0 µg/ml) from their binding sites. Cytochrome P450 metabolism: The effect of tolcapone upon the metabolism of various drugs has been investigated utilizing human liver microsomes preparations. Although tolcapone is not metabolized via CYP2C9, its affinity for the enzyme was greater than those of tolbutamide and diclofenac; consequently, tolcapone decreased the formation of their hydroxy metabolites in vitro. However, in a clinical study in healthy volunteers tolcapone did not affect either the pharmacokinetics or the hypoglycemic effect of tolbutamide. In vitro interaction between tolcapone and warfarin, a substrate of CYP2C9 was not evaluated. Since clinical information is limited regarding a potential interaction between these two drugs, coagulation parameters should be monitored when they are given concomitantly (see PRECAUTIONS). No relevant interactions were observed in vitro between tolcapone and substrates of CYP2A6 (coumarin), CYP1A2 (caffeine), CYP3A4 (midazolam, terfenadine, cyclosporin), CYP2C19 (S-mephenytoin) and CYP2D6 (desipramine). Effect of drugs on the metabolism of tolcapone: Glucuronidation: The major route of elimination of tolcapone is by glucuronidation. In vitro studies with desipramine and naproxen, drugs which are highly protein-bound and are metabolized via glucuronidation, did not indicate interference with tolcapone glucuronidation. Cytochrome P450 metabolism: Although under in vitro conditions midazolam, which is metabolized by CYP3A4, competed with the formation of the hydroxy metabolite of tolcapone, the fraction of tolcapone, which is metabolised by this isozyme, represents a minor metabolic pathway and no significant interactions are expected under clinical conditions.

## CLINICAL TRIALS

Up to April 1, 1996, 1685 patients have been exposed to Tasmar, with 647 patients being exposed for over a year and 117 patients being exposed for over two years. The effectiveness of Tasmar, as an adjunct to levodopa/AADC-I (carbidopa or benserazide) therapy in the treatment of Parkinson's disease, was demonstrated in randomized placebo-controlled trials in patients who experienced end of dose wearing off phenomena (fluctuating patients) and in patients whose response to levodopa was relatively stable (non-fluctuating patients). The majority of the patients in the clinical trials were at stages 1.5-2.5 on the Hoehn and Yahr scale and only limited experience is available in patients who were at stage 4 on the Hoehn & Yahr scale.

**ADJUNCT THERAPY IN FLUCTUATING PATIENTS** In three phase III multicentre placebo-controlled studies, patients with documented episodes of wearing off phenomena, despite optimal levodopa therapy, were randomized to receive placebo (n=196) or Tasmar at doses of 100 mg t.i.d. (n=198) or 200 mg t.i.d. (n=200). The primary outcome measure was a comparison between treatments in the change from baseline in the amount of time spent OFF/ON (based upon patient diaries recording time "on" and "off"). The formal double-blind portion of the trial was 3 months (two of the studies) or 6 weeks (one study). Based on a 16-hour 'waking day', the decreases in OFF time vs baseline ranged between 0.3-1.2, 1.9-2.1 and 1.6-2.9 hours in the placebo, 100 mg t.i.d. and 200 mg t.i.d. groups, respectively. Expressed as percentages, the decreases in OFF time ranged between 5-19%, 29-34% and 27-49% in the placebo, 100 mg t.i.d. and 200 mg t.i.d. groups, respectively. The difference between the placebo and Tasmar groups was significant. The Investigator's Global Assessment of Change also showed a statistically significant improvement in Tasmar-

treated patients. In addition, the total daily dose of levodopa was significantly reduced in the Tasmar groups. The improvement in OFF time, due to Tasmar treatment, was independent of the concomitant use of selegiline or dopamine agonist, the amount of slow-release-levodopa as a proportion of the total daily dose of levodopa, and the duration of levodopa therapy. There were no gender or age-related differences in effectiveness. Adjunct therapy in non-fluctuating patients: In a phase III multicentre study, 298 patients with Parkinson's disease on stable doses of levodopa/carbidopa, who were not experiencing wearing off phenomena, were randomized to placebo, Tasmar 100 mg t.i.d., or Tasmar 200 mg t.i.d. for 6 months. The primary measure of efficacy was the Activities of Daily Living (ADL) subscale of the UPDRS (Unified Parkinson's Disease Rating Scale). Mean ADL scores did not change in the placebo group while they decreased by 18% and 21% in patients treated with 100 mg t.i.d. or 200 mg t.i.d. of Tasmar, respectively. The differences between the placebo and Tasmar groups were significant. In non-fluctuating patients, the mean daily doses of levodopa at baseline were relatively low, namely 364 mg, 370 mg, and 382 mg in the placebo, 100 mg t.i.d. and 200 mg t.i.d. Tasmar groups, respectively. At 6 months, the mean daily dose of levodopa increased by 46.6 mg in the placebo group while it decreased in the Tasmar groups (100 mg t.i.d.: -20.8 mg t.i.d.; -32.3 mg). The difference between the placebo and Tasmar groups was significant. In Tasmar-treated patients the total scores and motor scores (subscale III) of the UPDRS decreased by 11-13%, while decreases in the placebo-treated patients ranged between one to two percent. The difference was statistically significant. The improvement in ADL, due to Tasmar treatment, was independent of concomitant use of selegiline and duration of levodopa therapy. There were no gender or age-related differences in effectiveness.

**INDICATIONS** Tasmar (tolcapone) is indicated as an adjunct to levodopa/carbidopa and levodopa/benserazide for the treatment of the signs and symptoms of idiopathic Parkinson's disease. Since Tasmar should be used in combination with levodopa, the prescribing information for levodopa/carbidopa and levodopa/benserazide are also applicable when Tasmar is added to the treatment regimen.

**CONTRAINDICATIONS** Tasmar (tolcapone) is contraindicated in patients with known hypersensitivity to tolcapone or the excipients of the drug product. Tasmar should not be given in conjunction with non-selective monoamine oxidase (MAO) inhibitors (e.g. phenelzine and tranylcypromine). The combination of MAO-A and MAO-B inhibitors is equivalent to non-selective MAO inhibition, therefore, they should not both be given concomitantly with Tasmar and levodopa preparations. Selective MAO-B inhibitors should not be used at higher than recommended doses (e.g. selegiline 10 mg/day) when co-administered with Tasmar.

**PRECAUTIONS** Orthostatic Hypotension: The incidence of orthostatic hypotension was slightly higher in the Tasmar (tolcapone) treatment groups than in the placebo group. Orthostatic hypotension at baseline was a predisposing factor, however, this was true for Tasmar and placebo-treated patients alike. Concomitant treatment with a dopamine agonist increased slightly the incidence of orthostatic hypotension in the 200 mg t.i.d. Tasmar group (17% versus 11% in the presence and absence of a dopamine agonist, respectively). Syncope and falling occurred with a higher incidence in patients who had orthostatic hypotension (at the 200 mg t.i.d. dose, syncope was 10.3% versus 4.2%, falling was 10.3% versus 5.4% in patients with or without orthostatic hypotension, respectively). Gender and age had no apparent effect on the rates of orthostatic hypotension.

**DYSKINESIA** In patients treated with Tasmar, dyskinesia was the most common adverse event. Dyskinesia was dose-related and much more prevalent in fluctuating than non-fluctuating patients (see ADVERSE REACTIONS). Concomitant treatment with selegiline, dopamine agonists and controlled-release levodopa (>70% of the daily dose) increased the incidence of dyskinesia. Although decreasing the dose of levodopa may ameliorate this adverse event, many patients in the controlled clinical trials continued to experience dyskinesia.

**HALLUCINATIONS** The incidence of hallucinations was higher in the Tasmar groups than in the placebo group, it occurred in a dose-related manner and was more prevalent in the fluctuating than non-fluctuating patients (see ADVERSE REACTIONS). Patients who had this adverse event prior to initiating Tasmar treatment and those with a pretreatment levodopa dose of >750 mg/day, had a higher rate of hallucinations. Hallucinations were commonly accompanied by confusion.

**DIARRHEA** Diarrhea was the most common non-dopaminergic adverse reaction associated with Tasmar treatment. In the clinical trials, diarrhea developed in 16% and 18% of patients receiving Tasmar, at 100 and 200 mg t.i.d. doses, respectively, compared to 8% of patients receiving placebo. In some of the patients diarrhea was persistent and severe. Diarrhea was also the adverse reaction which most commonly led to discontinuation of treatment with 1.0, 5.4 and 6.0% of patients treated with placebo, 100 mg and 200 mg Tasmar t.i.d., respectively, withdrawing from the trials prematurely. Diarrhea usually started during the second, third or fourth months of treatment but may appear as early as two weeks and as late as many months after the initiation of treatment. Tasmar-induced diarrhea was generally described as watery. The mechanism underlying the diarrhea has not yet been elucidated. In the clinical trials, diarrhea observed during Tasmar treatment was sometimes associated with anorexia (decreased appetite).

**ELEVATED LIVER TRANSAMINASES** An increase of liver transaminases (ALAT and/or ASAT) to more than three times the upper limit of normal (ULN) occurred in 1.7% and 3.1% of patients receiving Tasmar at 100 mg and 200 mg t.i.d. doses, respectively. Increases to more than eight times the ULN occurred in 0.3% and 0.7% of patients at the 100 mg and 200 mg t.i.d. doses, respectively. The incidence of elevated liver transaminases was higher in females than males (4.8% vs. 1.5%). Approximately one third of patients with elevated enzymes had diarrhea. Elevated liver enzymes led to discontinuation of treatment in 0.3% and 1.7% of patients treated with Tasmar, 100 mg and 200 mg t.i.d., respectively.

The majority of cases of elevated liver transaminases occurred one to six months after starting treatment, although elevated levels were seen at earlier times as well. In about half of the cases, transaminase levels returned to pretreatment levels within one to three months while patients continued treatment with "Tasmar". In patients who discontinued treatment, transaminase levels generally declined within two to three weeks but it may take as long as one to two months to return to normal. Liver transaminase levels should be determined prior to initiating treatment with "Tasmar" and monitored approximately every 6 weeks for the first 6 months. If elevations occur during this period, and the decision is made to continue treatment, monitoring of liver enzymes is recommended at approximately 2-week intervals. If transaminase levels keep on increasing or if clinical jaundice develops, treatment should be discontinued.

**NEUROLEPTIC MALIGNANT SYNDROME (NMS)** This rare and potentially life-threatening syndrome is characterised by muscular rigidity, elevated temperature and altered consciousness associated with elevated serum creatine phosphokinase (CPK). The syndrome has been reported in association with rapid dose reduction, withdrawal of, or changes in treatment with dopaminergic antiparkinson therapy. There have been four cases of NMS during "Tasmar" treatment. Three of the cases involved females (aged 74, 65 and 54 years), all these patients were Japanese. The fourth case involved a Caucasian male, aged 64 years. All patients were receiving levodopa/AADC-I and dopamine agonist treatment. The time of NMS, with respect to treatment with "Tasmar", varied greatly, namely it occurred after 153, 99, 15 and 362 days. In all cases, CPK levels and WBC counts were markedly elevated, mild to moderate fever was also present. Two of the four patients had muscle rigidity. One of the female patients died due to respiratory failure, the other patients recovered. The investigators considered all cases to be probably related to "Tasmar" treatment. If "Tasmar" is discontinued, physicians should consider increasing the patient's daily levodopa dose (see DOSAGE AND ADMINISTRATION).

**URINE DISCOLOURATION** Tolcapone and its metabolites are yellow and can cause a harmless intensification in the colour of the patient's urine.

**SPECIAL POPULATIONS Renal/Hepatic Impairment.** No information is available on the tolerability of tolcapone in patients with severe renal impairment (creatinine clearance <30 ml/min) (see PHARMACOKINETICS AND METABOLISM OF TOLCAPONE). These patients should be treated with caution. In patients with moderate cirrhotic liver disease, the clearance of unbound "Tasmar" is substantially reduced and the concentration of unbound drug increased approximately twofold (see PHARMACOKINETICS AND METABOLISM OF TOLCAPONE). These patients should receive only the lower recommended dose of "Tasmar" (see DOSAGE AND ADMINISTRATION).

**WOMEN** During "Tasmar" treatment, some adverse events occurred with a higher incidence in women than men. They included nausea, anorexia, diarrhea, and elevated liver transaminases.

**ELDERLY** During "Tasmar" treatment, some adverse events occurred with a higher incidence in patients over 75 years of age (n=95) compared to younger patients. They included diarrhea and hallucinations.

**CARCINOGENESIS** Carcinogenicity studies, in which tolcapone was administered in the diet for 104 weeks, were conducted in rats. The doses were approximately 50, 250 and 450 mg/kg/day. In male rats, tolcapone exposures (in terms of AUC) were 1, 6.3 and 13 times the maximal human exposure; in female rats, tolcapone exposures (in terms of AUC) were 1.7, 11.8 and 26.4 times the maximal human exposure. There was evidence of renal tubular injury and renal tubular formation. Minimal to marked damage to renal tubules, consisting of proximal tubule cell degeneration, single cell necrosis, hyperplasia and karyocytomegaly, occurred at the doses that were associated with renal tumors. A low incidence of renal tubular cell adenomas occurred in middle- and high-dose females and in high-dose males. The incidence of uterine adenocarcinomas was increased in high-dose female rats. In a 1-year toxicity study in rats, administered tolcapone at 150 and 450 mg/kg/day doses, renal tubule damage, characterized by proximal tubule cell degeneration and the presence of atypical nuclei, were observed. One adenocarcinoma in a high-dose male rat was also seen. The carcinogenic potential of tolcapone in combination with levodopa/AADC-I has not been examined.

**PREGNANCY** The use of "Tasmar" during pregnancy is not recommended. "Tasmar" will always be given concomitantly with levodopa/AADC-I preparations which are known to cause visceral and skeletal malformations in the rabbit. The combination of tolcapone (100 mg/kg/day) with levodopa/carbidopa alone when pregnant rabbits were treated throughout organogenesis. Tolcapone, when administered alone during organogenesis, was not teratogenic in rats at doses up to 300 mg/kg/day (5.7 times the recommended daily clinical dose of 600 mg on a mg/m<sup>2</sup> basis) or in rabbits at doses up to 400 mg/kg/day (15 times the recommended daily clinical dose of 600 mg on a mg/m<sup>2</sup> basis).

**NURSING WOMEN** In animal studies, tolcapone was excreted in maternal milk. It is not known whether tolcapone is excreted in human milk. Since the safety of "Tasmar" in infants is unknown, women should not breast-feed during treatment with "Tasmar".

**PEDIATRIC USE** Safety and efficacy of "Tasmar" have not been established in the pediatric population and use in patients below the age of 18 is not recommended.

**DRUG INTERACTIONS Protein Binding:** Although, tolcapone is highly protein bound, in vitro studies have shown that at 50 µg/ml (approximately 5 fold higher than therapeutic concentrations), it did not displace warfarin, tolbutamide, digitoxin and phenytoin from their binding sites. Drugs Metabolised by Catechol-O-methyltransferase (COMT): "Tasmar" may influence the pharmacokinetics of drugs metabolised by COMT. No effects were seen on the pharmacokinetics of the COMT substrate carbidopa. However, an interaction was observed with benserazide, which may lead to increased levels of benserazide and its active metabolite. The magnitude of the effect depended upon the dose of benserazide. Plasma concentrations of benserazide, observed after co-administration of "Tasmar"

and levodopa/benserazide, 100/25 mg were still within the range of values observed with levodopa/benserazide alone. However, after the co-administration of "Tasmar" and levodopa/benserazide, 200/50 mg, benserazide plasma concentrations could be increased above the levels usually observed with levodopa/benserazide alone. The most prominent sign of benserazide toxicity is fatty liver degeneration in dogs. However, pharmacokinetic data indicate that the median AUC values of benserazide in dogs, at subtoxic doses, were considerably higher than AUC values seen in humans. A subanalysis of "Tasmar" safety in patients, receiving 25 mg versus 50 mg doses of benserazide, did not indicate different rates of occurrence of liver transaminase elevations. The effect of tolcapone on the pharmacokinetics of other drugs metabolized by COMT, such as α-methyl dopa, dobutamine, apomorphine, epinephrine and isoproterenol has not been evaluated. A dose reduction of such compounds should be considered when they are coadministered with "Tasmar".

**EFFECT OF TOLCAPONE ON THE METABOLISM OF OTHER DRUGS**

Due to its in vitro affinity for cytochrome P450 2C9, "Tasmar" may interfere with drugs whose clearance is dependent on this metabolic pathway, such as tolbutamide and warfarin. In an interaction study (n=12 male volunteers, aged 21-39 years), "Tasmar" did not affect either the pharmacokinetics or the hypoglycemic effect of tolbutamide. During clinical trials, 23 patients received a combination of warfarin and "Tasmar" and no particular pattern of adverse events was observed. However, since clinical experience is limited, coagulation parameters should be monitored when these drugs are coadministered. Drugs that Increase Catecholamines: "Tasmar", in combination with Sinemet (n=12 male and female volunteers, aged 19-39 years), did not affect the pharmacokinetics of desipramine, a drug metabolized by cytochrome P450 2D6. While there were no significant changes in blood pressure or pulse rate, the frequency of adverse events, particularly dizziness, nausea and vomiting, increased. Therefore, caution should be exercised when potent norepinephrine reuptake inhibitors, such as desipramine, maprotiline or venlafaxine are administered to patients with Parkinson's disease who are being treated with "Tasmar" and levodopa preparations. "Tasmar" in combination with Sinemet (n=12 male and female volunteers, aged 21-30 years) had no effect on the hemodynamic parameters of ephedrine, an indirect acting sympathomimetic drug, either at rest or during exercise. Plasma levels of epinephrine and norepinephrine remained unchanged. Since "Tasmar" did not affect the tolerability of ephedrine, these drugs may be given concomitantly. In clinical trials, patients receiving "Tasmar"/levodopa preparations reported a similar adverse event profile independent of whether or not they were also concomitantly administered selegiline (a selective MAO-B inhibitor).

**ADVERSE REACTIONS**

Of the 1685 patients, who received "Tasmar" (tolcapone) during the pre-marketing clinical trials, 18.8% discontinued treatment due to adverse events. At the clinically recommended doses of "Tasmar", in the placebo-controlled, phase III trials, 16.2% (48/298) and 15.4% (46/298) of patients discontinued treatment at the 100 mg and 200 mg t.i.d. doses, respectively, compared to 10.1% (30/298) of patients receiving placebo. The most common reason for withdrawal in the "Tasmar" groups was diarrhea, with 5% and 6% of patients withdrawing at the 100 mg and 200 mg t.i.d. doses, respectively, compared to 1% of patients receiving placebo. Other adverse events which led to discontinuation of treatment in ≥ 1% of patients (placebo, 100 mg and 200 mg t.i.d., respectively) included nausea (2.0%, 1.7%, 2.0%), elevated liver transaminases (0.3%, 0.3%, 1.7%), hallucinations (0.3%, 1.4%, 1.0%), dyskinesia (0%, 0.3%, 1.0%), confusion (1.0%, 1.4%, 0.7%), and muscle cramps (1.0%, 1.4%, 0.3%). The most commonly reported serious adverse events, defined as those requiring hospitalization (placebo, 100 mg and 200 mg t.i.d., respectively), included diarrhea (0.3%, 0.7%, 1.7%), dyskinesia (0.3%, 0.3%, 1.3%), and hallucinations (0%, 1.7%, 0%). Of the 1685 patients who received tolcapone, four patients experienced symptoms suggestive of Neuroleptic Malignant Syndrome (see PRECAUTIONS AND DOSAGE AND ADMINISTRATION).

**INCIDENCE OF ADVERSE EVENTS IN PLACEBO CONTROLLED TRIALS**

The most frequently observed adverse events, associated with the use of "Tasmar" were dyskinesia, nausea, sleep disorders, anorexia, dystonia and diarrhea (Table 1). Incidences were somewhat higher at the 200 mg t.i.d. dose. The incidence of dyskinesia, hallucination and confusion was considerably higher in fluctuating patients, while the incidence of nausea, vomiting and anorexia was higher in non-fluctuating patients (Table 2). Orthostatic complaints and diarrhea occurred with similar frequencies in fluctuating and non-fluctuating patients.

TABLE 1. Treatment emergent adverse events (rates ≥ 2% higher during "Tasmar" treatment than during placebo treatment)

Adverse Events	Placebo	"Tasmar" t.i.d.	
	N=298 %	100 mg N=298 %	200 mg N=298 %
Dyskinesia	19.8	41.9	51.3
Nausea	17.8	30.4	34.9
Sleep Disorder	18.1	23.6	24.8
Anorexia	12.8	18.9	22.8
Dystonia	17.1	18.6	22.1
Diarrhea	7.7	15.5	18.1
Orthostatic Complaints*	13.8	16.6	16.8
Dreaming Excessive	17.1	21.3	16.4
Somnolence	13.4	17.9	14.4
Headache	7.4	9.8	11.4
Confusion	8.7	10.5	10.4
Hallucination	5.4	8.4	10.4
Vomiting	3.7	8.4	9.7
Constipation	5.0	6.4	8.4
Urine Discolouration	0.7	2.4	7.4
Upper Respiratory Tract Infection	3.4	4.7	7.4
Sweating Increased	2.3	4.4	7.4
Xerostomia	2.3	4.7	6.4
Dizziness	2.3	13.2	6.4
Abdominal Pain	2.7	4.7	5.7
Syncope	2.7	4.1	5.0
Influenza	1.7	3.0	4.0
Dyspepsia	1.7	4.1	3.0
Hypokinesia	0.7	0.7	2.7
Chest Pain	1.3	3.4	1.0

\* Orthostatic complaints refer to experiences of dizziness and light head-

edness when standing. Some of the most frequently reported adverse events (e.g., dyskinesia, nausea, orthostatic complaints, hallucinations, vomiting), which are considered levodopa-related, become enhanced in the presence of "Tasmar". The highest risk of experiencing these dopaminergic adverse events occurred when "Tasmar" was first added to levodopa/AADC-I therapy, i.e., during the first few weeks of treatment. The prevalence rates tended to drop during the first two months, probably reflecting re-optimization of levodopa therapy. Therefore, a reduction in the dosage of levodopa may be necessary when initiating tolcapone treatment (see DOSAGE AND ADMINISTRATION).

TABLE 2. Rates of some key adverse events in fluctuating and non-fluctuating patients

Adverse Events	Fluctuating			Non-fluctuating		
	Placebo (n=196) %	100mg (n=198) %	200 mg (n=200) %	Placebo (n=102) %	100mg (n=98) %	200 mg (n=98) %
Dyskinesia	19.4	50.5	61.5	20.6	24.5	30.6
Hallucinations	7.7	11.1	14.0	1.0	3.1	3.1
Orthostatic Complaints	15.3	19.2	17.5	10.8	11.2	15.3
Confusion	10.7	12.1	14.0	4.9	7.1	3.1
Nausea	16.3	28.8	31.0	20.6	33.7	42.9
Vomiting	2.0	8.1	7.5	6.9	9.2	14.3
Anorexia	9.7	16.7	20.0	18.6	23.5	28.6
Diarrhea	9.7	10.6	18.0	3.9	25.5	18.4

**LABORATORY TESTS** Liver transaminases, ALAT (SGPT) and ASAT (SGOT), increased in a dose-dependent manner in "Tasmar" treated patients (see PRECAUTIONS). The increases were observed within the first 6 months of treatment. In clinical trials, 0.3% and 1.7% of patients receiving "Tasmar", at 100 and 200 mg t.i.d. doses, respectively, withdrew due to elevated liver transaminases. Slight increases in alkaline phosphatase or total bilirubin occurred in 20% and 10% of patients, respectively. Liver transaminase levels should be monitored approximately every 6 weeks for the first 6 months of treatment with "Tasmar". If elevations occur during this period, and the decision is made to continue treatment, monitoring of liver enzymes is recommended at approximately 2-week intervals. If transaminase levels keep on increasing or if clinical jaundice develops, treatment should be discontinued (see PRECAUTIONS).

**ELECTROCARDIOGRAMS** In the course of the clinical trials, ventricular premature contractions were recorded in "Tasmar" treated patients but not in placebo treated patients. The incidence of ventricular premature contractions was 0.3% and 1.7% in the patients treated with the 100 mg and 200 mg t.i.d. doses, respectively. Adverse events reported by ≥ 1% of patients treated with "Tasmar": Body as a Whole: fatigue, lethargy, peripheral edema, malaise, weight decrease, trauma, fever; Nervous System: falling, tremor, loss of balance, hypoesthesia, hyperkinesia, paresthesia, paresis, speech disorder, burning, gait abnormal, vertigo, hyperactivity; Psychiatric: depression, agitation, asthenia, emotional lability, anxiety, impotence, irritability, mental deficiency, panic reaction, hypertonía, euphoria; Gastrointestinal System: flatulence, abdominal discomfort; Cardiovascular System: hypertension, chest discomfort, palpitation; Musculoskeletal System: muscle cramps, back pain, arthralgia, pain in limbs, stiffness, neck pain, myalgia, arthritis; Urogenital System: urinary tract infection, micturition disorder, micturition frequency, urinary incontinence; Skin and Appendages: rash, alopecia; Respiratory System: pneumonia, dyspnea, bronchitis, pharyngitis, sinusitis, sinus congestion; Special Senses: tinnitus, taste alteration, cataract, vision blurred, eye inflamed; Miscellaneous: tooth disorder, dermal bleeding, fractures, skin tumour, tumour of the uterus. Additional adverse events are listed below. They include all adverse events that were reported in the overall clinical program for "Tasmar". The events are enumerated using the following criteria: Infrequent: adverse events occur in less than 1% but at least 1/1000 patients; Rare: adverse events occur in less than 1/1000 patients.

Body as a Whole: Infrequent: hernia, pain, allergic reaction, cellulitis, fungal infection, viral infection, carcinoma, chills, abscess, face edema, joint edema. Nervous System: Infrequent: neuralgia, memory disturbance, aggravated parkinsonism, sensory disturbance, migraine, neuropathy, cerebral ischemia, stroke; Rare: dementia, spasms. Psychiatric: Infrequent: asthenia, aggressive reaction, paranoid reaction, delusion, nervousness; Rare: behavioural disturbances, libido disorder, compulsive reaction, personality disorder. Gastrointestinal System: Infrequent: dysphagia, GI hemorrhage, GI inflammation, oral canker sores, hernia inguinal, frequent bowel movements, esophagitis, hernia hiatal, tongue discoloration; Rare: appetite disturbances, tongue dryness. Cardiovascular System: Infrequent: hypertension, vasodilation, angina pectoris, heart failure, atrial fibrillation, tachycardia, aortic stenosis, arrhythmia, arteriospasm, bradycardia, cerebral hemorrhage, coronary artery disorder, heart arrest, myocardial infarct, myocardial ischemia, pulmonary embolus; Rare: arteriosclerosis, cardiovascular disorder, pericardial effusion, thrombosis. Musculoskeletal System: Infrequent: sprains and strains, carpal tunnel syndrome, intervertebral disc disorder, bone spur, tendinitis; Rare: pathological fracture, leg discomfort, muscle disorder. Urogenital System: Infrequent: prostatic disorder, hematuria, urinary retention, urinary tract bleeding, dysuria, nocturia, polyuria, kidney calculus, vaginitis, enlarged prostate, bladder disorder; Rare: bladder calculus, ovarian carcinoma, uterine hemorrhage, kidney failure, abnormal renal function. Skin and Appendages: Infrequent: herpes zoster, skin disorder, herpes simplex, erythema multiforme, pruritus, skin discoloration, cellulitis, seborrhea, eczema, furunculosis, urticaria. Respiratory System: Infrequent: increased cough, asthma, epistaxis, hyperventilation, rhinitis, laryngitis, dryness of pharynx, hiccup; Rare: lung edema, apnea, wheezing, hypoxia. Special Senses: Infrequent: diplopia, ear pain, eye hemorrhage, eye pain, lacrimation disorder, otitis media, parosmia; Rare: glaucoma. Metabolic and Nutritional: Infrequent: edema, hypercholesteremia, thirst, dehydration. Miscellaneous: Infrequent: anemia, surgical procedure.

(continued from page A-43)

**OVERDOSAGE**

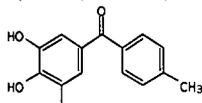
The highest dose of 'Tasmar' (tolcapone) administered to humans was 800 mg t.i.d., with and without levodopa coadministration. This was in a one week study in elderly, healthy volunteers. The peak plasma concentrations of tolcapone at this dose were on average 30 µg/ml (compared to 3 and 6 µg/ml with the 100 mg and 200 mg t.i.d. doses of tolcapone, respectively). Nausea, vomiting and dizziness were observed, particularly in combination with levodopa. The threshold for the lethal plasma concentration for tolcapone based on animal data is >100 µg/ml. Respiratory difficulties were observed in rats at high oral (gavage) and intravenous doses and in dogs with rapidly injected intravenous doses. Management of overdose: Hospitalisation is advised. General supportive care is indicated. Based on the physicochemical properties of the compound, hemodialysis is unlikely to be of benefit.

**DOSAGE AND ADMINISTRATION**

**METHOD OF ADMINISTRATION** 'Tasmar' (tolcapone) is administered orally three times a day, as an adjunct to levodopa/AADC-I (carbidopa or benserazide) therapy. The first dose of the day of 'Tasmar' should be taken together with the first dose of the day of a levodopa/AADC-I preparation, and the subsequent doses of 'Tasmar' should be given approximately 6 and 12 hours later. 'Tasmar' may be taken with or without food (see ACTIONS AND CLINICAL PHARMACOLOGY, PHARMACOKINETICS AND METABOLISM OF TOLCAPONE). 'Tasmar' can be combined with all pharmaceutical formulations of levodopa/carbidopa and levodopa/benserazide. Dosage: Therapy with 'Tasmar' should be initiated with 100 mg t.i.d. In clinical trials, the majority of patients required a decrease in daily levodopa dose if their daily dose of levodopa was >600 mg or if patients had moderate or severe dyskinesias. After adjustment of levodopa dose, an increase to 200 mg 'Tasmar' t.i.d. is recommended, if in the opinion of the physician further benefit may be expected without excessive dopaminergic adverse reactions. After increasing the dose of 'Tasmar' to 200 mg t.i.d., a further readjustment of the dose of levodopa may be needed. In clinical trials, the average reduction in daily levodopa dose was about 30% in those patients who required a levodopa dose reduction. (Greater than 70% of patients with levodopa doses above 600 mg daily required such a reduction). The maximum therapeutic dose of 200 mg t.i.d. (600 mg/day) should not be exceeded since the safety and efficacy of higher doses have not been evaluated systematically and there is no evidence that higher doses provide any additional benefit. Patients with Impaired Hepatic or Renal Function (see ACTIONS AND CLINICAL PHARMACOLOGY and PRECAUTIONS). In patients with moderate to severe cirrhosis, the dose of 'Tasmar' should be kept at 100 mg t.i.d. and not escalated to 200 mg t.i.d. No dose adjustment of 'Tasmar' is recommended for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min). The safety of 'Tasmar' has not been evaluated in patients whose creatinine clearance was < 30 ml/min.

**DISCONTINUATION OF 'TASMAR'** Due to the possibility for the occurrence of Neuroleptic Malignant Syndrome (NMS) upon a sudden decrease in the dose of dopaminergic drugs, including 'Tasmar' (see PRECAUTIONS), physicians should consider increasing the patient's levodopa dose if 'Tasmar' is discontinued.

**PHARMACEUTICAL INFORMATION** Proper Name: Tolcapone  
Chemical Name: 3, 4 dihydroxy- 4'- methyl-5-nitrobenzophenone  
Structural Formula:



Molecular Formula: C<sub>14</sub>H<sub>11</sub>NO<sub>5</sub>  
Molecular Weight: 273.24

**Description:** Tolcapone is a yellow, odourless, non-hygroscopic, crystalline powder. It is practically insoluble in water and in acidic aqueous medium, but easily soluble in most organic solvents. The partition coefficient in n-octanol/phosphate buffer pH 7.5 is 6.1. Its dissociation constant (pKa) is 4.3. Its melting point is 143.0 to 146.0°C. **Composition:** 'Tasmar' 100 mg and 200 mg film coated tablets contain 100 mg and 200 mg tolcapone, respectively. The non-medicinal ingredients are (in alphabetical order): calcium hydrogen phosphate, ethylcellulose, hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, microcrystalline cellulose, povidone K30, sodium lauryl sulfate, sodium starch glycolate, talc, titanium dioxide, triacetin.

**Storage:** 'Tasmar' tablets should be stored at room temperature (15-30°C).

**AVAILABILITY OF DOSAGE FORMS** 'Tasmar' (tolcapone) 100 mg is a pale to light yellow, hexagonal, biconvex film-coated tablet, with 'Roche' and '100' engraved on one side. 'Tasmar' tablets are available in blisters (30 and 60 tablets) and in glass bottles of 100 tablets. 'Tasmar' (tolcapone) 200 mg is a brown to orange yellow, hexagonal, biconvex film-coated tablet, with 'Roche' and '200' engraved on one side. 'Tasmar' tablets are available in blisters (30 and 60 tablets) and in glass bottles of 100 tablets.

**PM available on request.**

**References:** 6. 'Tasmar' product monograph, 1997. 9. Rajput AH et al. Tolcapone 200 mg t.i.d. improves motor function in parkinsonian patients with 'wearing-off' phenomenon: a double-blind, placebo-controlled, multicenter trial. *Neurology* 1997. 10. Waters CH et al. Tolcapone in stable Parkinson's disease: Efficacy and safety of long-term treatment. *Neurology* 1997; 49:1-7. 12. Agid Y et al. Tolcapone, bromocriptine, and Parkinson's disease. *The Lancet*, 1997

(continued from page A-41)

In a reported case of overdosage with valproic acid after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An EEG recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. Since EPIVAL tablets are enteric-coated, the benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the prevention of hypovolemia and the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproic acid overdosage.

Because naloxone could theoretically also reverse the anti-epileptic effects of valproate, it should be used with caution in patients with epilepsy.

**DOSAGE AND ADMINISTRATION:**

**Epilepsy:** EPIVAL (divalproex sodium) is administered orally. 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 250 mg, it should be given in a divided regimen (See Table 2).

**Table 2**  
Initial Doses by Weight (based on 15 mg/kg/day)

Weight	Total Daily Dose (mg)	Dosage (mg) equivalent to valproic acid		
		Dose 1	Dose 2	Dose 3
kg	lb			
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	1000	250	250 500
75-89.9	165-197.9	1250	500	250 500

A good correlation has not been established between daily dose, total serum valproate concentration and therapeutic effect. However, therapeutic valproate serum concentrations for most patients with epilepsy will range from 50 to 100 µg/mL (350 to 700 µmol/L). Some patients may be controlled with lower or higher serum concentrations (see PRECAUTIONS).

Patients receiving combined antiepileptic therapy require careful monitoring when another agent is started, stopped or when the dose is altered (see PRECAUTIONS; under Drug Interactions). As the dosage of divalproex sodium is titrated upward, blood concentrations of phenobarbital, carbamazepine and/or phenytoin may be affected (see PRECAUTIONS; under Drug Interactions). Antiepileptic drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

**Conversion from Depakene to EPIVAL:** EPIVAL (divalproex sodium) dissociates to the valproate ion in the gastrointestinal tract. Divalproex sodium tablets are uniformly and reliably absorbed, however, because of the enteric coating, absorption is delayed by an hour when compared to Depakene (valproic acid). The bioavailability of divalproex sodium tablets is equivalent to that of DEPAKENE<sup>®</sup> (valproic acid) capsules.

In patients previously receiving Depakene (valproic acid) therapy, EPIVAL should be initiated at the same daily dosing schedule. After the patient is stabilized on EPIVAL, a dosing schedule of two or three times a day may be elected in selected patients. Changes in dosage administration of valproate or concomitant medications should be accompanied by increased monitoring of plasma concentrations of valproate and other medications, as well as the patient's clinical status.

**Acute Mania:** The recommended initial dose is 250 mg three times a day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect or the desired range of plasma concentrations. In placebo-controlled trials, 84% of patients received and tolerated maximum daily doses of between 1000 mg/day to 2500 mg/day. The maximum recommended dosage is 60 mg/kg/day. The relationship of plasma concentration to clinical response has not been established for EPIVAL. In controlled clinical studies, 79% of patients achieved and tolerated serum valproate concentrations between 50 µg/mL and 125 µg/mL.

When changing therapy involving drugs known to induce hepatic microsomal enzymes (e.g., carbamazepine) or other drugs with valproate interactions (see PRECAUTIONS; Drug Interactions), it is advisable to monitor serum valproate concentrations.

**General Dosing Advice**

**Dosing in Elderly Patients** - Due to a decrease in unbound clearance of valproate, the starting dose should be reduced; the ultimate therapeutic dose should be achieved on the basis of clinical response.

**Dose-Related Adverse Events** - The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may increase with increasing dose (see PRECAUTIONS). Therefore, the benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse effects.

**G.I. Irritation** - 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.

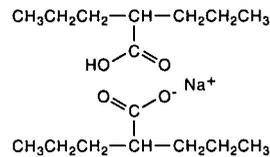
**PHARMACEUTICAL INFORMATION:**

**Drug Substance**

**Trade Name:** EPIVAL<sup>®</sup>  
**Proper Name:** Divalproex sodium  
**USAN Names:** INN: Valproate semisodium  
BAN: Semisodium valproate  
**Chemical Name:** Sodium hydrogen bis (2-propylpentanoate) or Sodium hydrogen bis (2-propylvalerate)

**Molecular Weight:** 310.14 **Molecular Formula:** C<sub>16</sub>H<sub>31</sub>NaO<sub>4</sub>

**Structural Formula:**



**Description:** Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. It is a white powder with a characteristic odor, freely soluble in many organic solvents and in aqueous alkali solutions.

**Non-Medicinal Ingredients:** EPIVAL<sup>®</sup> Enteric-Coated Tablets: Cellulosic polymers, silica gel, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch), talc, titanium dioxide, and vanillin.

In addition, individual tablets contain:  
125 mg tablets: FD&C Blue No.1 and FD&C Red No. 40  
250 mg tablets: FD&C Yellow No. 6 and iron oxide  
500 mg tablets: D&C Red No. 30, FD&C Blue No. 2, and iron oxide.

**Storage Recommendations:** Store between 15°- 30°C (59°- 86°F).

**AVAILABILITY OF DOSAGE FORMS:** EPIVAL (divalproex sodium) particle coated tablets are available as salmon-pink coloured tablets of 125 mg; peach-coloured tablets of 250 mg; lavender-coloured tablets of 500 mg. Supplied in bottles of 100 and 500 tablets.

**INFORMATION FOR THE CONSUMER:** Since EPIVAL (divalproex sodium) may produce CNS depression, especially when combined with another CNS depressant (e.g., alcohol), patients should be advised not to engage in hazardous activities, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

**References:** 1. Dean JC. Valproate. In: Wyllie E, ed. The treatment of epilepsy: principles and practices. Philadelphia: Lea and Febiger, 1993:915-22. 2. Wilder BJ, Ramsay RE, Murphy JV, et al. Comparison of valproic acid and phenytoin in newly diagnosed tonic-clonic seizures. *Neurology* 1983;33:1474-6. 3. Turnbull DM, Howell D, Rawlins MD, et al. Which drug for the adult epileptic patient: phenytoin or valproate? *Br Med J* 1985;290:815-9. 4. Covanis A, Gupta AK, Jeavons PM. Sodium valproate: monotherapy and polytherapy. *Epilepsia* 1982;23: 693-720. 5. Kakegawa N, Miyakoshi M, Seino M. Monotherapy by sodium valproate (SV) and the blood concentration. In: Program and abstracts of the XI Epilepsy International Symposium; September 30, 1979; Firenze, Italy. Abstract:153. 6. Dreifuss FE, Langer OH. Side effects of valproate. *Am J Med* 1988;84 Suppl 1A:34-41. 7. Epival Product Monograph. Abbott Laboratories, Limited.

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**PERMAX**<sup>®</sup>  
pergolide mesylate

## A Renewed Opportunity In Parkinson's Disease

Pergolide Mesylate tablets

**THERAPEUTIC CLASSIFICATION:** Dopamine Agonist

**PRESENTATION:** Tablets containing 0.05 mg or 0.25 mg or 1 mg of pergolide base.

**INDICATIONS AND CLINICAL USE:** As an adjunctive treatment to levodopa in the management of the signs and symptoms of Parkinson's disease.

**CONTRAINDICATIONS:** Hypersensitivity to this drug or other ergot derivatives.

**WARNINGS:** Patients should be warned to begin therapy with low doses and to increase dosage in carefully adjusted increments over a period of 3 to 4 weeks, to minimize the risk of syncope, symptomatic postural and/or sustained hypotension. In controlled trials, pergolide mesylate with L-dopa caused hallucinosis in about 14 percent of patients, as opposed to 3 percent taking placebo with L-dopa. Caution should be exercised when administering to patients prone to cardiac dysrhythmias or with significant underlying cardiac disease. In a placebo-controlled study, patients taking pergolide mesylate had significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia. Care should be exercised with regard to engaging in activities requiring rapid and precise responses, such as driving an automobile or operating machinery.

**PRECAUTIONS:** Abrupt discontinuation of pergolide mesylate, in patients receiving it chronically as an adjunct to L-dopa, may precipitate the onset of hallucinations and confusion. Administration to patients receiving L-dopa, may cause and/or exacerbate pre-existing dyskinesias. Patients and their families should be informed of the common adverse consequences of the use of pergolide mesylate and the risk of hypotension. Patients should be advised to tell their doctors if they become pregnant, intend to become pregnant, or if they are breast feeding. **Drug interactions:** Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide, ordinarily should not be administered concurrently with pergolide mesylate (a dopamine agonist); these agents may diminish the effectiveness of pergolide mesylate. Caution should be exercised if pergolide mesylate is co-administered with anti-hypertensive agents. **Pregnancy:** In animal studies there was no evidence of harm to the fetus due to pergolide mesylate. There are, however, no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the benefits outweigh the potential risk to the fetus. **Nursing mothers:** It is not known whether pergolide mesylate is excreted in human milk. The pharmacological action of pergolide mesylate suggests it may interfere with lactation. A decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

**ADVERSE REACTIONS:** Body as a whole: Pain, abdominal pain, injury, accident, headache, asthenia, chest pain, back pain, flu syndrome, neck pain. Gastrointestinal: Nausea, constipation, diarrhea, dyspepsia, anorexia, dry mouth, dysphagia. Special senses: Diplopia, abnormal vision, taste perversion, eye disorder. Other events that have been reported include hypotension, atrial premature contractions and sinus tachycardia. Nervous system: Hallucinations, psychosis, paranoid reaction, personality disorder, akinesia, dyskinesia, choreoathetosis, dystonia, tremor, abnormal gait, incoordination, speech disorders, dizziness, confusion, depression, anxiety, somnolence, insomnia, abnormal dreams, amnesia. Respiratory system: Rhinitis, dyspnea, pneumonia, pharyngitis, cough increased. Metabolic and nutritional findings: Peripheral edema, weight loss, weight gain. Musculoskeletal system: Twitching myalgia, arthralgia. Skin and appendages system: Sweating rash. Urogenital system: Urinary tract infection, urinary frequency, urinary incontinence, prostatic disorder, dysmenorrhea, hematuria. Hemetic and lymphatic system: Anemia.

**OVERDOSAGE:** There is no clinical experience with massive overdosage. Symptoms and signs have included vomiting, hypotension, agitation, severe hallucinations, severe involuntary movements, tingling sensations, palpitations and ventricular extrasystoles. Treatment: Symptomatic supportive therapy is recommended to maintain blood pressure. Cardiac function should be monitored. An antiarrhythmic agent may be necessary. If signs of CNS stimulation are present a phenothiazine, or other butyrophenone neuroleptic agent, may be indicated.

**DOSAGE AND ADMINISTRATION:** Pergolide is administered orally. Administration should be initiated with a daily dosage of 0.05 gm for the first two days. The dosage should then be gradually increased by 0.1 or 0.15 mg/day every third day over the next 12 days of therapy. The dosage may then be increased by 0.15 mg/day every third day until an optimal therapeutic dosage is achieved. Pergolide mesylate is usually administered in divided doses 3 times per day. During dosage titration, the dosage of current L-dopa may be cautiously decreased. **SUPPLIED:** 0.05 mg: Each ivory coloured, modified rectangle-shaped tablet, scored and engraved with the company logo and identi-code 4131, contains pergolide mesylate 0.05 mg. Also contains lactose. Gluten- and tartrazine free. Amber HDPE bottles of 30. 0.25 mg: Each green coloured, modified rectangle-shaped tablet, scored and engraved with the company logo and identi-code 4133, contains pergolide mesylate 0.25 mg. Also contains lactose. Gluten- and tartrazine free. Amber HDPE bottles of 100. 1 mg: Each pink-coloured, modified rectangle-shaped tablet, scored and engraved with the company logo and identi-code 4135, contains pergolide mesylate 1 mg. Also contains lactose. Gluten- and tartrazine free. Amber HDPE bottles of 100. Store at room temperature.

The product monograph is available upon request.

Permax is a schedule F drug.

### References:

1. Jankovic J. Pergolide: Short-term and long-term experience in Parkinson's disease. Recent Developments in Parkinson's Disease, ed by S Fahn et al. Raven Press, New York 1986
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4. Goetz CG et al. Chronic agonist therapy for Parkinson's disease: A 5-year study of bromocriptine and pergolide. Neurology (1985 May) 35(5):749-51.
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6. Goetz CG et al. Agonist substitution in advanced Parkinson's disease. Neurology 1989;39:1121-1122.



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Mississauga, Ontario

PAAB

See page A-25

**TOPAMAX\***  
Tablets (Topiramate)

**Therapeutic Classification: Anti-epileptic**

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

**TOPAMAX** (topiramate) is a novel antiepileptic agent classified as a sulphamate substituted monosaccharide. Three pharmacological properties of topiramate are believed to contribute to its anticonvulsant activity. First, topiramate reduces the frequency at which action potentials are generated when neurons are subjected to a sustained depolarization indicative of a state-dependent blockade of voltage-sensitive sodium channels. Second, topiramate markedly enhances the activity of GABA at some types of GABA receptors. Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine insensitive subtype of GABA<sub>A</sub> receptor. Third, topiramate antagonizes the ability of kainate to activate the kainate/AMPA subtype of excitatory amino acid (glutamate) receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This pharmacologic effect is much weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major component of topiramate's antiepileptic activity.

**PHARMACOKINETICS**

**Absorption and Distribution**

Topiramate is rapidly and well-absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C<sub>max</sub>) of 1.5 µg/mL was achieved within 2 to 3 hours (T<sub>max</sub>). The mean extent of absorption from a 100 mg oral dose of <sup>14</sup>C-topiramate was at least 81% based on the recovery of radioactivity from the urine.

Topiramate exhibits low intersubject variability in plasma concentrations and, therefore, has predictable pharmacokinetics. The pharmacokinetics of topiramate are linear with plasma clearance remaining constant and area under the plasma concentration curve increasing in a dose-proportional manner over a 100 to 400 mg single oral dose range in healthy subjects. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations. The mean C<sub>max</sub> following multiple, twice-a-day oral doses of 100 mg to healthy subjects was 6.76 µg/mL. The mean plasma elimination half-lives from multiple 50 mg and 100 mg q12h doses of topiramate were approximately 21 hours. The elimination half-life did not significantly change when switching from single dose to multiple dose.

Concomitant multiple-dose administration of topiramate, 100 to 400 mg q12h, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

There was no clinically significant effect of food on the bioavailability of topiramate.

Approximately 13% to 17% of topiramate is bound to plasma proteins. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 µg/mL has been observed.

The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 L/kg for a single dose range of 100 to 1200 mg.

**Metabolism and Excretion**

Topiramate is not extensively metabolized (~20%) in healthy volunteers. It is metabolized up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolizing enzymes. Six metabolites formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterized and identified from plasma, urine and feces of humans. Each metabolite represents less than 3% of the total radioactivity excreted following administration of <sup>14</sup>C-topiramate.

Two metabolites, which retained most of the structure of topiramate, were tested and found to have little or no pharmacological activity.

In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney (at least 81% of the dose). Approximately 66% of a dose of <sup>14</sup>C-topiramate was excreted unchanged in the urine within 4 days. The mean renal clearance for 50 mg and 100 mg of topiramate, following q12h dosing, was approximately 18 mL/min and 17 mL/min, respectively. Evidence exists for renal tubular reabsorption of topiramate. This is supported by studies in rats where topiramate was co-administered with probenecid, and a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, plasma clearance is approximately 20 to 30 mL/min in humans following oral administration.

**Special Populations**

**Renal Impairment:**

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function (CLCR ≤ 60 mL/min), and the plasma clearance is decreased in patients with end-stage renal disease. As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renally-impaired patients as compared to those with normal renal function. Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

**Hemodialysis:**

Topiramate is effectively removed from plasma by hemodialysis. (See DOSAGE AND ADMINISTRATION.)

**Hepatic Impairment:**

The plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment.

**Age and Gender:**

Age (18-67) and gender appear to have no effect on the plasma clearance of topiramate. In well-controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations and its clinical efficacy.

No evidence of tolerance requiring increased dosage has been demonstrated in man during 4 years of use.

**Pediatric Pharmacokinetics**

Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. As in adults, topiramate pharmacokinetics were linear with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Compared with adult epileptic patients, mean topiramate clearance is approximately 50% higher in pediatric patients. Steady-state plasma topiramate concentrations for the same mg/kg dose are expected to be approximately 33% lower in children compared to adults. As with adults, hepatic enzyme-inducing antiepileptic drugs (AEDs) decrease the plasma concentration of topiramate.

**Clinical Experience**

The results of clinical trials established the efficacy of **TOPAMAX** as adjunctive therapy in patients with refractory partial onset seizures with or without secondarily generalized seizures. Six multicentre, outpatient, randomized, double-blind, placebo controlled trials were completed. Patients in all six studies were permitted a maximum of two antiepileptic drugs (AEDS) in addition to **TOPAMAX** therapy (target doses of 200, 400, 600, 800, or 1,000 mg/day) or placebo.

In all six add-on trials, the primary efficacy measurement was reduction in seizure rate from baseline during the entire double-blind phase; responder rate (fraction of patients with a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 1.

**Table 1**

Median Percent Seizure Rate Reduction and Percent Responders in Six Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Efficacy Results	Target Topiramate Dosage (mg/day)					
		Placebo	200	400	600	800	1,000
YD	N	45	45	45	46	-	-
	Median % Reduction	13.1	29.6*	47.8*	44.7*	-	-
	% Responders	18	27	47*	46*	-	-
YE	N	47	-	-	48	48	47
	Median % Reduction	1.2	-	-	40.7*	41.0*	37.5*
	% Responders	9	-	-	44*	40*	38*
Y1	N	24	-	23	-	-	-
	Median % Reduction	1.1	-	40.7*	-	-	-
	% Responders	8	-	35*	-	-	-
Y2	N	30	-	-	30	-	-
	Median % Reduction	-12.2	-	-	46.4*	-	-
	% Responders	10	-	-	47*	-	-
Y3	N	28	-	-	-	28	-
	Median % Reduction	-17.8	-	-	-	35.8*	-
	% Responders	0	-	-	-	43*	-
YF/YG	N	42	-	-	-	-	167
	Median % Reduction	1.2	-	-	-	-	50.8*
	% Responders	19	-	-	-	-	52*

Comparisons with placebo: \* p < 0.051; † p < 0.05; ‡ p < 0.01; § p < 0.001; ¶ p = 0.053; †† p = 0.065

Across the six efficacy trials, 232 of the 527 topiramate patients (44%) responded to treatment with at least a 50% seizure reduction during the double-blind phase; by comparison, only 25 of the 216 placebo-treated patients (12%) showed the same level of treatment response. When the treatment response was defined more rigorously as a 75% or greater decrease from baseline in seizure rate during double-blind treatment, 111 of the 527 topiramate patients (21%) in the 200 to 1,000 mg/day groups, but only 8 of the 216 placebo patients (4%), demonstrated this level of efficacy. At target dosages of 400 mg/day and higher, the percent of treatment responders was statistically greater for topiramate-treated than placebo-treated patients.

Pooled analyses of secondarily generalized seizure rates for all patients who had this seizure type during the studies show statistically significant percent reductions in the **TOPAMAX** groups when compared with placebo. The median percent reduction in the rate of generalized seizures was 57% for topiramate-treated patients compared with 4% for placebo-treated patients. Among topiramate-treated patients, 109 (55%) of 198 had at least a 50% reduction in generalized seizure rate compared with 24 (27%) of 88 placebo-treated patients.

The dose titration in the original clinical trials was 100 mg/day the first week, 100 mg bid/day the second week, and 200 mg bid/day the third week. In a 12-week, double-blind trial, this titration rate was compared to a less rapid rate beginning at 50 mg/day. There were significantly fewer adverse experiences leading to discontinuation and/or dosage adjustment in the group titrated at the less rapid rate. Seizure rate reductions were comparable between the groups at all time points measured.

**INDICATIONS AND CLINICAL USE**

**TOPAMAX** (topiramate) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled with conventional therapy. There is limited information on the use of topiramate in monotherapy at this time.

**CONTRAINDICATIONS**

**TOPAMAX** (topiramate) is contraindicated in patients with a history of hypersensitivity to any components of this product.

**WARNINGS**

Antiepileptic drugs, including **TOPAMAX** (topiramate), should be withdrawn gradually to minimize the potential of increased seizure frequency. In clinical trials, dosages were decreased by 100 mg/day at weekly intervals.

**Central Nervous System Effects**

Adverse events most often associated with the use of **TOPAMAX** (topiramate) were central nervous system-related. The most significant of these can be classified into two general categories: i) psychomotor slowing; difficulty with concentration, and speech or language problems, in particular, word-finding difficulties and ii) somnolence or fatigue.

Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression).

These events were generally mild to moderate, and generally occurred early in therapy. While the incidence of psychomotor slowing does not appear to be dose-related, both language problems and difficulty with concentration or attention increased in frequency with increasing dosage in the six double-blind trials suggesting that these events are dose-related (see ADVERSE REACTIONS).

**PRECAUTIONS**

**Effects Related to Carbonic Anhydrase Inhibition**

**Kidney Stones**

A total of 32/1,715 (1.5%) of patients exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 10 times that expected in a similar, untreated population (M/F ratio; 27/1092 male; 5/623 female). In the general population, risk factors for kidney stone formation include gender (male), ages between 20-50 years, prior stone formation, family history of nephrolithiasis, and hypercalcaemia. Based on logistic regression analysis of the clinical trial data, no correlation between mean topiramate dosage, duration of topiramate therapy, or age and the occurrence of kidney stones was established; of the risk factors evaluated, only gender (male) showed a correlation with the occurrence of kidney stones.

Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorophenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. Concomitant use of **TOPAMAX**, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Patients, especially those with a predisposition to nephrolithiasis, may have an increased risk of renal stone formation. Increased fluid intake increases the urinary output lowering the concentration of substances involved in stone formation. Therefore, adequate hydration is recommended to reduce this risk. None of the risk factors for nephrolithiasis can reliably predict stone formation during **TOPAMAX** treatment.

**Paresthesia**

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of **TOPAMAX**. These events were usually intermittent and mild and not necessarily related to the dosage of topiramate.

**Adjustment of Dose in Renal Failure**

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with impaired renal function (CLCR ≤ 60 mL/min) or with end-stage renal disease receiving hemodialysis treatments may take 10 to 15 days to reach steady state plasma concentrations as compared to 4 to 8 days in patients with normal renal function. As with all patients, the titration schedule should be guided by clinical outcome (i.e. seizure control, avoidance of side effects) with the knowledge that patients with known renal impairment may require a longer time to reach steady state at each dose. (See DOSAGE AND ADMINISTRATION.)

### Decreased Hepatic Function

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate was decreased compared with normal subjects.

### Information for Patients

#### Adequate Hydration

Patients, especially those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation.

#### Effects on Ability to Drive and Use Machines

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

### Drug Interactions

#### Anti-epileptic Drugs

Potential interactions between topiramate and standard AEDs were measured in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on plasma concentrations are summarized in Table 2:

**Table 2**  
Drug Interactions with TOPAMAX Therapy

AED Co-administered	AED Concentration	TOPAMAX Concentration
Phenytoin	↔**	↓59%
Carbamazepine (CBZ)	↔	↓40%
CBZ epoxide*	↔	NS
Valproic acid	↓11%	↓14%
Phenobarbital	↔	NS
Primidone	↔	NS

\* Is not administered but is an active metabolite of carbamazepine

↔ No effect on plasma concentration

\*\* Plasma concentrations increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin

↓ Plasma concentrations decrease in individual patients

NS Not studied

AED Antiepileptic drug

The effect of topiramate on steady-state pharmacokinetics of phenytoin may be related to the frequency of phenytoin dosing. A slight increase in steady-state phenytoin plasma concentrations was observed, primarily in patients receiving phenytoin in two divided doses. The slight increase may be due to the saturable nature of phenytoin pharmacokinetics and inhibition of phenytoin metabolism.

The addition of TOPAMAX therapy to phenytoin should be guided by clinical outcome. In general, as evidenced in clinical trials, patients do not require dose adjustments. However, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

#### Other Drug Interactions

##### Digoxin:

In a single-dose study, serum digoxin AUC decreased 12% due to concomitant TOPAMAX administration. Multiple dose studies have not been performed. When TOPAMAX is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

##### CNS Depressants:

Concomitant administration of TOPAMAX and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. It is recommended that TOPAMAX not be used concomitantly with alcohol or other CNS depressant drugs.

##### Oral Contraceptives:

In an interaction study with oral contraceptives using a combination product containing norethindrone plus ethinyl estradiol, TOPAMAX did not significantly affect the oral clearance of norethindrone. The serum levels of the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400 and 800 mg, respectively. Consequently, the efficacy of low dose (e.g., 20 µg) oral contraceptives may be reduced in this situation. Patients taking oral contraceptives should receive a preparation containing not less than 50 µg of estrogen. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns.

##### Others:

Concomitant use of TOPAMAX, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorophenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided if possible.

### Laboratory Tests

There are no known interactions of TOPAMAX with commonly used laboratory tests.

### Use in Pregnancy and Lactation

Like other antiepileptic drugs, topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier.

There are no studies using TOPAMAX in pregnant women. However, TOPAMAX therapy should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Topiramate is excreted in the milk of lactating rats. It is not known if topiramate is excreted in human milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to TOPAMAX exists, the prescriber should decide whether to discontinue nursing or discontinue the drug, taking into account the risk/benefit ratio of the importance of the drug to the mother and the risks to the infant.

The effect of TOPAMAX on labor and delivery in humans is unknown.

### Pediatric Use

Safety and effectiveness in children under 18 years of age have not been established.

### Geriatric Use

There is limited information in patients over 65 years of age. The possibility of age-associated renal function abnormalities should be considered when using TOPAMAX.

### Race and Gender Effects

Although direct comparison studies of pharmacokinetics have not been conducted, analysis of plasma concentration data from clinical efficacy trials have shown that race and gender appear to have no effect on the plasma clearance of topiramate. In addition, based on pooled analyses, race and gender appear to have no effect on the efficacy of topiramate.

### ADVERSE REACTIONS

The most commonly observed adverse events associated with the adjunctive use of TOPAMAX (topiramate) at dosages of 200 to 400 mg/day in controlled trials that were seen at greater frequency in topiramate-treated patients and did not appear to be dose-related within this dosage range were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, nystagmus, and paresthesia (see Table 3). The most common dose-related adverse events at dosages of 200 to 1,000 mg/day were: nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, and mood problems (see Table 4).

**Table 3**

Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials<sup>a</sup>  
(Events that occurred in ≥ 2% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

Body System/ Adverse Event	TOPAMAX <sup>®</sup> Dosage (mg/day)		
	Placebo (N=216)	200-400 (N=113)	600-1,000 (N=414)
<b>Body as a Whole</b>			
Asthenia	1.4	8.0	3.1
Back Pain	4.2	6.2	2.9
Chest Pain	2.8	4.4	2.4
Influenza-Like Symptoms	3.2	3.5	3.6
Leg Pain	2.3	3.5	3.6
Hot Flashes	1.9	2.7	0.7
<b>Nervous System</b>			
Dizziness	15.3	28.3	32.1
Ataxia	6.9	21.2	14.5
Speech Disorders/Related Speech Problems	2.3	16.8	11.4
Nystagmus	9.3	15.0	11.1
Paresthesia	4.6	15.0	19.1
Tremor	6.0	10.6	8.9
Language Problems	0.5	6.2	10.4
Coordination Abnormal	1.9	5.3	3.6
Hypoaesthesia	0.9	2.7	1.2
Abnormal Gait	1.4	1.8	2.2
<b>Gastrointestinal System</b>			
Nausea	7.4	11.5	12.1
Dyspepsia	8.5	8.0	6.3
Abdominal Pain	3.7	5.3	7.0
Constipation	2.3	5.3	3.4
Dry Mouth	0.9	2.7	3.9
<b>Metabolic and Nutritional</b>			
Weight Decrease	2.8	7.1	12.8
<b>Neuropsychiatric</b>			
Somnolence	9.7	30.1	27.8
Psychomotor Slowing	2.3	16.8	20.8
Nervousness	7.4	15.9	19.3
Difficulty with Memory	3.2	12.4	14.5
Confusion	4.2	9.7	13.8
Depression	5.6	8.0	13.0
Difficulty with Concentration/Attention	1.4	8.0	14.5
Anorexia	3.7	5.3	12.3
Agitation	1.4	4.4	3.4
Mood Problems	1.9	3.5	9.2
Aggressive Reaction	0.5	2.7	2.9
Apathy	0	1.8	3.1
Depersonalization	0.9	1.8	2.2
Emotional Lability	0.9	1.8	2.7
<b>Reproductive, Female</b>			
Breast Pain, Female	(N=59)	(N=24)	(N=128)
Dysmenorrhea	1.7	8.3	0
Menstrual Disorder	6.8	8.3	3.1
Prostatic Disorder	0	4.2	0.8
<b>Reproductive, Male</b>			
Prostatic Disorder	(N=157)	(N=89)	(N=286)
Prostatic Disorder	0.6	2.2	0
<b>Respiratory System</b>			
Pharyngitis	2.3	7.1	3.1
Rhinitis	6.9	7.1	6.3
Sinusitis	4.2	4.4	5.6
Dyspnea	0.9	1.8	2.4
<b>Skin and Appendages</b>			
Pruritus	1.4	1.8	3.1
<b>Vision</b>			
Diplopia	5.6	14.2	10.4
Vision Abnormal	2.8	14.2	10.1
<b>White Cell and RES</b>			
Leukopenia	0.5	2.7	1.2

<sup>a</sup> Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX or placebo.

<sup>b</sup> Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

**Table 4**

Dose-Related Adverse Events From Six Placebo-Controlled, Add-On Trials

Adverse Event	TOPAMAX <sup>®</sup> Dosage (mg/day)			
	Placebo (N = 216)	200 (N = 45)	400 (N = 68)	600 - 1,000 (N = 414)
Fatigue	13.4	11.1	11.8	29.7
Nervousness	7.4	13.3	17.6	19.3
Difficulty with Concentration/Attention	1.4	6.7	8.8	14.5
Confusion	4.2	8.9	10.3	13.8
Depression	5.6	8.9	7.4	13.0
Anorexia	3.7	4.4	5.9	12.3
Language problems	0.5	2.2	8.8	10.1
Anxiety	6.0	2.2	2.9	10.4
Mood problems	1.9	0.0	5.9	9.2

In double-blind clinical trials, 10.6% of subjects (N=113) assigned to a topiramate dosage of 200 to 400 mg/day in addition to their standard AED therapy discontinued due to adverse events compared to 5.8% of subjects (N=69) receiving placebo. The percentage of subjects discontinuing due to adverse events appeared to increase at dosages above 400 mg/day. Overall, approximately 17% of all subjects (N=527) who received topiramate in the double-blind trials, discontinued due to adverse events compared to 4% of the subjects (N=216) receiving placebo.

Nephrolithiasis was reported rarely. Isolated cases of thromboembolic events have also been reported, a causal association with the drug has not been established.

When the safety experience of patients receiving TOPAMAX as adjunctive therapy in both double-blind and open-label trials (n=1,446) was analyzed, a similar pattern of adverse events emerged.

(continued on page A-49)

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(continued from page A-47)

#### SYMPTOMS AND TREATMENT OF OVERDOSAGE

In acute **TOPAMAX** (topiramate) overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdose is not recommended. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdose reported, including doses of over 20 g in one individual, hemodialysis has not been necessary.

#### DOSAGE AND ADMINISTRATION

##### Adults

The recommended total daily dose of **TOPAMAX** (topiramate) as adjunctive therapy is 200-400 mg/day in two divided doses. It is recommended that therapy be initiated at 50 mg/day, followed by titration to an effective dose. Doses above 400 mg/day have not been shown to improve responses and have been associated with a greater incidence of adverse events. The maximum recommended dose is 800 mg/day. Daily doses above 1,600 mg have not been studied.

Titration should begin at 50 mg/day. At weekly intervals, the dose should be increased by 50 mg/day and taken in two divided doses. Dose titration should be guided by clinical outcome. Some patients may achieve efficacy with once-a-day dosing.

##### THE RECOMMENDED TITRATION RATE IS:

	AM Dose	PM Dose
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

**TOPAMAX** Tablets can be taken without regard to meals. Tablets should not be broken.

##### Geriatrics

See PRECAUTIONS section.

##### Pediatrics

As yet there is limited experience on the use of **TOPAMAX** (topiramate) in children aged 18 years and under and dosing recommendations cannot be made for this patient population.

##### Patients with Renal Impairment

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m<sup>2</sup>), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

##### Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

##### Patients with Hepatic Disease

In hepatically impaired patients topiramate plasma concentrations are increased approximately 30%. This moderate increase is not considered to warrant adjustment of the topiramate dosing regimen. Initiate topiramate therapy with the same dose and regimen as for patients with normal hepatic function. The dose titration in these patients should be guided by clinical outcome, i.e., seizure control and avoidance of adverse effects. Such patients will require a longer time to reach steady-state at each dose.

#### PHARMACEUTICAL INFORMATION

##### i) Drug Substance

Proper Name: topiramate

Chemical Name: 2,3,4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate

Molecular Formula: C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>8</sub>S

Molecular Weight: 339.36

Description: Topiramate is a white crystalline powder having a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate with a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3.

##### ii) Composition

**TOPAMAX** (topiramate) contains the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80 and may contain synthetic iron oxide.

##### iii) Stability and Storage Recommendations

**TOPAMAX** Tablets should be stored in tightly closed containers at controlled room temperature (15 to 30°C). Protect from moisture.

#### AVAILABILITY OF DOSAGE FORMS

**TOPAMAX** (topiramate) is available as embossed tablets in the following strengths as described below:

25 mg:	white, round, coated tablets containing 25 mg topiramate.
100 mg:	yellow, round, coated tablets containing 100 mg topiramate.
200 mg:	salmon-coloured, round, coated tablets containing 200 mg topiramate.

Supplied: Bottles of 60 tablets with desiccant.

Product Monograph available on request

#### REFERENCES:

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The Society for Progressive Supranuclear Palsy, Inc., (SPSP) is pleased to announce the annual Eloise H. Troxel Memorial Grant and Memorial Fellowship, each of \$50,000 for research in PSP. The application deadline is December 1. SPSP also announces an increase in the maximum award for its regular grants program to \$20,000 annually. Deadlines are April 1 and October 1.

For further information contact the Chairman of the Medical Advisory Board, SPSP, Lawrence I. Golbe, MD at  
golbe@umdnj.edu  
or fax (732) 235-7041.

SPSP offers educational materials for patients and their families as well as for medical professionals. Call 1-800-457-4777 or access <http://www.psp.org>

## UNIVERSITY OF MANITOBA NEUROLOGIST

The Department of Internal Medicine, University of Manitoba, invites applications for one academic neurologist with a special interest/expertise in clinical neurophysiology and epilepsy to take a leadership position in the hospital clinical neurophysiology laboratory and in the diagnosis and management of epilepsy. This will be a geographical full-time, contingent position located at the Health Sciences Centre. The responsibilities would include administration of the Clinical Neurophysiology EEG/EP Laboratory, Interpretation of procedures, commitment in patient care, teaching (undergraduate and postgraduate) and research.

The candidate must have senior specialty qualifications in Neurology in the country of current practice and be eligible for registration with the College of Physicians and Surgeons of Manitoba. Certification in Neurology by the Royal College of Physicians and Surgeons of Canada is preferred.

The University of Manitoba encourages applications from qualified women and men, including members of visible minorities, Aboriginal peoples, and persons with disabilities. This advertisement is directed to Canadian citizens and permanent residents.

Salary will be commensurate with rank and qualifications. Applications should be accompanied by a curriculum vitae, a list of publications, and indication of special interests or research activities, if present, and the names of three references to:

Dr. L.E. Nicolle,  
H.E. Sellers Professor and Head,  
Department of Internal Medicine,  
Room GC430, Health Sciences Centre,  
820 Sherbrook Street, Winnipeg, Manitoba R3A 1R9

Closing date for receipt of applications is April 30, 1998.



University of Alberta  
Edmonton

## Division of Neurology, Department of Medicine

The Division of Neurology at the University of Alberta has opportunities for three full-time and two part-time neurologists looking for a career in academic neurology and private practice neurology with the following qualifications:

1. The candidates must have passed the Royal College Fellowship examinations in neurology or the examination of the American Board of Psychiatry and Neurology (Neurology).
2. Candidates wishing to pursue an academic career with a full-time appointment must have completed a fellowship in an academic institution following residency.
3. Teaching and research experience beyond fellowship is desirable.
4. Candidates applying for full-time appointments must have a commitment to academic neurology as evidenced by scholarly publications or proficiency in an area of clinical or basic research.
5. Preference will be given to candidates with interests in the area of cerebral vascular disease, epilepsy, neurodegenerative diseases, particularly Alzheimer's or related disorders.

Candidates applying to the full-time positions would have protected time for academic activities. The rank and salary would be commensurate with the candidate's experience.

The Division of Neurology is part of the Department of Medicine. The University provides an active and stimulating academic environment with excellent basic science facilities. We provide services for Edmonton and Northern Alberta and surrounding provinces with a patient population of over one million. Areas of active research include neuromuscular diseases, multiple sclerosis, movement disorders and cerebral vascular disease. As well, collaboration exists with an active neurosurgical division.

In accordance with Canadian Immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. If suitable Canadian citizens and permanent residents cannot be found, other individuals will be considered.

Interested applicants are asked to forward their CV and the names and addresses of three references to:

**Dr. Ashfaq Shuaib**  
Director, Division of Neurology  
Faculty of Medicine  
Room 2E3.13, Mackenzie Health Sciences Centre  
University of Alberta  
Edmonton, Alberta, T6G 2B1 Canada

Deadline for applications is April 1, 1998.

*The University of Alberta is committed to the principle of equity in employment. As an employer, we welcome diversity in the workplace and encourage applications from all qualified women and men, including Aboriginal peoples, persons with disabilities, and members of visible minorities.*

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## **Clinical and Laboratory Research Fellowship in Neurodegenerative Diseases**

The fellow would participate in the care of patients under expert supervision in specialty clinics dedicated to ALS or Alzheimer's disease and be primarily responsible for a number of clinical trials related to drug therapy and evaluation using advance MR techniques including MR spectroscopy.

Contact Dr. D.L. Arnold, MRS Unit,  
Montreal Neurological Institute,  
McGill University, 3801 University St.,  
Montreal, Quebec, Canada H3A 2B4  
Email: doug@mrs.mni.mcgill.ca.  
FAX 514-398-2975.

## **MS/Electrophysiology Fellowship**

St. Michael's Hospital  
University of Toronto  
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Offered at the MS Clinic, St. Michael's Hospital  
for July 1998-June 1999. Training will include  
potential involvement in all aspects of MS  
clinical practice and research including evoked  
potentials, clinical trials, imaging, basic science  
and clinical epidemiology.

Applicants must be eligible for FRCPC  
licensure. Send CV and 3 letters of reference to:

P. O'Connor MD, MSc FRCPC  
St. Michael's Hospital  
30 Bond Street - Suite 3133D,  
Toronto, Ontario, Canada M5B 1W8  
Tel. No. (416) 864-5830  
Fax No.: (416) 864-5147

## **MEMORIAL UNIVERSITY OF NEWFOUNDLAND NEUROLOGIST**

The Discipline of Internal Medicine in the Faculty of Medicine, Memorial University of Newfoundland and the Health Care Corporation, St. John's invites applications for a faculty position in the field of Neurology. Applicants must hold an MD degree, and FRCPC in Neurology (or equivalent), and be eligible for licensure in the province of Newfoundland.

The successful candidate will be expected to participate in the provision of neurology clinical care for the Health Care Corporation of St. John's and within the province, to teach undergraduate and graduate students, housestaff and to pursue research activities.

In accordance with Canadian Immigration requirements, this advertisement is directed to Canadian citizens and permanent residents of Canada. Memorial University is committed to employment equity.

Applicants should submit a curriculum vitae and name and addresses of three references to:

Dr. Alan Goodridge  
Chief, Division of Neurology  
Discipline of Medicine  
Faculty of Medicine  
Memorial University of Newfoundland  
The Health Sciences Centre  
300 Prince Philip Drive  
St. John's, Newfoundland, Canada  
A1B 3V6  
Telephone: (709) 737-6737 Fax: (709) 737-6656  
E-mail: agoodrid@morgan.ucs.mun.ca

## **NEUROSURGEON UNITED STATES SOUTHWEST**

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Please send CV and cover letter to:

Canadian Journal of Neurological Sciences  
ATTENTION: Neurosurgery Southwest  
P.O. Box 4220, Station C  
Calgary, Alberta, Canada T2T 5N1

# Is It Alzheimer Disease?

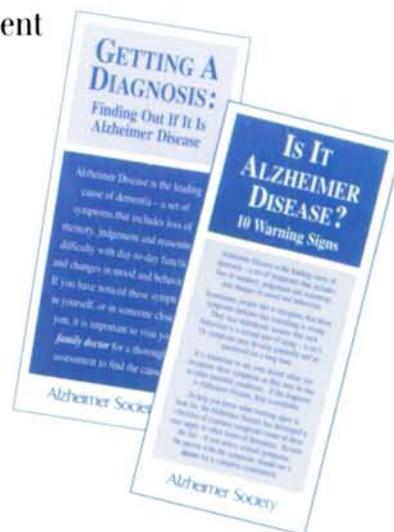
As the population ages and the prevalence of Alzheimer Disease increases, more Canadians are asking: “Is It Alzheimer Disease?” To help them recognize the symptoms, the Alzheimer Society has produced two brochures. One covers ten warning signs to look for, and encourages those who have several of the signs to see their doctor as soon as possible, in order to get a proper assessment.

The second brochure explains how the diagnosis is made, what to expect and how to prepare for the assessment, as the physician determines whether the condition is reversible or if it is, indeed Alzheimer Disease.

Early detection is important to allow the family time to plan for the future, discuss treatment options and find the support they’re going to need.

The Alzheimer Society recognizes that by working together with members of the health care team, we can keep our commitment of providing Help for Today, Hope for Tomorrow.

*For a copy of these brochures, contact your local Alzheimer Society or the Alzheimer Society of Canada at (416) 925-3552. Or visit our website at [www.alzheimer.ca](http://www.alzheimer.ca)*



## Alzheimer Society

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*Achieve and maintain good seizure control with a low incidence of concentration - dependent side effects.<sup>4</sup>*

One of the most commonly reported side effects with carbamazepine is drowsiness. This reaction usually occurs only during the initial phase of therapy<sup>4</sup> and can be minimized by using controlled-release carbamazepine (Pr Tegretol<sup>®</sup> CR).<sup>2</sup>

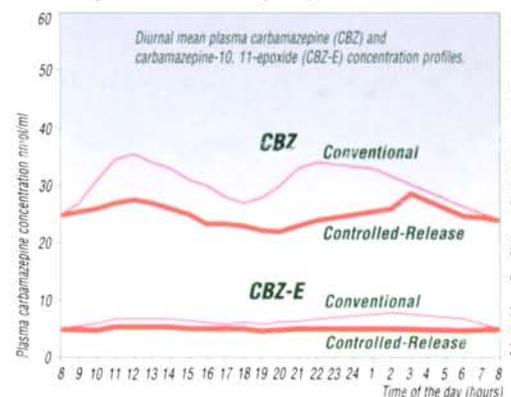
Carbamazepine is not effective in controlling absence, myoclonic or atonic seizures, and does not prevent the generalization of epileptic discharge. Moreover, exacerbation of seizures may occasionally occur in patients with atypical absences.<sup>4</sup>

\*See Product Monograph for important warnings prior to prescribing.

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Adapted from Egg-Olofsson O. J Child Neurol 1990; 5: 159-165

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- Equivalent and/or improved efficacy and tolerability.<sup>6</sup>
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