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Pr **Nimotop®**
I.V. / Capsules

THERAPEUTIC CLASSIFICATION

Adjunct in the Management of Subarachnoid Hemorrhage
Calcium Channel Blocking Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Delayed neurologic deterioration secondary to cerebral ischemic deficits is believed to be a major determinant of outcome in patients who survive their initial subarachnoid hemorrhage (SAH). NIMOTOP® (nimodipine) is a calcium channel blocker of the dihydropyridine group. It appears to have a more marked effect on the cerebral circulation than on the peripheral circulation. Since it acts on the vascular smooth muscle tone by modifying the contractile process which is dependent upon the movement of extracellular calcium into the cells during depolarization, it was tested in patients with SAH in an effort to improve the neurologic outcome in these patients. Clinical studies with nimodipine support its usefulness as an adjunct in the management of some patients with SAH from ruptured aneurysm by improving their neurologic outcome, particularly in Hunt and Hess grades 1 to 3 patients (see References: Clinical Studies 1-5).

A prospective, multicentre, randomized, double-blind placebo-controlled study was conducted with nimodipine in patients with traumatic head injuries in which traumatic subarachnoid hemorrhage (tSAH) was confirmed by computer tomography (CT) scanning. Within 12 hours of head injury, patients received either a sequential course of intravenous nimodipine (2 mg/hour) for 7-10 days followed by oral nimodipine (60 mg q4h) until day 21 or matching placebo. The majority of the patients (approximately 80%) in both nimodipine and placebo groups did not receive cytochrome P450 enzyme-inducing anticonvulsants (i.e. phenytoin or carbamazepine) as a concomitant medication. The incidence of unfavourable outcomes (death, severe disability, vegetative state as defined by the Glasgow Outcome Scale) at six months was 25% in nimodipine treated patients (n=60) vs 46% in placebo treated patients (p=0.02, n=61). The incidence of favourable outcomes (good recovery or moderate disability) in the nimodipine group was 75% vs 54% in placebo treated patients (p=0.02) (see Reference 7: Clinical Studies). Due to the small number of patients in this study, the results can only be considered to be preliminary.

The actual mechanism of the possible beneficial effect of nimodipine is, however, unknown. The original rationale for using nimodipine after SAH was to reduce cerebral arterial spasm, but available evidence indicates that nimodipine does not reduce the incidence or severity of cerebral spasm as seen on angiography.

Nimodipine is rapidly and completely absorbed after oral administration of the capsule. Because of a strong first-pass metabolism in the liver, only about 10% of the unchanged drug enters the systemic circulation. The drug is detectable in plasma 15 minutes after oral administration and peak levels occur within 90 minutes. The earlier elimination half-life is approximately 2 hours indicating the need for frequent dosing, although the terminal half-life is 8 to 9 hours. The absolute bioavailability of nimodipine capsule is approximately 13%. No change in the average maximum and minimum plasma concentration occurred after a repeated oral dosage regimen of three times a day for seven days in volunteers.

Nimodipine injection exhibits a terminal half-life of about 1 hour and a plasma clearance of approximately 125 L/hour.

Nimodipine is metabolized through the cytochrome P450 system, mainly by the CYP 3A4 isoenzyme.

Nimodipine is 99% bound to serum proteins. Approximately 80% is excreted in the bile and 20% by the kidney. The metabolites of nimodipine are believed to be either inactive or considerably less active than the parent compound.

INDICATIONS AND CLINICAL USE

NIMOTOP® (nimodipine) may be useful as an adjunct to improve the neurologic outcome following subarachnoid hemorrhage (SAH) from ruptured intracranial aneurysm.

CONTRAINDICATIONS

Hypersensitivity to nimodipine.

WARNINGS

Intestinal pseudo-obstruction (paralytic ileus) has been reported rarely. A causal relationship to NIMOTOP® (nimodipine) cannot be ruled out. In three cases, the condition responded to conservative management, but a fourth patient required surgical decompression of the extremely distended colon.

Management of patients with SAH - In view of the potential usefulness of NIMOTOP® (nimodipine) in improving the neurologic outcome in some patients with SAH, an early decision (whenever possible within 4 days of the ictus) should be made regarding the use of the drug. Since nimodipine is an adjunct in the management of SAH, an early assessment and a complete management program for the individual patient, including the possible indication of neurosurgery, are imperative.

Blood Pressure - NIMOTOP® (nimodipine) has the hemodynamic effects of a calcium channel blocker. In the course of clinical studies in patients with SAH, hypotension was reported in 6.6% of patients with Hunt and Hess grades III to V given 90 mg doses (n = 91), and in 7.5% of patients with grades I and II using 30 to 60 mg doses (n = 255). A fall in blood pressure requiring discontinuation of the drug was reported in 2.2% of the patients in the former group. Hypertensive patients may be more susceptible to a lowering of the blood pressure. Blood pressure should, nevertheless, always be carefully monitored during treatment with nimodipine. The use of nimodipine is, however, not generally recommended in patients taking antihypertensive drugs, including other calcium channel blockers, since it may potentiate the effects of these medications.

Simultaneous intravenous administration of beta blockers can lead to mutual potentiation of negative inotropic effects and even to decompensated heart failure.

Patients with Myocardial Infarction

Since there has not been a study of NIMOTOP® in acute myocardial infarction reported, similar effects of NIMOTOP® to that of immediate-release nifedipine cannot be excluded in acute myocardial infarction. *Immediate-release nifedipine is contraindicated in acute myocardial infarction.*

Patients with Unstable Angina

Some clinical trials have shown that treatment with the immediate-release formulation of the dihydropyridine, nifedipine, in this setting increases the risk of myocardial infarction and recurrent ischemia.

Cerebral Edema or Severely Raised Intracranial Pressure -

NIMOTOP® (nimodipine) should be used only with great caution under these conditions.

Use in Pregnancy - NIMOTOP® (nimodipine) has been shown to have a teratogenic effect in rabbits and to be embryotoxic, causing resorption, stunted growth, and higher incidence of skeletal variations, in rats (for details see Toxicology). The safety of nimodipine with respect to adverse effects on human fetal development has not been established. Nimodipine should, therefore, not be used during pregnancy unless the potential benefits are considered to justify the potential risk to the fetus.

PRECAUTIONS

Use in Nursing Mothers - Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma, although it is not known whether the drug is excreted in human milk. Nursing mothers are advised not to breast feed their babies when taking the drug.

Pediatric Use - The safety and effectiveness of nimodipine in children have not been established.

Hepatic Dysfunction - The metabolism of nimodipine is decreased in patients with impaired hepatic function. Such patients should be given lower doses of the drug and their blood pressure and pulse should be closely monitored.

Renal Dysfunction - There are insufficient data on patients with impaired renal function. Patients with known renal disease and/or receiving nephrotoxic drugs should have renal function closely monitored during intravenous treatment with nimodipine.

Administration with Food - A pharmacokinetic study has shown that the bioavailability of nimodipine capsule is reduced in the presence of a American standard breakfast to about two thirds its value in the fasted condition. Patients should be advised to be consistent in the timing of nimodipine capsule administration with or without food.

Interaction with Grapefruit Juice: Published data indicate that through inhibition of cytochrome P-450 , grapefruit juice can increase plasma levles and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Therefore, consumption of grapefruit juice prior to or during treatment with nimodipine should be avoided.

Drug Interactions:

General: As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P-450 system, mainly via the CYP 3A4 isoenzyme. Coadministration of nimodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered nimodipine to maintain optimum therapeutic blood levels.

Drugs known to be inhibitors of the cytochrome P-450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.

Drugs known to be inducers of the cytochrome P-450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P-450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.

Cimetidine - A pharmacokinetic study has shown that concurrent administration of cimetidine and oral nimodipine results in an almost doubling of the area under the nimodipine plasma concentration curve and about a 50% increase in the peak nimodipine plasma concentration. Patients receiving the two drugs concomitantly should be watched carefully for the possible exaggeration of the effects of nimodipine. It may be necessary to adjust the dosage of nimodipine.

Warfarin - An interaction study with nimodipine and warfarin has shown no clinically significant interactions between these drugs.

Diazepam - An interaction study with nimodipine and diazepam has shown no clinically significant interactions between these drugs.

Antiepileptic Drugs - A pharmacokinetic study in epileptic patients receiving long-term treatment has shown that concurrent administration of oral nimodipine and antiepileptic drugs (phenobarbital, phenytoin and/or carbamazepine) reduces the bioavailability of nimodipine by about 80%. In those patients receiving sodium valproate and oral nimodipine, the bioavailability of the nimodipine increased by about 50%. Therefore, the concomitant use of oral nimodipine and these antiepileptic drugs requires close monitoring and appropriate adjustment of the dosage of nimodipine.

Rifampicin - From experience with the calcium antagonist nifedipine it is to be expected that rifampicin accelerates the metabolism of NIMOTOP® capsules due to enzyme induction. Thus, efficacy of NIMOTOP® capsules could be reduced when concomitantly administered with rifampicin.

Ethanol - Since ethanol is a solvent in nimodipine for injection, interactions with alcohol-incompatible drugs may occur.

ADVERSE EVENTS

NIMOTOP® (nimodipine capsule)

The most commonly reported adverse events in double-blind clinical studies for patients receiving 60 mg or 90 mg of nimodipine capsule every four hours (n = 666) were decreased blood pressure (5.0%), nausea (1.1%), bradycardia (0.9%), rash (0.8%), edema (0.6%), and diarrhoea (0.5%). Adverse events reported with a frequency greater than 1% are as follows (by dose):

	No. of Patients (%)					
	Nimodipine (dose q4h)					Placebo
Sign/Symptom	0.35 mg/kg (n = 82)	30 mg (n = 71)	60 mg (n = 494)	90 mg (n = 172)	120 mg (n = 4)	(n = 479)
Decreased Blood Pressure	1 (1.2)	0	19 (3.8)	14 (8.1)	2 (50.0)	6 (1.2)
Abnormal liver Function Test	1(1.2)	0	2 (0.4)	1(0.6)	0	7 (1.5)
Edema	0	0	2 (0.4)	2 (1.2)	0	3 (0.6)
Diarrhea	0	3 (4.2)	0	3 (1.7)	0	3 (0.6)
Rash	2 (2.4)	0	3 (0.6)	2 (1.2)	0	3 (0.6)
Headache	0	1 (1.4)	6 (1.2)	0	0	1 (0.2)
Gastrointestinal Symptoms	2 (2.4)	0	0	2 (1.2)	0	0
Nausea	1 (1.2)	1 (1.4)	6 (1.2)	1 (0.6)	0	0
Dyspnea	1 (1.2)	0	0	0	0	0
EKG Abnormalities	0	1 (1.4)	0	1 (0.6)	0	0
Tachycardia	0	1 (1.4)	0	0	0	0
Bradycardia	0	0	5 (1.0)	1 (0.6)	0	0
Muscle Pain/Cramp	0	1 (1.4)	1 (0.2)	1 (0.6)	0	0
Acne	0	1 (1.4)	0	0	0	0
Depression	0	1 (1.4)	0	0	0	0

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Adverse events for the 60 mg and 90 mg q4h doses with an incidence of less than 1% at all dosages were hepatitis, itching, diaphoresis, GI hemorrhage, vomiting, thrombocytopenia, anemia, jaundice, hematoma, hyponatremia, decreased platelet count, disseminated intravascular coagulation, deep vein thrombosis, palpitation, hypertension, congestive heart failure, light headedness, dizziness, rebound vasospasm, neurological deterioration, wheezing, and phenytoin toxicity.

In severely ill patients, there was overall increased mortality in the nimodipine group using the 90 mg q4h dose as compared to placebo.

Laboratory Values
Isolated cases of non-fasting elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet counts (0.3%), elevated BUN (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported.

NIMOTOP® I.V. (nimodipine injection)
The most commonly reported adverse events in patients receiving nimodipine injection (n = 1306) classified as possibly/probably related to the drug were predominantly mild to moderate decreases in blood pressure (3.4%), abnormal liver function test (1.9%), headache (1.2%), and extrasystoles (0.6%). Discontinuation of therapy was required in 21 patients (1.6%) because of adverse events.

Other adverse events reported were hypertension (0.3%), hyperglycaemia (0.3%), diaphoresis (0.2%), thrombophlebitis (0.2%), and vomiting (0.2%). Adverse events with an incidence of less than 0.1% were agitation, hypernatemia, hypokalemia, injection site pain, paraesthesia, vasodilation, anxiety, asthma, depression, diabetes mellitus, dizziness, atrial fibrillation, heart arrest, laboratory test abnormalities (increased SGOT/AST and SGPT/ALT), liver damage, abdominal pain, phlebitis, and rash. Electrocardiographic (ECG) abnormalities, such as bradycardia (1.5%), extrasystoles (0.8%), tachycardia (0.6%), and arrhythmias (0.2%), were reported in 39/1306 patients (3.0%). Since the association of ECG abnormalities with SAH is well known, it is likely that some or all of these abnormalities occurred as a result of the natural course of the disease due to stimulation of the parasympathetic/sympathetic system by hemorrhage.

In one study, there were more deaths caused by re-bleeding in the nimodipine group (8 patients) compared to 4 deaths in the placebo group.

Adverse events known to be associated with calcium channel blockers should be appropriately monitored.

DOSAGE AND ADMINISTRATION
For the management of neurological deficits following subarachnoid hemorrhage (SAH), NIMOTOP® (nimodipine) therapy should commence as soon as possible or within 4 days of the diagnosis of SAH. Sequential administration (see below) provides an opportunity to obtain therapeutic concentrations as rapidly as possible and/or to provide the drug to patients unable to swallow.

Sequential Administration
NIMOTOP® I.V. (nimodipine injection) must be administered by co-infusion via three-way stop cock to the central catheter. The initial dosage is 5 mL NIMOTOP® I.V. (nimodipine injection) (equivalent to 1 mg nimodipine) per hour infused continuously for the first 2 hours; this is approximately 15 µg/kg body weight per hour. Co-infusion solution must be administered at a rate of 20 mL per hour with this initial dosage. If this dosage is tolerated, particularly if there is no severe reduction in blood pressure, the dosage should then be increased to 10 mL NIMOTOP® I.V. solution per hour with a corresponding increase in rate of co-infusion solution to 40 mL per hour. Infusion should continue for 7 to 10 days after diagnosis of SAH.

Rates of administration of recommended co-infusion solutions must be followed due to the possibility of crystal formation as seen in "in vitro" tests with NIMOTOP® I.V. at higher dilutions.

Intravenous lines must be changed every 24 hours.

Thereafter, the recommended dosage of NIMOTOP® (nimodipine capsule) is 60 mg (2 capsules of 30 mg) administered orally every 4 hours up to 21 days after diagnosis of SAH. Doses of up to 90 mg every 4 hours have been used in some patients, although the safety of higher doses in severely ill patients has not been well established.

Patients weighing considerably less than 70 kg or those having labile blood pressure should receive an initial dosage of 2.5 mL NIMOTOP® I.V. per hour with corresponding reduction in rate of co-infusion solution and, if at all possible, the dosage should not be raised above 5 mL NIMOTOP® I.V. per hour.

Patients with hepatic insufficiency may have substantially reduced clearance and approximately doubled maximum plasma concentration; dosage should be reduced to 2.5 mL NIMOTOP® I.V. per hour and/or one 30 mg NIMOTOP® capsule every 4 hours in these patients.

NIMOTOP® may be used during anaesthesia or surgical procedures. In the event of surgical intervention, administration of NIMOTOP® should be continued, with dosages as above, for at least 5 days in the case of NIMOTOP® I.V. to complete the 21 day period in the case of NIMOTOP® capsules.

Due to the possibility of hydrolysis in high alkaline pH, alkaline mixtures should not be given for 2 hours before or after administering NIMOTOP® capsules.

Drug effects should be carefully monitored in all patients, particularly if higher doses are used.

For further information, especially regarding NIMOTOP® I.V., see Pharmaceutical Information.

Oral Administration
The recommended dosage of NIMOTOP® (nimodipine capsule) is 60 mg (2 capsules of 30 mg) administered orally every 4 hours for 21 consecutive days after diagnosis of SAH. Doses of up to 90 mg every 4 hours have been used in some patients, although the safety of higher doses in severely ill patients has not been well established.

If the patient is unable to swallow, the capsule contents may be aspirated into a syringe, emptied into the patient's in-situ naso-gastric tube and washed down the tube with 30 mL normal saline.

Patients with hepatic insufficiency may have substantially reduced clearance and approximately doubled maximum plasma concentration; accordingly, dosage should be reduced to one 30 mg NIMOTOP® capsule every 4 hours in these patients.

NIMOTOP® may be used during anaesthesia or surgical procedures. In the event of surgical intervention, administration of NIMOTOP® should be continued, with dosages as above, to complete the 21 day period.

Due to the possibility of hydrolysis in high alkaline pH, alkaline mixtures should not be given for 2 hours before or after administering NIMOTOP® capsules.

Drug effects should be carefully monitored in all patients, particularly if higher doses are used.

PARENTERAL PRODUCTS

Continuous intravenous infusion: NIMOTOP® I.V. (nimodipine injection) should be administered by means of an infusion pump in the bypass together with the recommended infusion solution via three-way stop cock to the central catheter.

The ratio of NIMOTOP® solution to concomitant infusion solution should be maintained at 1 to 4 by volume to ensure appropriate dilution of NIMOTOP® I.V. This avoids the possibility of precipitating NIMOTOP® with resulting crystal formation seen in "in-vitro tests" at higher dilutions.

The following intravenous infusion fluids found to be compatible at recommended administration rates:
* Glucose 5%
* Ringer's Lactate
* Dextran 40
* Saline

Other common infusion solutions must not be used.

Intravenous lines must be changed every 24 hours.

Since the nimodipine is absorbed by polyvinylchloride (PVC) only polyethylene (PE) infusion tubing, and polyethylene (PE) or polypropylene (PPE) extensions, taps, connectors may be used.

Nimodipine is slightly light-sensitive such that its use in direct sunlight should be avoided. No special protective measures need to be taken for up to 10 hours if NIMOTOP® I.V. is being administered in diffuse daylight or in artificial light.

The simultaneous use of nimodipine with other calcium antagonists, beta-receptor-blockers or methyl dopa should be avoided, especially during continuous intravenous infusion of the drug.

NIMOTOP® I.V. contains 20% ethanol and 17% polyethylene glycol 400; this should be taken into account during treatment.

NIMOTOP® I.V. must not be added to an infusion bag or bottle.

NIMOTOP® Capsules and NIMOTOP® I.V. may be used during anaesthesia or surgical procedures.

AVAILABILITY OF DOSAGE FORMS

Nimodipine Capsules
Each ivory coloured, soft gelatin NIMOTOP® (nimodipine) capsule is imprinted with the word NIMOTOP and contains 30 mg of nimodipine. The 30 mg capsules are individually packed in foil and supplied in strips of 100 capsules per carton.

Nimodipine Injection
250 mL Bottle: Each package contains 1 X 250 mL (0.2 mg/mL solution) brown glass bottle.

Note: Store in original manufacturer's containers. Nimodipine is a Schedule F drug.

COMPLETE PRODUCT MONOGRAPH AVAILABLE UPON REQUEST

REFERENCES:

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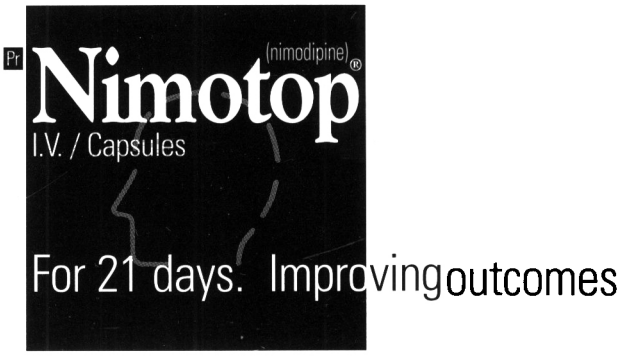
2. Harders A. et al. Traumatic subarachnoid hemorrhage and its treatment with nimodipine. *J Neurosurg.* 1996; 85: 82-89.

Bayer Inc.
Healthcare Division
77 Belfield Road
Toronto, Ontario
M9W 1G6

PAAB MEMBER PMAC

Healthcare Division



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Intermediate Prescribing Information

P TEGRETOL®

Tablets
(Carbamazepine)
Suspension (100 mg/tsp)

THERAPEUTIC CLASSIFICATION

A. Anticonvulsant
B. For Symptomatic Relief of Trigeminal Neuralgia
C. 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 LYELL 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_1 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 hirsuitism 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_4, T_4, T_3, and increased TSH, usually without clinical manifestations), disturbances of bone metabolism (decrease in plasma calcium and 25-OH-calciferol), leading in isolated cases to osteomalacia, as well as reports of elevated levels of cholesterol, including HDL cholesterol and triglycerides.
Musculoskeletal system: Isolated cases: arthralgia, muscle pain or cramp.
Respiratory: Isolated cases: pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.
Hypersensitivity reactions: 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.

DOSAGE AND ADMINISTRATION

Use in Epilepsy (See INDICATIONS): TEGRETOL may be used alone or with other anticonvulsants. A low initial daily dosage of TEGRETOL with a gradual increase in dosage adjusted to the needs of the individual patient, is advised.
TEGRETOL 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 quadrisected 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

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NOVARTIS

Novartis Pharmaceuticals Canada Inc.
Dorval, Québec H9R 4P5

PAAB CCPP PMAC ACIM

TEG-98-03-4654E

See pages obc, A3

Recombinant human interferon beta-1a

11 µg (3MIU), 44 µg (12MIU) lyophilized powder for injection
22 µg (6MIU)/0.5mL, 44 µg (12MIU)/0.5mL liquid formulation for injection

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTIONS AND CLINICAL PHARMACOLOGY

Description: Rebif® (Interferon beta-1a) is a purified, sterile glycoprotein product produced by recombinant DNA techniques and formulated for use by injection. The active ingredient of Rebif® is produced by genetically engineered Chinese Hamster Ovary (CHO) cells. Interferon beta-1a is a highly purified glycoprotein that has 166 amino acids and an approximate molecular weight of 22,500 daltons. It contains a single N-linked carbohydrate moiety attached to Asn-80 similar to that of natural human Interferon beta. The specific activity of Rebif® is approximately 0.27 million international units (MIU)/mcg Interferon beta-1a. The unit measurement is derived by comparing the antiviral activity of the product to an in-house natural hIFN-ß NIH standard that is obtained from human fibroblasts (BILS 11), which has been calibrated against the NIH natural hIFN-ß standard (GB 23-902-531). 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, gamma. Interferon beta, Interferon alpha and Interferon gamma have overlapping yet distinct biologic activities.

Interferon beta-1a acts through various mechanisms:

- Immunomodulation through the induction of cell membrane components of the major histocompatibility complex i.e., MHC Class I antigens, an increase in natural killer (NK) cell activity, and an inhibition of IFN-γ induced MHC Class II antigen expression, as well as a sustained reduction in TNF level.
- Antiviral effect through the induction of proteins like 2'-5' oligoadenylate synthetase and p78.
- Antiproliferative effect through direct cytostatic activity and indirect through antitumoral immune response enhancement.

The mechanism of action of Rebif® in relapsing-remitting multiple sclerosis is still under investigation.

Relapsing-Remitting Multiple Sclerosis

Two pivotal studies, including a total of 628 patients, evaluated the long-term safety and efficacy of Rebif® when administered subcutaneously three times weekly to relapsing-remitting multiple sclerosis patients. The results indicate that Rebif® alters the natural course of relapsing-remitting multiple sclerosis. Efficacy was demonstrated with respect to the 3 major aspects of this disease: disability (patients EDSS 0-5), exacerbations, and burden of disease and activity as measured by MRI scans.

PRISMS STUDY

In the larger trial, a total of 560 patients diagnosed with clinically definite or laboratory-supported relapsing-remitting multiple sclerosis EDSS 0-5 with at least a 1-year history before study entry, were enrolled and randomized to the 3 treatments (placebo, 22 µg (6MIU) Rebif®, or 44 µg (12MIU) Rebif®) in a ratio of 1:1:1. About 90% of patients completed the 2 years of treatment, and very few patients withdrew from the study due to adverse events.

The main criteria for inclusion were:

- history of 2 or more acute exacerbations in the 2 years prior to study entry
- no previous systemic treatment with interferons
- no treatment with corticosteroids or ACTH in the 2 months preceding study entry
- no exacerbation in the 8 weeks prior to study entry.

Patients were evaluated at 3-month periods, during exacerbations and coinciding with MRI scanning. Each patient underwent cranial proton density/T_2-weighted (PD/T2) MRI scans at baseline and every 6 months during the study. A subset of patients underwent PD/T2 and T_1-weighted (T1) Gd-MRI scans one month before the start of treatment, at baseline and then monthly until the end of the first 9 months of treatment. Of those, another subset of 39 continued with the monthly scans throughout the 24 month treatment period.

This study demonstrated that Rebif® at a total dose of 66 or 132 µg weekly, significantly improved all 3 major outcomes, including exacerbation rate, disease activity and burden of disease as measured by MRI scanning and progression of disability. In addition, the study showed that Rebif® is effective in delaying the progression in disability in patients with an EDSS of 4.0 or higher who are known to progress more rapidly. Also, the drug reduced the requirements for steroids to treat multiple sclerosis and, at 132 µg weekly Rebif® reduced the numberof hospitalizations for multiple sclerosis.

Effect on exacerbation

Efficacy parameters	Treatment Groups			p-value	
	Placebo	Rebif® 66 µg/wk	Rebif® 132 µg/wk	Rebif® 66 µg/wk vs placebo	Rebif® 132 µg/wk vs placebo
Mean # exacerbations over the 2 year study	2.56	1.82	1.73	0.0002	<0.0001
Percentage of exacerbation-free patients at 2 years	14.6%	25.6%	32.0%	0.0140	<0.0001
Median time to first exacerbation (months)	4.5	7.6	9.6	0.0008	<0.0001
Median time to second exacerbation (months)	15.0	23.4	>24*	0.0020	<0.0001
Mean # of moderate and severe exacerbations during the 2 year period	0.99	0.71	0.62	0.0025	0.0003

* Median time to second exacerbation not reached in 132 µg/week dose group.

The results after one year of treatment were significant.

Effect on time to first progression in disability

Efficacy parameters	Treatment Groups			p-value	
	Placebo	Rebif® 66 µg/wk	Rebif® 132 µg/wk	Rebif® 66 µg/wk vs placebo	Rebif® 132 µg/wk vs placebo
Time to confirmed progression in disability, first quartile (months)	11.8	18.2	21.0	0.0398	0.0136
Median change in EDSS score at 2 years	0.5	0	0	0.0263	0.0519

Effect on multiple sclerosis pathology as detected by MRI scans

Efficacy parameters	Treatment Groups			p-value	
	Placebo	Rebif® 66 µg/wk	Rebif® 132 µg/wk	Rebif® 66 µg/wk vs placebo	Rebif® 132 µg/wk vs placebo
Burden of disease (BOD) Median % change	+10.9	-1.2	-3.8	<0.0001	<0.0001

MRI activity					
All patients					
Number of active lesions (per 6 months)	2.25	0.75	0.5	<0.0001	<0.0001
% active scans	75%	50%	25%	<0.0001	<0.0001
Patients with monthly MRIs (9 months)					
Number active lesions (per month)	0.88	0.17	0.11	<0.0001	<0.0001
% active scans	44%	12.5%	11%	<0.0001	<0.0001
Patients with monthly MRIs throughout the study (2 years)					
Number active lesions	0.9	0.1	0.02	0.0905	0.0105
% active scans	52%	10%	2%	0.0920	0.0117

Requirement for steroids: The proportion of patients requiring steroids for MS (excluding non-MS indications) was higher in the placebo group (more than 50%) than in either of the 2 Rebif® groups (around 40% in each group).

Hospitalisation for multiple sclerosis: The observed mean numbers of hospitalisations for MS in the Rebif® 66 and 132 µg weekly groups represented reductions of 21% and 48%, respectively, from that in the placebo group.

Immunogenicity: Antibodies to IFN-beta were tested in all patients pre-entry, and at Months 6, 12, 18 and 24. The results of testing for the presence of neutralizing antibodies (NAb) are shown below.

Percentage of patients positive for neutralizing antibodies

Placebo	Rebif® 66 µg weekly	Rebif® 132 µg weekly
0%	24%	12.5%

Due to concern about the potential impact of neutralizing antibody formation on efficacy, exacerbation counts (primary endpoint) were analysed according to patients' neutralizing antibody status. Over the 2 years of the study, there was no trend to a higher exacerbation rate in the neutralizing antibody-positive groups compared to the neutralizing antibody-negative groups. There is no clear indication that the development of serum neutralising antibodies affected either safety or efficacy in either of the Rebif® groups.

Cohort of patients with high baseline EDSS (baseline EDSS >3.5)

Additional analyses were conducted in order to study the efficacy of Rebif® in populations of patients with adverse predictive outcome factors, who were likely to be at higher risk for progression in disability. The primary predictive factor examined was baseline EDSS >3.5. Patients in this cohort have a more severe degree of disability and are at higher risk for progression than those with lower EDSS: natural history studies have shown that patients at EDSS levels of 4.0 to 5.0 spend less time at these EDSS levels than at lower levels of disability.

Treatment with Rebif® at both doses significantly reduced the mean exacerbation count per patient compared to placebo treatment. Progression in this group of patients is of particular concern, as it involves development of difficulty in ambulation. The 132 µg weekly dose significantly prolonged time to confirmed progression whereas the 66 µg weekly dose did not. Both doses of Rebif® significantly affected percent change from baseline in MRI burden of disease in the high-EDSS cohort, and the 132 µg weekly dose significantly reduced the number of T2 active lesions in this population. The efficacy results in this cohort of patients with established disability confirms that the 132 µg weekly dose has a marked effect on progression in disability and the underlying pathology of the disease.

Effect on exacerbation (High-EDSS cohort)

Efficacy parameters	Placebo	Rebif® 66 µg / week	Rebif® 132 µg / week
Mean # exacerbations	3.07	1.83	1.22
# and % of exacerbation-free patients	2 (7%)	7 (20%)	10 (32%)
p-value* (Rebif® vs placebo)		p=0.0121	p=0.0002

*Log-linear model

Progression in disability by one point on the EDSS (High-EDSS cohort)

Treatment Group	% of progressors*	Time to Progression		
		# patients	Median (days)	Q1 (days)
Placebo	56%	28	638	216
Rebif® 66 µg weekly	41%	35	not reached	226
Rebif® 132 µg weekly	27%	31	not reached	638

*excludes patients lost to follow-up without progression

Progression in disability: statistical comparisons

Test	Group Comparison	p-value
Log-rank test	66 µg weekly vs placebo	p=0.4465
	132 µg weekly vs placebo	p=0.0481

MRI Burden of Disease: % Change (High-EDSS cohort)

	Placebo	Rebif® 66µg / week	Rebif® 132 µg / week
Burden of disease - Median % change	5.3	-2.3	-6.9
Burden of disease - Mean % change	12.2	13.6	0.7
p-value* (Rebif® vs placebo)		p=0.0146	p=0.0287

*ANOVA on the ranks

Number of T2 Active Lesions (High-EDSS cohort)

	Number of T2 Active Lesions		
Treatment Group	Median	Mean	p-value*
Placebo	1.9	2.6	
Rebif® 66 µg weekly	0.9	1.7	Rebif® 66 µg vs placebo: p=0.0612
Rebif® 132 µg weekly	0.5	0.9	Rebif® 132 µg vs placebo: p=0.0042

*ANOVA on the ranks

CROSS-OVER STUDY

The other study was an open cross-over design, with MRI evaluations conducted in a blinded fashion. Enrolled in this study were 68 patients between the ages of 15 and 45 years, with clinically definite and/or laboratory supported relapsing-remitting MS for up to 10 years in duration. The main inclusion criteria included:

- at least 2 relapses in the previous 2 years
- EDSS score between 1-5
- no corticosteroid or plasmapheresis treatments or administration of gamma globulins within the 3 months prior to study
- no immunomodulating or immunosuppressive therapy for the 6 months prior to the study
- absence of HBsAg and HIV antibodies.

Once enrolled, patients remained under clinical observation for 6 months with assessments of their neurological status and other parameters, and extensive monitoring of exacerbations. Patients were then randomized to treatment with either 11 µg (3MIU) (n=35) or 33 µg (9MIU) (n=33) of Rebif®, self-administered subcutaneously three times per week. The total dose was therefore 33 or 99 µg weekly.

Six-months observation vs six-months treatment

Treatment with Rebif® at both doses used in this study, achieved a statistically significant reduction in both the MRI evidence of MS activity in the brain and the clinical relapse rate versus the corresponding observation periods. This pattern of improvement was also reflected in additional MRI measures. In the biannual T2-weighted scans, a reduction in the mean number of new lesions and in the mean number of enlarging lesions was demonstrated.

	Dosage	Observation period	Treatment period	Reduction %	p value
Exacerbation rate / patient	33 µg weekly 99 µg weekly	0.914 0.788	0.429 0.242	53% 69%	p=0.007 p=0.003
# exacerbation-free patients	33 µg weekly 99 µg weekly	15/35 17/33	23/35 26/33		p=0.059 p=0.02
# of monthly lesions / patient	33 µg weekly 99 µg weekly	3.47 2.42	1.77 0.86	49% 64%	p<0.001 p<0.001
Volume of lesions / patient	33 µg weekly 99 µg weekly	557 mm^3 379 mm^3	220 mm^3 100 mm^3	61% 73%	p<0.001 p<0.001
Total mean # new T2 lesions	33 µg weekly 99 µg weekly	5.67 3.93	1.97 1.18	65% 70%	p<0.001 p<0.001
Total mean # of T2 enlarged lesions	33 µg weekly 99 µg weekly	2.26 1.81	0.97 0.45	57% 75%	p=0.001 p=0.004

Two-year results

At the end of this study, 62 patients continued treatment for a further 18 months. Each of these patients continued to receive the dose to which they were randomized. Validation of the results of the 2 year treatment period is ongoing, however, the results from the continuation of treatment at both doses demonstrate that Rebif® maintained its dose-dependent effect in reducing the relapse rate and the brain lesion volume detected by T2 weight MRI scans compared to the observation period, which corroborates the findings of the longer, placebo-controlled study.

Condyloma acuminatum

The results from four double-blind, placebo-controlled studies, including 349 patients (aged 17-62), each reveal that Rebif®, when injected intralesionally at a dose of 3.67 µg (1MIU)/lesion 3 times per week for 3 weeks, is efficacious in the treatment of condyloma acuminatum in men and women. This efficacy is evidenced by both the induction of complete disappearance of lesions as well as the reduction in the area of lesions. The majority of treated patients in these studies had recurrent warts that had failed previous treatments. The number of lesions treated per patient was between 3 and 8, as stated in the summary table below.

Study	# patients/ % previously treated	# lesions treated	Treatment	Results
1	25/80%	3	0.12 or 3.67 µg of Rebif®/lesion, or placebo, 3 times per week for 3 weeks	Rebif® at a dose of 3.67 µg/lesion is efficacious, as evidenced by the induction of complete disappearance of lesions and the reduction in the area of lesions. The 0.12 µg dose of Rebif® did not show advantages over placebo treatment.
2	100/72%	6	3.67 µg of Rebif®/lesion, or placebo, 3 times per week for 3 weeks	There was a significant increase in Major Response rate at Month 3 in patients who received Rebif® vs placebo (p<0.0001). The Complete Response rate at Month 3 was significantly in favour of patients who received Rebif® (p≤0.0162).
3	100/52%	8	3.67 µg of Rebif®/lesion, or placebo, 3 times per week for 3 weeks	For the Israeli centre, the results from Week 6, supported by those from study Day 19 demonstrate the efficacy of Rebif®. Because of the study design and the non-compliance with the study protocol at the German centre, indications of efficacy were not supported by the results from the analyses where patients from both centres were pooled.
4	124/72%	6	3.67 µg of Rebif®/lesion, or placebo, 3 times per week for 3 weeks	This study showed that Rebif® was effective with the proportion of patients achieving a complete or Partial Response at Day 19 and Week 6, and a significant reduction in the total area of lesions on Day 19 and Week 6. Because of the study design, the effect of Rebif® at Month 3 was not demonstrated.

Immunogenicity: The determination of the presence of antibodies to human IFN-ß was performed in all 4 studies. A total of four patients had anti beta-interferon antibodies at pre-entry, and 6 other patients had at least a positive result for total binding antibodies at some point during the study. Antibodies were of low titer, and none of the antibodies were neutralizing to human IFN-ß biological activity.

INDICATIONS AND CLINICAL USE

Multiple Sclerosis: Rebif® (Interferon beta-1a) is indicated for the treatment of relapsing-remitting multiple sclerosis in patients with an EDSS between 0 and 5.0, to reduce the number and severity of clinical exacerbations, slow the progression of physical disability, reduce the requirement for steroids, and reduce the number of hospitalizations for treatment of multiple sclerosis. The efficacy has been confirmed by T1-Gd enhanced and T2 (burden of disease) MRI evaluations. Evidence of efficacy beyond 2 years is not known since the primary evidence of efficacy derives from 2-year trials. **Condyloma acuminatum:** Rebif® is best suited for the patient who has less than nine lesions, and who has failed several prior treatments. In the case of patients with nine or more lesions, if the first Rebif® treatment is successful, the remaining lesions could be treated with a second course of Rebif® therapy. Rebif® should also be considered for the treatment of condyloma acuminatum in patients for whom the side-effects from other treatments, e.g., scarring, are of concern. While not all patients who were treated with Rebif® attained a complete response, patients whose lesions decreased in size and had at least a partial response may have also benefitted from treatment because lesion shrinkage may facilitate subsequent management with other therapies, as has been reported with IFNα.

CONTRAINDICATIONS

Rebif® (Interferon beta-1a) is contraindicated in patients with a known hypersensitivity to natural or recombinant interferon beta, albumin (human), or any other component of the formulation.

WARNINGS

Rebif® (Interferon beta-1a) should be used under the supervision of a physician.

Relapsing-Remitting Multiple Sclerosis: Depression and suicidal ideation are known to occur at an increased frequency in the multiple sclerosis population. The use of Rebif® has not been associated with an increase in the incidence and/or severity of depression, or with an increased incidence of suicide attempts or suicide. In the relapsing-remitting multiple sclerosis study, a similar incidence of depression was seen in the placebo-treated group and in the two Rebif® patient groups. Nevertheless, patients with depression should be closely monitored for signs of significant worsening of depression or suicidal ideation.

The first injection should be performed under the supervision of an appropriately qualified health care professional.

Condyloma All injections should be administered by a qualified health care professional.

PRECAUTIONS

General Patients should be informed of the most common adverse events associated with interferon beta administration, including symptoms of the flu-like syndrome (see Adverse Reactions). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment.

Serum neutralising antibodies against Rebif® (interferon beta-1a) may develop. The precise incidence and clinical significance of antibodies is as yet uncertain.

Intralesional injections can be painful to some patients treated for condyloma acuminata. In such cases an anaesthetic cream such as lidocaine-prilocaine can be used.

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Pregnancy and Lactation Rebif® should not be administered in case of pregnancy and lactation. There are no studies of interferon beta-1a in pregnant women. At high doses in monkeys, abortifacient effects were observed with other interferons. Fertile women receiving Rebif® should take appropriate contraceptive measures. Patients planning for pregnancy and those becoming pregnant should be informed of the potential hazards of interferons to the foetus and Rebif® should be discontinued. It is not known whether Rebif® is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made either to discontinue nursing or to discontinue Rebif® therapy.

Pediatric use

There is no experience with Rebif® in children under 16 years of age with multiple sclerosis or condyloma and therefore Rebif® should not be used in this population.

Patients with Special Diseases and Conditions

Caution should be used and close monitoring considered when administering Rebif® to patients with severe renal and hepatic failure, patients with severe myelosuppression, and depressive patients.

Drug Interaction

No formal drug interaction studies have been conducted with Rebif® in humans. Interferons have been reported to reduce the activity of hepatic cytochrome p450-dependent enzymes in humans and animals. Caution should be exercised when administering Rebif® in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome p450 system for clearance, e.g. antiepileptics and some classes of antidepressants. The interaction of Rebif® with corticosteroids or ACTH has not been studied systematically. Clinical studies indicate that multiple sclerosis patients can receive Rebif® and corticosteroids or ACTH during relapses. Rebif® should not be mixed with other drugs in the same syringe.

Laboratory Tests

Relapsing-Remitting Multiple Sclerosis: Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete and differential white blood cell counts, platelet counts and blood chemistries, including liver function tests are recommended during Rebif® therapy.

Condyloma acuminata: Same as relapsing remitting multiple sclerosis but tend not to be as severe because of dose and length of treatment.

Information to be provided to the patient

Flu-like symptoms (fever, headache, chills, muscle aches) are not uncommon following initiation of therapy with Rebif®. Acetaminophen may be used for relief of flu-like symptoms. Patients should contact their physician or pharmacist if they experience any undesirable effects.

Depression may occur in patients with relapsing-remitting multiple sclerosis and may occur while patients are taking Rebif®. Patients should be asked to contact their physician should they feel depressed.

Patients should be advised not to stop or modify their treatment unless instructed by their physician.

Instruction on self-injection technique and procedures: patients treated for relapsing-remitting multiple sclerosis should be instructed in the use of aseptic technique when administering Rebif®. Appropriate instruction for reconstitution of Rebif® and self-injection should be given including careful review of the Rebif® patient leaflet. The first injection should be performed under the supervision of an appropriately qualified health care professional. Injection sites should be rotated at each injection. Injections may be given prior to bedtime as this may lessen the perception of side effects. Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture resistant container for disposal of used needles and syringes should be supplied to the patient along with instructions for safe disposal of full containers.

In the controlled MS trial reported injection site reactions were commonly reported by patients at one or more times during therapy. In general, they did not require discontinuation of therapy, but 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 re-evaluated.

ADVERSE REACTIONS

Multiple Sclerosis

As with other interferon preparations, flu-like symptoms are not uncommon. The use of interferon beta may cause flu-like syndrome, asthenia, pyrexia, chills, arthralgia, myalgia, headache, and injection site reactions.

Less frequent adverse reactions include cold sores, stuffy nose, light headedness, mucosal irritation, haematological disorders (leukopenia, lymphopenia, granulocytopenia), and alterations in liver function tests such as elevated SGOT and SGPT. These effects are usually mild and reversible. Tachyphylaxis with respect to most side-effects is well recognised. Fever and flu-like symptoms can be treated with acetaminophen. Depending on the severity and persistence of the side-effects, the dose may be lowered or temporarily interrupted, at the discretion of the physician. Most injection site reactions are mild to moderate. Rare cases of skin ulceration/necroses at the site of injection have been reported with long term treatment.

The most frequently reported adverse events and the most common laboratory abnormalities observed during the placebo-controlled study in relapsing-remitting multiple sclerosis (560 patients, 2 years treatment) are presented in the table below for patients on placebo and Rebif® (interferon beta-1a). The frequencies are patients who reported this event at least once during the study, as a percentage of the total number of patients, by study-arm.

	Placebo	Rebif® 66 µg / weekly	Rebif® 132 µg / weekly
Adverse Events			
Injection site disorders (all)	38.5	89.9	92.4
Upper respiratory tract infections	85.6	75.1	74.5
Headache	62.6	64.6	70.1
Flu-like symptoms	51.3	56.1	58.7
Fatigue	35.8	32.8	41.3
Depression	27.8	20.6	23.9
Fever	15.5	24.9	27.7
Back pain	21.4	19.6	23.4
Myalgia	19.8	24.9	25.0
Nausea	23.0	24.9	24.5
Insomnia	21.4	19.6	23.4
Diarrhoea	18.7	17.5	19.0
Laboratory Test Abnormalities			
Lymphopenia	11.2	20.1	28.8
Leukopenia	3.7	12.7	22.3
Granulocytopenia	3.7	11.6	15.2
AST increase	3.7	10.1	17.4
ALT increase	4.3	19.6	27.2

For the events in bold, observed differences reached statistical significance as compared to placebo.

The adverse events experienced during the study are listed below, by WHOART System Organ Class. The most common amongst the injection site reactions was in the form of mild erythema. The majority of the other injection site reactions were also mild in the 2 Rebif® groups. Necrosis was reported in 8 patients treated with Rebif®. Two of these patients were in the 66 µg weekly and six in the 132 µg weekly groups. All patients completed the planned treatment period, with only 1 requiring temporary dose reductions and another patient stopping treatment for 2 weeks. Those that required treatment, received antibiotics.

Adverse events experienced by patients enrolled in the double-blind, placebo-controlled, multiple sclerosis study

Body System	Preferred term	Placebo (n=187)	Rebif® 66 µg weekly (n=189)	Rebif® 132 µg weekly (n=184)
Application Site Disorders	Injection site	15.0%	65.6%	65.8%
	Inflammation (a)(b)	13.4%	31.2%	34.8%
	Injection site reaction (a)(b)	14.4%	20.1%	22.8%
	Injection site pain (b)			
Body as a Whole - General Disorders	Influenza like symptoms	51.3%	56.1%	58.7%
	Fatigue	35.8%	32.8%	41.3%
	Fever (a)(b)	15.5%	24.9%	27.7%
	Leg pain	14.4%	10.1%	13.0%
	Rigors(b)(c)	5.3%	6.3%	13.0%
Centr & Periph Nervous System Disorders	Headache	62.6%	64.6%	70.1%
	Dizziness	17.6%	14.3%	16.3%
	Paraesthesia	18.7%	19.6%	16.3%
	Hypoaesthesia	12.8%	12.2%	7.6%
Respiratory System Disorders	Rhinitis	59.9%	52.4%	50.5%
	Upper Resp Tract Infection	32.6%	36.0%	29.3%
	Pharyngitis (b)	38.5%	34.9%	28.3%
	Coughing	21.4%	14.8%	19.0%
	Bronchitis	9.6%	10.6%	9.2%
Gastro-Intestinal System Disorders	Nausea	23.0%	24.9%	24.5%
	Abdominal pain	17.1%	22.2%	19.6%
	Diarrhoea	18.7%	17.5%	19.0%
	Vomiting	12.3%	12.7%	12.0%
Musculo-Skeletal System Disorders	Back pain	19.8%	23.3%	24.5%
	Myalgia	19.8%	24.9%	25.0%
	Arthralgia	17.1%	15.3%	19.0%
	Skeletal pain	10.2%	14.8%	9.8%
Psychiatric Disorders	Depression	27.8%	20.6%	23.9%
	Insomnia	21.4%	19.6%	23.4%
White Cell & Res Disorders	Lymphopenia (a)(b)	11.2%	20.1%	28.8%
	Leucopenia (a)(b)(c)	3.7%	12.7%	22.3%
	Granulocytopenia (a)(b)	3.7%	11.8%	15.2%
	Lymphadenopathy	8.0%	11.1%	12.0%
Skin & Appendages Disorders	Pruritus	11.8%	9.0%	12.5%
Liver & Biliary System Disorders	SGPT increased (a)(b)	4.3%	19.6%	27.2%
	SGOT increased (a)(b)(c)	3.7%	10.1%	17.4%
Urinary System Disorders	Urinary tract infection	18.7%	18.0%	16.8%
Vision Disorders	Vision abnormal	7.0%	7.4%	13.0%
Secondary Terms	Fall	16.0%	16.9%	15.8%

(a) Significant difference between placebo and Rebif® 66 µg weekly groups (p≤0.05)
(b) Significant difference between placebo and Rebif® 132 µg weekly groups (p≤0.05)
(c) Significant difference between Rebif® 66 µg and Rebif® 132 µg weekly groups (p≤0.05)
(n) Number of patients

In addition to the above listed adverse events, the following events have been experienced less frequently, in one or both of the relapsing remitting multiple sclerosis studies: asthenia, fluid retention, anorexia, gastroenteritis, heartburn, paradentium affections, dental abcess or extraction, stomatitis, glossitis, sleepiness, anxiety, irritability, confusion, lymphadenopathy, weight gain, bone fracture, dyspnoea, cold sores, fissure at the angle of the mouth, menstrual disorders, cystitis, vaginitis.

Condyloma acuminata

Most common adverse events for patients treated for Condyloma Acuminatum

Body System / Preferred Term	Preferred term	Trial 1 n = 25	Trial 2 n = 52	Trial 3 n = 50	Trial 4 n = 65
Body as a Whole - General	asthenia	24.0 %	3.8 %	36.0 %	15.4 %
	fever	8.0 %	21.2 %	4.0 %	0.0 %
	flu-syndrome	4.0 %	7.7 %	24.0 %	26.1 %
	injection site reaction	8.0 %	11.5 %	-	-
	injection site inflammation	-	5.8 %	-	-
	headache	28.0 %	42.3 %	20.0 %	36.9 %
	bodily discomfort	-	15.4 %	-	-
	back pain	-	9.6 %	-	10.8 %
	pain	-	-	-	9.2 %
	pelvic pain	4.0 %	-	6.0 %	-
	chills	-	28.8 %	-	6.2 %
	malaise	-	1.9 %	16.0 %	1.5 %
	injection site pain	4.0 %	36.5 %	66.0 %	13.8 %
	non-inflammatory swelling	-	7.7 %	-	-
	fatigue	-	28.8%	-	-
Digestive System	nausea	8.0 %	17.3 %	-	1.5 %
	vomiting	8.0 %	1.9 %	-	3.0 %
Musculoskeletal System	myalgia	12.0 %	3.8 %	2.0 %	9.2 %
	muscle ache	-	26.9 %	-	-
	muscle pain	-	1.9 %	-	-
Respiratory System	pharyngitis	16.0 %	0.0 %	-	3.0 %

Other adverse events were experienced by less than 5% of the patients, and included eye pain, skin disorder, rhinitis, bronchitis, coughing, diarrhoea, abdominal pain, postural hypotension, palpitation, vasodilatation, rectal disorder, lymphocytosis, thrombocytopenia, delirium, somnolence, joint pain, joint stiffness, lightheadedness, paraesthesia distal, disorientation, irritability, sleeplessness, lethargy, bruise, purpura, sweating increased, shortness of breath, upper respiratory tract infection, tachycardia, flushing, urethral pain, infection, chest pain, lymphadenopathy, PBI increased, arthralgia, dizziness, nervousness, tremor, abnormal vision, vulvovaginal disease, balanitis, penis disease, testis disease, urethritis, infection urinary tract, vaginitis, leukopenia, herpes simplex, pruritis, rash mac pap, skin neoplasia, rash.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No case of overdose has thus far been described. However, in case of overdosage, patients should be hospitalised for observation and appropriate supportive treatment should be given.

DOSAGE AND ADMINISTRATION

RELAPSING-REMITTING MULTIPLE SCLEROSIS: The recommended posology of Rebif® (interferon beta-1a) is 22 µg (6MIU) given three times per week by subcutaneous injection. This dose is effective in the majority of patients to delay progression of the disease. Patients with a higher degree of disability (an EDSS of 4.0 or higher) may require a dose of 44 µg (12 MIU) 3x/week.

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease. When first starting treatment with Rebif®, in order to allow tachyphylaxis to develop thus reducing adverse events, it is recommended that 20% of the total dose be administered during the initial 2 weeks of therapy, 50% of total dose be administered in week 3 and 4, and the full dose from the fifth week onwards.

At the present time, it is not known for how long patients should be treated. Safety and efficacy with Rebif® have been demonstrated following 2 years of treatment. Therefore, it is recommended that patients should be evaluated after 2 years of treatment with Rebif® and a decision for longer-term treatment be made on an individual basis by the treating physician.

Preparation of Solution: Lyophilized formulation (Relapsing-Remitting Multiple Sclerosis) Reconstitute the contents of a vial of Rebif® with 0.5 mL of the accompanying sterile diluent (see table below for diluent volume and resulting concentration). The reconstituted solution should be used immediately.

Reconstitution Table

Strength	Volume of Diluent to be added to vial	Approximate available volume	Nominal concentration/mL
11 µg (3 MIU)	0.5 mL	0.5 mL	22 µg (6 MIU)
44 µg (12 MIU)	0.5 mL	0.5 mL	88 µg (24 MIU)

Preparation of the solution: liquid formulation The liquid formulation in a pre-filled syringe is ready for use. These syringes are graduated to facilitate therapy initiation. The pre-filled syringes contain 22 µg and 44 µg of Rebif® respectively. The pre-filled syringes are ready for subcutaneous use only.

CONDYLOMA ACUMINATUM: The recommended posology is 3.67 µg (1MIU) per lesion three times per week for 3 weeks. The recommended route of administration is intra- or peri-lesional. The pre-filled syringes are not to be used for this indication. **Preparation of Solution: Lyophilized formulation (Condyloma acuminatum)** Reconstitute the contents of a vial of Rebif® in sterile diluent in order to obtain a final concentration of 3.67 µg per 0.1 mL solution. The reconstituted solution should be used immediately.

Reconstitution Table

Strength	Volume of Diluent to be added to vial	Approximate available volume	Nominal concentration/mL
11 µg (3 MIU)	0.3 mL	0.3mL	37 µg (10 MIU)
44 µg (12 MIU)	1.2 mL	1.2 mL	37 µg (10 MIU)

COMPOSITION

Lyophilized formulation Each 3 mL vial of sterile lyophilized powder contains Interferon beta-1a, albumin (human), mannitol and sodium acetate, as indicated in the table below. Acetic acid and sodium hydroxide are used to adjust the pH.

Interferon beta-1a	Albumin (Human)	Mannitol	Sodium acetate
11 µg (3 MIU)	9 mg	5 mg	0.2 mg
44 µg (12 MIU)	9 mg	5 mg	0.2 mg

Rebif® (Interferon beta-1a) is supplied with a 2 mL diluent ampoule containing 2 mL of 0.9% NaCl in Water for Injection. No preservatives are present.

Liquid formulation

The liquid formulation is supplied in syringes containing 0.5 mL of solution. Each syringe contains Interferon beta-1a, albumin (human), mannitol and 0.01 M sodium acetate buffer, as indicated in the table below. The solution does not contain preservatives.

Interferon beta-1a	Albumin (Human)	Mannitol	0.01 M Sodium acetate buffer
22 µg (6 MIU)	2 mg	27.3 mg	q.s. to 0.5 mL
44 µg (12 MIU)	4 mg	27.3 mg	q.s. to 0.5 mL

STABILITY AND STORAGE RECOMMENDATIONS

Lyophilized formulation: Refer to the date indicated on the labels for the expiry date.

Rebif® (Interferon beta-1a) lyophilized product should be stored at 2-8°C.

Liquid formulation: Refer to the date indicated on the labels for the expiry date.

Rebif® liquid in a pre-filled syringe should be stored at 2-8°C. Do not freeze.

RECONSTITUTED SOLUTIONS

Lyophilized formulation: Lyophilized Rebif® should be reconstituted with 0.9 % NaCl in Water for Injection (supplied in 2 mL neutral glass ampoules containing 2.0 mL). The reconstituted solution should be administered immediately. Although not recommended, it may be used later during the day of reconstitutionif stored in a refrigerator (2-8°C). Do not freeze. The reconstituted solution may have a yellow colouration which is a normal product characteristic. **Liquid formulation:** The liquid in the prefilled syringe is ready for use.

PARENTERAL PRODUCTS

See "Preparation of Solution" for table of reconstitution.

AVAILABILITY OF DOSAGE FORM

Rebif® (Interferon beta-1a) is available in two strengths (11 µg (3MIU), and 44 µg (12MIU) per vial), as a lyophilized sterile powder. It is accompanied by diluent (0.9% NaCl in Water for Injection) in 2mL ampoules. Both lyophilized strengths are supplied in cartons of 1 vial of drug and 1 x 2 mL ampoule of diluent, 3 vials of drug and 3 x 2mL ampoules of diluent, and 12 vials of drug and 12 x 2mL ampoules of diluent.

Rebif® is also available as a liquid formulation, in prefilled syringes ready for use. Two package strengths are available: 22 µg (6MIU)/0.5mL and 44 µg (12MIU)/0.5mL. The pre-filled syringes are supplied as single units, 3-packs and 12-packs. The pre-filled syringes are ready for subcutaneous use only.

The route of administration for Relapsing-Remitting Multiple Sclerosis is subcutaneous .

The route of administration for condyloma acuminatum is intra- and peri-lesional.

Reference: 1. Rebif® Product Monograph, 1998. Serono Canada Inc.

Serono

PAAB

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See page A28

ropinirole

REQUIP™

ropinirole (as ropinirole hydrochloride)

Tablets
0.25 mg, 1.0 mg, 2.0 mg, 5.0 mg

THERAPEUTIC CLASSIFICATION
AntiParkinsonian 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 D_2, D_3 and D_4 receptors. The antiparkinson activity of ropinirole is believed to be due to its stimulatory effects on central post-synaptic dopamine D_2 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 D_1 receptors. Ropinirole also has very low affinity for 5-HT_1, 5-HT_2, benzodiazepine, $GABA_A$, 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 D_2-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.

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, C_{max} 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

Unit Dose mg	C_{max} ng/mL	C_{min} ng/mL	T_{max}* h	AUC_{0-8} ng.h/mL
1	5.3 (3.1-9.0)	2.6 (0.9-4.2)	2.0 (0.5-7.0)	27.5 (14.9-46.5)
2	9.8 (5.0-18.0)	4.8 (2.3-10.0)	1.0 (0.6-4.0)	53.8 (23.9-108)
4	23.7 (14.2-40.9)	13.1 (4.8-23.9)	1.0 (1.0-3.0)	136 (66.1-241)

*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 T_{max} was increased by 2.6 hours and C_{max} 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 D_2 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* D_2 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 ^{14}C-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=63). 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" and "off") and permitted a reduction in levodopa dose. The subsequent section describes 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.

Therapeutic Effect – Plasma Concentration
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 (C_{ss}) were higher in patients classified as responders versus non-responders, although considerable overlap in the range of C_{ss} between the two groups was noted. Mean (±SD) REQUIP C_{ss} 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 Pathology in Rats
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 (C_{max}) 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/10 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 will 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 prescriber should be aware that these figures can not be used to predict the incidence 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 ≥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
Autonomic Nervous System				
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
Body as a Whole General				
Peripheral Edema	13.4	4.1	3.9	2.5
Fatigue	10.8	4.1	a	–
Injury	–	–	10.6	9.2
Pain	7.6	4.1	5.3	3.3
Asthenia	6.4	1.4	–	–
Drug Level Increased	4.5	2.7	6.7	3.3
Chest Pain	3.8	2.0	–	–
Malaise	3.2	0.7	1.4	0.8
Therapeutic Response Decreased	1.9	0.7	–	–
Cellulitis	1.3	0.0	–	–
Influenza-Like Symptoms	–	–	1.0	0.0
Fever	–	–	1.4	0.0
Cardiovascular General				
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
Central and Peripheral Nervous System				
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
Paresthesia	–	–	5.3	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	–	–
Gastrointestinal System				
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	–	–	4.8	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
Eructation	–	–	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
Hearing and Vestibular				
Tinnitus	1.3	0.0	–	–
Heart Rate and Rhythm				
Palpitation	3.2	2.0	2.9	2.5
Extrasystoles	1.9	0.7	–	–
Tachycardia	1.9	0.0	1.0	0.0
Fibrillation Atrial	1.9	0.0	–	–
Tachycardia Supraventricular	1.3	0.0	–	–
Bradycardia	–	–	1.0	0.0
Liver and Biliary System				
Gamma - GT Increased	1.3	0.7	1.0	0.0
Hepatic Enzymes Increased	1.3	0.0	–	–
Metabolic and Nutritional				
Alkaline Phosphate Increased	2.5	1.4	1.0	0.0
Weight Decrease	–	–	2.4	0.8
Hypoglycemia	1.3	0.0	–	–
Musculoskeletal System				
Arthralgia	–	–	6.7	5.0
Arthritis	–	–	2.9	0.8
Arthritis Aggravated	1.3	0.0	1.4	0.0
Myocardial, Endocardial, Pericardial Valve				
Myocardial Ischemia	1.3	0.7	–	–
Psychiatric				
Somnolence	40.1	6.1	20.2	8.3
Anxiety	–	–	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	1.9	0.0	1.0	0.0
Illusion	1.3	0.0	–	–
Thinking Abnormal	–	–	1.4	0.8
Apathy	–	–	1.0	0.0
Increased Libido	–	–	1.0	0.0
Personality Disorder	–	–	1.0	0.0
Red Blood Cell				
Anemia	–	–	2.4	0.0
Reproductive Male				
Impotence	2.5	1.4	–	–
Prostatic Disorder	–	–	1.0	0.0
Penis Disorder	–	–	1.3	0.0
Resistance Mechanism				
Upper Respiratory Tract Infection	–	–	8.7	8.3
Infection Viral	10.8	3.4	7.2	6.7
Respiratory System				
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
Skin/Appendages				
Pruritis	–	–	1.0	0.0
Urinary System				
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
Vascular Extracardiac				
Peripheral Ischemia	2.5	0.0	–	–
Vision				
Vision Abnormal	5.7	3.4	–	–
Eye Abnormality	3.2	1.4	–	–
Diplopia	–	–	1.9	0.8
Xerophthalmia	1.9	0.0	1.4	0.8
Cataract	–	–	1.4	0.8
Lacrimation Abnormal	–	–	1.4	0.0
White Cell and Reticuloendothelial System				
Eosinophilia	–	–	1.4	0.0

a: 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: asthenia, chest pain, fatigue, hot flushes, postural hypotension, abnormal gait, hyperkinesia, aggravated Parkinsonism, vertigo, abdominal pain, constipation, back pain, myalgia, depression, insomnia, paroniria (*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: *infrequent,* 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,* hypertonia, 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,* gynecomastia, 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 amylase, 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.

Neoplasm: *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, neurosis, personality disorder, somnambulism; *rare,* suicide attempt.

Red Blood Cell: *infrequent,* hypochromic anemia, anemia B_{12} deficiency; rare, polycythemia.

Female Reproductive: *infrequent,* amenorrhea, menstrual disorder, vaginal haemorrhage, 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,* infection; *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, psoriaform rash, seborrhea, skin disorder, urticaria, furunculosis; *rare,* bullous 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, blepharospasm, 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 OVERDOSAGE

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, grogginess, 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.

DOSAGE 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.

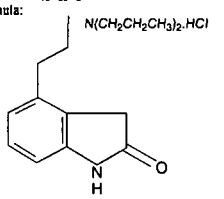
PHARMACEUTICAL INFORMATION

Drug Substance:
Proper Name: Ropinirole Hydrochloride

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

Molecular Formula: $C_{16}H_{25}N_2OCl$

Stuctural 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-medicinal ingredients include: Hydrous lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, iron oxide yellow (1.0 and 2.0 mg tablets), iron oxide red (2.0 mg tablets), FD&C Blue No. 2 aluminum lake (1.0 and 5.0 mg tablets), polysorbate 80 (0.25 mg tablets), talc (5.0 mg tablets). They do not contain sucrose, tartrazine or any other azo dyes.

AVAILABILITY OF DOSAGE FORM

REQUIP is supplied as a pentagonal film-coated Tiltab® tablet with beveled edges containing ropinirole (as ropinirole hydrochloride) as follows: 0.25 mg – white imprinted with SB and 4890; 1.0 mg – pale green imprinted with SB and 4892; 2.0 mg – pale pink imprinted with SB and 4893; 5.0 mg – pale blue tablets imprinted with SB and 4894.

REQUIP is available in bottles in the pack size of 100 tablets. It is also available in 0.25 mg as a single unit blister pack of 21 tablets.

Full Product Monograph available to practitioners upon request.

REFERENCES:

1. Product Monograph, 1997.
2. Adler CH, Sethi KD, Hauser RA, *et al.* Ropinirole For The Treatment of Early Parkinson's Disease. Neurology. In press.
3. Rascol O, Brooks DJ, Brunt ER, *et al.* Ropinirole For The Treatment of Early Parkinson's Disease: A 6-Month Interim Report of a 5-Year L-Dopa-controlled Study. Movement Disorders. In press.
4. Data on file, SB 1036.

SmithKline Beecham Pharma

See pages A20, A21

COPAXONE™
(glatiramer acetate for injection)

20 mg, single use vials for Subcutaneous Injection

Therapeutic Classification: Immunomodulator

PHARMACOLOGY – COPAXONE™ [glatiramer acetate (formerly known as copolymer-1) for injection] is a sterile, lyophilized mixture of synthetic polypeptides containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine with an average molar fraction of 0.141, 0.427, 0.095 and 0.338, respectively. The mechanism(s) by which glatiramer acetate exerts its effect on Multiple Sclerosis (MS) is (are) unknown. Pre-clinical study results suggest that glatiramer acetate may modulate immune processes that are currently thought involved in the pathogenesis of MS. In particular, glatiramer acetate has been shown to reduce the incidence and severity of experimental allergic encephalomyelitis (EAE), a condition which may be induced in several animal species through immunization against CNS derived material containing myelin and an often used experimental animal model of MS. Because the immunological profile of glatiramer acetate remains to be fully elucidated, concerns exist about its potential to alter naturally occurring immune responses (See Precautions).

Pharmacokinetics – There is no information regarding the absorption, distribution, metabolism or excretion profile of COPAXONE™ (glatiramer acetate for injection) in humans as appropriate pharmacokinetic studies have not been done. Based on preclinical studies it is assumed that a large fraction of a subcutaneously administered dose of glatiramer acetate would be hydrolyzed locally. Some fraction of injected material is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

Clinical Studies – The efficacy of COPAXONE™ (glatiramer acetate for injection) was evaluated in two similarly designed placebo-controlled trials in patients with relapsing-remitting MS (RR-MS). In both these studies, a dose of 20 mg/day was used. No other dose of glatiramer acetate has been evaluated in this patient population. The first was a pilot study (Trial I) which was conducted at a single-centre and was a double-blind, randomized, matched-pair, parallel group placebo-controlled trial. Fifty patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n = 25) or placebo (n = 25) subcutaneously. The protocol specified primary outcome measure was the proportion of patients who were relapse free during the 2 year duration of the trial, but two additional relevant outcomes were also specified as endpoints: frequency of attacks during the trial, and the change in the number of attacks compared to the rate of attacks in the 2 years prior to study entry. Results from this study (see Table 1) provided preliminary evidence of effectiveness.

Table 1 Outcome	Trial I*		
	Glatiramer acetate n=25	Placebo n=25	p-Value
Mean relapse rate (2 years)	0.6	2.4	0.005
% Relapse free	56%	28%	0.085
Change in Relapse rate	3.2	1.6	0.025
Median Time to first Relapse (days)	>700	150	0.03
% of patients progression free*	80%	52%	0.07

* The primary efficacy measure for Trial I was the proportion of patients who were relapse free during the 2 year duration of the trial (% Relapse Free). Analyses were based on the intent-to-treat population.

* Progression defined as an increase of at least 1 point on the EDSS that persists for at least 3 consecutive months.

Trial II was a multicentre double-blind, randomized, placebo-controlled trial. Two hundred and fifty-one patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n = 125) or placebo (n = 126) subcutaneously. Patients were diagnosed with RR-MS by standard criteria, and had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients had a score of no more than 5 on the Kurtzke Expanded Disability Scale Score (EDSS), a standard scale ranging from 0 (normal) to 10 (death due to MS). A score of 5 is defined as one at which a patient is still ambulatory but for whom full daily activities are impaired due to disability, a score of 6 is defined as one at which the patient is still ambulatory but requires assistance and a score of 7 on this scale means that the patient requires a wheelchair. Patients were seen every 3 months for 2 years, as well as within several days of a presumed exacerbation. In order for an exacerbation to be confirmed, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the lesion for at least 48 hours). The protocol specified primary outcome measure was the mean two-year relapse rate. Table 2 shows results of the analysis of primary and secondary outcome measures from Trial II based on the intent-to-treat population.

Table 2 Outcome	Trial II*		
	Glatiramer acetate n=125	Placebo n=126	p-Value
Mean relapse rate (2 years)	1.19	1.68	0.055
% Relapse free	34%	27%	0.25
Median Time to first Relapse (days)	287	198	0.23
% of patients progression free*	78%	75%	0.48
Mean change in EDSS	-0.05	+0.21	0.023

* The primary efficacy measure for Trial II was the mean two-year relapse rate [Mean relapse rate (2 years)]. Analyses were based on the intent-to-treat population.

* Progression defined as an increase of at least 1 point on the EDSS that persists for at least 3 consecutive months.

The effects of glatiramer acetate on relapse severity were not evaluated in either trial.

Both studies showed a beneficial effect of glatiramer acetate on relapse rate, and on this basis glatiramer acetate is considered effective.

INDICATIONS – For use in ambulatory patients with Relapsing-Remitting Multiple Sclerosis to reduce the frequency of relapses. A correlation between a reduction in attack frequency alone and a decreased risk of future disability remains to be established. The safety and efficacy of COPAXONE™ (glatiramer acetate for injection) beyond 2 years have not been adequately studied in placebo-controlled trials. The safety and efficacy of COPAXONE™ in chronic progressive MS have not been evaluated. COPAXONE™ should only be prescribed by clinicians who are experienced in the diagnosis and management of Multiple Sclerosis.

CONTRAINDICATIONS – COPAXONE™ (glatiramer acetate for injection) is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

WARNINGS – The only recommended route of administration of COPAXONE™ (glatiramer acetate for injection) injection is the subcutaneous route. COPAXONE™ should not be administered by the intravenous route.

Symptoms of Potentially Cardiac Origin – Approximately 26% of COPAXONE™ patients in the multicentre controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain (see Adverse Reactions: Chest Pain). While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see Adverse Reactions: Immediate Post-Injection Reaction), many did not. ECG monitoring was not performed during any of these episodes and the pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New Heart Association Class I and II) and thus the risks associated with COPAXONE™ treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown. COPAXONE™ has been associated with an Immediate Post-Injection Reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see Adverse Reactions: Immediate Post- Injection Reaction). COPAXONE™ has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE™ in such patients.

PRECAUTIONS – Patients should be instructed in aseptic reconstitution and self-injection techniques to assure the safe administration of COPAXONE™ (glatiramer acetate for injection). The first injection should be performed under the supervision of an appropriately qualified healthcare professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture-resistant container for disposal of used needles and syringes should be used by the patient. Patients should be instructed on the safe disposal of full containers.

Considerations Involving the Use of a Product Capable of Modifying Immune Responses COPAXONE™ is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. There is also no information on whether COPAXONE™ can alter normal human immune responses, such as the recognition of foreign antigens. It is therefore possible that treatment with COPAXONE™ may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done. Studies in both the rat and monkey have shown that immune complexes are deposited in renal glomeruli. Furthermore, in a controlled trial of 125 patients with relapsing-remitting MS treated for 2 years with 20 mg/day COPAXONE,™ serum IgG levels reached approximately 3 times baseline values in 80% of patients within 3 to 6 months of treatment. These values returned to about 50% greater than baseline during the remainder of treatment. Although COPAXONE™ is intended to attenuate the autoimmune response to myelin, whether chronic treatment with COPAXONE,™ and in consequence, continued alteration of cellular immunity can result in detrimental effects is unknown. Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats are still in progress.

Drug Interactions – Interactions between COPAXONE™ and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE™ with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE™ has not been formally evaluated in combination with Interferon beta. However, 10 patients who switched from therapy with Interferon beta to COPAXONE™ have not reported any serious and unexpected adverse events thought to be related to treatment.

Use in Pregnancy – There are no adequate and well-controlled studies in pregnant women. No evidence of reproductive toxicity was observed in preclinical studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During three clinical trials with COPAXONE,™ seven women conceived while being treated with the active drug. One case was lost to follow-up. Three of the patients electively discontinued pregnancy. Three patients stopped treatment 1, 1.5 and 2 months after learning they were pregnant; all delivered healthy babies.

Nursing Mothers – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, treating a nursing woman with COPAXONE™ should only be considered after careful risk/benefit assessment and be used with caution.

Use in Children – The safety and effectiveness of COPAXONE™ have not been established in individuals below 18 years of age.

Use in the Elderly – COPAXONE™ has not been studied in the elderly (> 65 years old).

Use in Patients with Impaired Renal Function – The pharmacokinetics of COPAXONE™ in patients with impaired renal function have not been determined.

ADVERSE REACTIONS – Approximately 850 MS patients and 50 healthy volunteers have received at least one dose of COPAXONE™ (glatiramer acetate for injection) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE™ in clinical trials ranged from 6 months (693 patients) to 2 years (306 patients), and to over 5 years (28 patients) at a daily dose of 20 mg.

In controlled clinical trials the most commonly observed adverse event associated with the use of COPAXONE™ which occurred at a higher frequency than in placebo treated patients were: injection site reactions, vasodilation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety and hypertonia. Of a total of 844 patients who could be evaluated for safety, approximately 8% discontinued treatment due to an adverse event. The adverse events most commonly associated with discontinuation were: injection site reaction (6.5%), vasodilation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness and tremor. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE™ treatment included a case of life threatening serum sickness.

Immediate Post-Injection Reaction – Approximately 10% of Multiple Sclerosis patients exposed to COPAXONE™ in pre-marketing studies reported a post-injection reaction immediately following subcutaneous injection of COPAXONE.™ Symptoms experienced could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria. These symptoms were invariably transient, self-limited, did not require specific treatment and in general arose after several months after initiation of treatment, although they may occur earlier in the course of treatment. A given patient may experience one or several episodes of these symptoms during treatment with COPAXONE.™ Whether these episodes are mediated by an immunologic or non-immunologic mechanism, and whether several similar episodes seen in a given patient have identical mechanisms is unknown. In fact, whether or not this constellation of symptoms actually represents a specific syndrome is unknown.

Chest Pain – Approximately 26% of glatiramer acetate patients in the multicentre controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. ECG monitoring was not performed during any of these episodes. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. Patients in clinical trials were free of significant cardiovascular disease (New York Heart Association Class I or II) therefore, the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown. Table 3 lists the adverse experiences after up to 35 months of treatment (> 27 - 33 months: COPAXONE,™ n = 84; Placebo, n = 75; > 33 months: COPAXONE,™ n = 12; Placebo, n = 24) in the multicentre placebo-controlled study (Trial II) in relapsing-remitting Multiple Sclerosis patients that occurred at an incidence of at least 2% among patients who received COPAXONE™ and at an incidence that was at least 2% more than that observed in the same trial for placebo patients regardless of their causal relationship to treatment. No laboratory adverse experiences that met these criteria were reported. It should be noted that the figures cited in Table 3 cannot be used to predict the incidence of side effects during the course of usual medical practice, where patient characteristics and other factors differ from those that prevailed in the clinical trials. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Other events which occurred in at least 2% of patients but were present at equal or greater rates in the placebo group included:

Body as a whole – Headache, injection site ecchymosis, accidental injury, abdominal pain, allergic rhinitis and malaise.

Digestive System – Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth.

Musculoskeletal – Myasthenia and myalgia

Nervous System – Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign, abnormal thinking, twitching, euphoria, and sleep disorder.

Respiratory System – Pharyngitis, sinusitis, increased cough and laryngitis.

Skin and Appendages – Acne, alopecia, and nail disorder

Special Senses – Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness.

Urogenital System – Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender related differences. No clinically significant differences were identified. In these clinical trials 92% of patients were Caucasian, which is representative of the population of patients with Multiple Sclerosis. In addition, the vast majority of patients treated with COPAXONE™ were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups. Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE™. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE™ and placebo groups in blinded clinical trials. No patient receiving COPAXONE™ withdrew from any trial due to abnormal laboratory findings.

Table 3. Adverse Experiences ≥ 2% Incidence and ≥ 2% Above Placebo

	COPAXONE™ (n=125)		Placebo (n=126)	
Adverse Experience	**n**	**%**	**n**	**%**
Body as a Whole				
Injection Site Pain	83	66.4	46	36.5
Asthenia	81	64.8	78	61.9
Injection Site Erythema	73	58.4	17	13.5
Injection Site Pruritus	48	38.4	5	4.0
Flu syndrome	38	30.4	34	27.0
Injection Site Inflammation	35	28.0	9	7.1
Back pain	33	26.4	28	22.2
Chest pain	33	26.4	13	10.3
Injection Site Mass	33	26.4	10	7.9
Injection Site Induration	25	20.0	1	0.8
Injection Site Welt	19	15.2	5	4.0
Neck pain	16	12.8	9	7.1
Face Edema	11	8.8	2	1.6
Injection Site Urticaria	9	7.2	0	.0
Injection Site Hemorrhage	8	6.4	4	3.2
Chills	5	4.0	1	0.8
Cyst	5	4.0	1	0.8
Injection Site Reaction	4	3.2	1	0.8
Injection Site Atrophy	3	2.4	0	.0
Abscess	3	2.4	0	.0
Cardiovascular				
Vasodilatation	34	27.2	14	11.1
Palpitation	14	11.2	6	4.8
Migraine	9	7.2	5	4.0
Syncope	8	6.4	4	3.2
Digestive				
Nausea	29	23.2	22	17.5
Vomiting	13	10.4	7	5.6
Anorexia	6	4.8	3	2.4
Gastroenteritis	6	4.8	2	1.6
Oral Moniliasis	3	2.4	0	.0
Tooth Caries	3	2.4	0	.0
Hemic and Lymphatic				
Lymphadenopathy	23	18.4	12	9.5
Ecchymosis	15	12.0	12	9.5
Metabolic and Nutritional				
Peripheral Edema	14	11.2	7	5.6
Weight gain	7	5.6	0	.0
Edema	5	4.0	1	0.8
Musculo-Skeletal				
Arthralgia	31	24.8	22	17.5
Nervous System				
Hypertonia	44	35.2	37	29.4
Tremor	14	11.2	7	5.6
Agitation	7	5.6	4	3.2
Confusion	5	4.0	1	0.8
Nystagmus	5	4.0	2	1.6
Respiratory				
Rhinitis	29	23.2	26	20.6
Dyspnea	23	18.4	8	6.3
Bronchitis	18	14.4	12	9.5
Skin and Appendages				
Sweating	15	12.0	10	7.9
Erythema	8	6.4	4	3.2
Skin Disorder	5	4.0	2	1.6
Skin Nodule	4	3.2	1	0.8
Wart	3	2.4	0	.0
Special Senses				
Ear Pain	15	12.0	12	9.5
Eye Disorder	8	6.4	1	0.8
Urogenital System				
Urinary Urgency	20	16.0	17	13.5
Vaginal Moniliasis	16	12.8	9	7.1
Dysmenorrhea	12	9.6	9	7.1
Unintended Pregnancy	4	3.2	0	.0
Impotence	3	2.4	0	.0

Other Adverse Events Observed During All Clinical Trials – COPAXONE™ has been administered to approximately 900 individuals during all clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using COSTART II dictionary terminology. The frequencies presented represent the proportion of the 860 individuals exposed to COPAXONE™ who had data available for this determination. All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and those not reasonably related to drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: Frequent adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients.

Body as a whole – ***Frequent:*** Injection site edema, injection site atrophy, and abscess ***Infrequent:*** Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma and photosensitivity reaction.

Cardiovascular – ***Frequent:*** Hypertension. ***Infrequent:*** Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

Digestive – ***Infrequent:*** Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration and duodenal ulcer.

Endocrine – ***Infrequent:*** Goiter, hyperthyroidism, and hypothyroidism.

Gastrointestinal – ***Frequent:*** Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis.

Hemic and Lymphatic – ***Infrequent:*** Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

Metabolic and Nutritional – ***Infrequent:*** Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma.

Musculoskeletal – ***Infrequent:*** Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

Nervous – ***Frequent:*** Abnormal dreams, emotional lability, and stupor. ***Infrequent:*** Ataxia, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, paranoid reaction, paraplegia, psychotic depression and transient stupor.

Respiratory – ***Frequent:*** Hyperventilation. ***Infrequent:*** Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages – ***Frequent:*** Eczema, herpes zoster, pustular rash, skin atrophy and warts. ***Infrequent:*** Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

Special Senses – ***Infrequent:*** Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

Urogenital – ***Frequent:*** Amenorrhea, hematuria, impotence, menorrhagia, suspicious Papanicolaou smear, and vaginal hemorrhage. ***Infrequent:*** Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, breast pain, carcinoma cervix *in situ*, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE – Overdose with COPAXONE™ has been reported in three patients. One patient injected four doses (80 mg total) of COPAXONE™ at once. No sequelae were noted. Two other patients, a 28-year old male and a 37-year old female, were given 3 injections of 20 mg of COPAXONE™ at one half hour intervals by error. Neither patient evidenced any change in blood pressure, heart rate, or temperature. Telephone follow-up several hours later produced no report of adverse experiences from either patient.

DOSAGE AND ADMINISTRATION – *COPAXONE™ should only be prescribed by clinicians who have experience in the diagnosis and management of Multiple Sclerosis.* The recommended dose of COPAXONE™ (glatiramer acetate for injection) for the treatment of relapsing-remitting MS is a daily injection of 20 mg given subcutaneously.

Instructions for Use – To reconstitute lyophilized COPAXONE™ for injection, use a sterile syringe and needle to transfer 1.1 mL of the diluent supplied, Sterile Water for injection, into the COPAXONE™ vial. Gently swirl the vial of COPAXONE™ and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist before use if it contains particulate matter. Use within 8 hours after reconstitution. Withdraw 1.0 mL of the solution into a sterile syringe fitted with a new 27-gauge needle and inject the solution subcutaneously. Sites for self-injection include arms, abdomen, hips, and thighs. A vial is suitable for single use only; unused portions should be discarded.

COMPOSITION – COPAXONE™ (glatiramer acetate for injection) is a sterile, lyophilized drug product, intended for subcutaneous injection following reconstitution with Sterile Water for injection. Each vial of lyophilized drug product contains 20 mg glatiramer acetate, plus a 2 mg overage to allow for losses in reconstitution and transfer, and 40 mg mannitol. Each vial of Sterile Water for injection contains 1.0 mL of Sterile Water for injection plus a 0.2 mL overage to allow for losses in reconstitution and transfer.

STABILITY AND STORAGE RECOMMENDATIONS – Vials of lyophilized COPAXONE™ should be stored under refrigeration (2 - 8°C). The vials of diluent should be stored at room temperature.

Reconstituted Solutions – To reconstitute lyophilized COPAXONE™ prior to injection, use a sterile syringe and 25-gauge needle to transfer the diluent supplied, Sterile Water for injection, into the COPAXONE™ vial. Gently swirl the vial of COPAXONE™ and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist if it contains particulate matter. Soon after the product is completely dissolved, withdraw 1.0 mL of the solution into a sterile syringe fitted with a new 27-gauge needle and inject the solution subcutaneously. A vial is suitable for single use only; unused portions should be discarded. The reconstituted solution should not be left longer than 8 hours at room temperature.

Parenteral Products – COPAXONE™ should be reconstituted only with the provided diluent, Sterile Water for injection.

Vial Size	2 mL
Volume of Diluent to be Added	1.1 mL
Volume to be Injected	1.0 mL
Nominal Concentration per mL	20 mg

AVAILABILITY OF DOSAGE FORMS – COPAXONE™ (glatiramer acetate for injection) is supplied as a 20 mg dose of sterile lyophilized glatiramer acetate with mannitol, packaged in single use 2 mL vials. A separate vial, containing 1.1 mL of diluent (Sterile Water for injection) plus 0.1 mL of overage of diluent is included for each vial of drug. COPAXONE™ is available in packs of 32 amber vials of sterile lyophilized material for subcutaneous injection. The diluent (Sterile Water for injection) for COPAXONE™ is supplied in packs of 32 clear vials. Product Monograph available upon request.

References

1. Johnson, KP et al, Extended use of glatiramer acetate (COPAXONE™) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability, *Neurology*, vol. 50, 3:701 - 709, March 1998. **2.** Johnson, KP et al, Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis, *Neurology*, 45:1268 - 1275, July 1995. **3.** COPAXONE™ Product Monograph, Teva Marion Partners Canada.

COPAXONE™ (glatiramer acetate for injection)

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Once-a-day Aricept*

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 (Cl/F) is 0.13L/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) and pharmaco-dynamic effect (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_{ss}[1] (ng/mL)	E_{min} %	E_{max} %	E_{ss}[2] %
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

1 C_{ss}: Plasma concentration at steady state
2 E_{ss}: Inhibition of erythrocyte membrane acetylcholinesterase at steady state

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_{0-24} (ng•hr/mL)	Cl_p/F (L/hr/kg)	V_d/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_{0-24} Area under the plasma concentration versus time curve from 0 -to- 24 hours
Cl_p/F Mean apparent plasma clearance
V_d/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 α_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 ^{14}C-labelled 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 faeces (total recovery of 72%) over a period of 10 days. Approximately 28% of the labelled donepezil remained uncovered, 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^2), 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 ≥10 and ≤26 as well as a 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 36% 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.

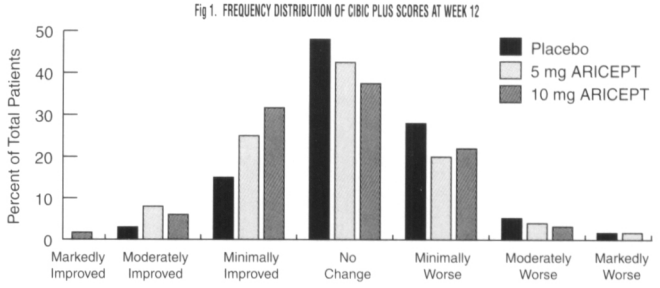
The data shown below for the two primary outcome measures in donepezil clinical trials were obtained from the Intent-To-Treat population (ITT analysis, i.e., All patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete 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 difference 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 ± 0.08 and 0.34 ± 0.08 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

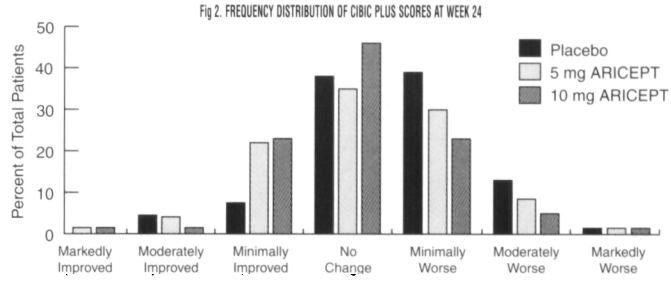


Thirty-Week Study (24 weeks of treatment + 6-week placebo washout): In this study, 473 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of donepezil for 24 weeks of double-blind active treatment followed by a 6-week single-blind placebo washout period. As in the 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
Anaesthesia: 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<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. Syncopal 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 syncopal episodes.

Gastrointestinal: Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid 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 dose than with the 5 mg 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 ≥85 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 ≥ 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.

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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_d, about 50 - 130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interferences.*

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
Number of Patients Randomized	355	350	315
Events/% Discontinuing			
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 cholinomimetic 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 prior to 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 trial patients 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

	No Initial Treatment		One-Week Initial Treatment with 5 mg/day	Six-Week Initial Treatment with 5 mg/day
Adverse Event	**Placebo (n = 315)**	**5 mg/day (n = 311)**	**10 mg/day (n = 315)**	**10 mg/day (n = 269)**
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle Cramps	2%	6%	8%	3%
Anorexia	2%	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	**Metabolic and Nutritional**		
Body as a Whole			Weight Decrease	1	3
Headache	9	10	**Musculoskeletal System**		
Pain, Various Locations	8	9	Muscle Cramps	2	6
Accident	6	7	Arthritis	1	2
Fatigue	3	5	**Nervous System**		
Cardiovascular System			Insomnia	6	9
Syncope	1	2	Dizziness	6	8
Digestive System			Depression	<1	3
Nausea	6	11	Abnormal Dreams	0	3
Diarrhea	5	10	Somnolence	<1	2
Vomiting	3	5	**Urogenital**		
Anorexia	2	4	Frequent Urination	1	2
Hemic and Lymphatic Systems					
Ecchymosis	3	4			

Other Adverse Events Observed During Clinical Trials: ARICEPT has been administered to over 1760 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 980 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 2/100 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, peritoneal edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, head pressure, listlessness.

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%) faecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; (<1%) eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, haemorrhoids, ileus, increased thirst, jaundice, melena, polydypsia, duodenal ulcer, stomach ulcer.

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

Hemic & Lymphatic System: (<1%) anaemia, thrombocythemia, 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, hypertonia, 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, hirsutism, 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 OVERDOSAGE

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) overdosage. 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 colouring 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.

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Full Product Monograph available upon request.

Pfizer

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See page A15

Lamotrigine

Lamictal®

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 longterm 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=29.9-211 h•µg/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[2]	LAMICTAL + Enzyme-Inducing AEDs	LAMICTAL + Valproic Acid	LAMICTAL + Valproic Acid + Enzyme-Inducing AEDs
T_{max} (hrs)	Single Dose	2.2 (0.25-12.0)[1]	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 SIGNALLED 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 oedema 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[1]	1,788	9.2%	1.8%	0.1%
Enzyme-Inducing AEDs[1] + VPA	318	8.8%	3.5%	0.9%
VPA ± Non-Enzyme-Inducing AEDs[2]	159	20.8%	11.9%	2.5%
Non-Enzyme-Inducing AEDs[2]	27	18.5%	0.0%	0.0%

1 Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone
2 Non-enzyme-inducing AEDs include clonazepam, clobazam, ethosuximide, methsuximide, vigabatrin, and gabapentin

Table 3: Effect of the Initial Daily Dose[1] 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[2]		Enzyme-Inducing AEDs[2] + VPA		VPA ± Non-Enzyme-Inducing AEDs[3]	
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 clonazepam, 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 ethinyloestradiol 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

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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[1]

Body System / *Adverse Experience*[2]	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)
BODY AS A WHOLE			
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
DIGESTIVE			
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
MUSCULOSKELETAL			
Myalgia	2.8	3.1	0.0
Arthralgia	2.0	0.2	0.0
NERVOUS			
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
RESPIRATORY			
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
SKIN AND APPENDAGES			
Rash	10.0	5.0	1.1
Pruritus	3.1	1.7	0.3
SPECIAL SENSES			
Diplopia	27.6	6.7	0.7
Blurred Vision	15.5	4.5	1.1
Vision Abnormality	3.4	1.0	0.0
UROGENITAL			
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

1 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.

2 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, hematemesis, 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[1] *With* Valproic Acid	Enzyme-Inducing AEDs[1] *Without* Valproic Acid	Patients Taking Valproic Acid *Only*
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.

1 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).

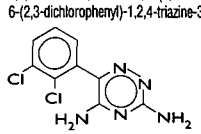
There have been no controlled studies to establish the effectiveness or optimal dosing regimen of add-on LAMICTAL therapy in patients receiving only non-enzyme-inducing AEDs or valproic acid. However, available data from open clinical trials indicate that the addition of LAMICTAL under these conditions 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 $t_{1/2}$ 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 $t_{1/2}$ 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: $C_9H_7Cl_2N_5$ 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-medicinal 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.** Faught 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

Glaxo Wellcome Inc.
7333 Mississauga Rd. N.
Mississauga, Ontario, Canada L5N 6L4

See pages A4, A5, A18, A19

Amerge
naratriptan hydrochloride

1 & 2.5 mg Tablets

Therapeutic Classification: Migraine Therapy

Pharmacological Classification: 5-HT_1 Receptor Agonist

Actions and Clinical Pharmacology: AMERGE (naratriptan hydrochloride) has been demonstrated to be a selective agonist for a vascular 5-hydroxytryptamine$_1$ receptor subtype (probably a member of the 5-$HT_{1B/1D}$ family) with little or no binding affinity for 5-$HT_{2/3}$ receptor subtypes, alpha$_1$-, alpha$_2$-, or beta-adrenergic; dopamine$_1$; dopamine$_2$; muscarinic; or benzodiazepine receptors. Naratriptan did not exhibit agonist or antagonist activity in *ex vivo* assays of 5-HT_4 and 5-HT_7 receptor-mediated activities.

The therapeutic activity of AMERGE in migraine is generally attributed to its agonist activity at 5-HT_{1B}/5-HT_{1D} receptors. Two current theories have been proposed to explain the efficacy of 5-HT_1 receptor agonists in migraine. One theory suggests that activation of 5-HT_1 receptors located on intracranial blood vessels, including those on the arteriovenous anastomoses, leads to vasoconstriction, which is believed to be correlated with the relief of migraine headache. The other hypothesis suggests that activation of 5-HT_1 receptors on perivascular fibres of the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release. These theories are not mutually exclusive.

Pharmacokinetics: ***Absorption:*** AMERGE tablets are well absorbed, with 74% oral bioavailability in females and 63% in males. After oral administration, the absorption is rapid and peak concentrations are obtained in 2 to 5 hours. A two-period crossover study was performed in 15 female migraine patients who received AMERGE as a single 2.5 mg tablet during a migraine attack, followed 3-7 days later by another 2.5 mg treatment during a non-migraine period. During a migraine attack, absorption is slower, although exposure (AUC) and elimination half-life are not significantly affected.

Table 1: Pharmacokinetic Parameters in Female Migraine Patients after receiving 2.5 mg AMERGE Tablets*

Parameter	Migraine Attack (N=15)	Non-Migraine Period (N=15)
C_{max} (ng/mL)	7.66 (3.07)	9.50 (3.63)
t_{max} (h)	3.8 (2.1)	2.0 (1.0)
AUC (ng/mL.h)	86.7 (32.5)	92.0 (33.7)
Cl/F (mL/min)	467.5 (126.4)	520.7 (222.6)
$t_{1/2}$ (h)	6.75 (1.44)	7.02 (2.39)

* values quoted are arithmetic mean (standard deviation)

C_{max} - maximum concentrations Cl/f - apparent clearance t_{max} - time to maximum concentration $t_{1/2}$ - elimination half-life
AUC - area under the curve of concentration vs time extrapolated to infinity

Plasma levels of naratriptan increase in a dose-proportional manner consistent with linear pharmacokinetics over a 1 to 10 mg dose range. The absorption and elimination are independent of the dose. Administration with food does not appreciably influence the pharmacokinetics of naratriptan. Repeat administration of AMERGE tablets (up to 10 mg once daily for 5 days) does not result in drug accumulation.

Metabolism and Distribution: *In vitro*, naratriptan is metabolized by a wide range of cytochrome P450 isoenzymes into a number of inactive metabolites. Naratriptan is a poor inhibitor of cytochrome P450 isoenzymes, and does not inhibit monoamine oxidase (MAO) enzymes; metabolic interactions between naratriptan and drugs metabolized by P450 or MAO are, therefore, unlikely. According to a population pharmacokinetic estimate, naratriptan is distributed into a volume of approximately 261 L.

Protein Binding: Plasma protein binding is low (29%).

Elimination: The elimination half-life generally ranges from 5-8 hours. Oral clearance is 509 mL/min in females and 770 mL/min in males. The renal clearance (220 mL/min) exceeds the glomerular filtration rate, suggesting that the drug undergoes active tubular secretion. Naratriptan is predominantly eliminated in urine, with 50% of the dose recovered unchanged and 30% as metabolites.

Special Populations:

Age Effects: A study was performed to compare the pharmacokinetics of naratriptan in young (6 female/6 male, 24-44 years) and elderly (6 female/6 male, 65-77 years) subjects. The subjects received two doses each of placebo, 1 mg naratriptan, and 2.5 mg naratriptan separated by 4 hour intervals. A minimum 96 hour period intervened between consecutive treatment days.

Elderly subjects experienced a higher degree of exposure to naratriptan than did younger subjects. Mean C_{max} and area under the plasma concentration time curve values were 28% and 38% higher, respectively, for the 1 mg treatment group and 15% and 32% higher, respectively, for the 2.5 mg group. Total and renal clearance were decreased by about 30%, while the elimination half-life was increased by about 1 hour.

Elevations in systolic blood pressure at the 2.5 mg dose were more pronounced in the elderly subjects than in the young subjects (mean peak increases 12 mmHg in elderly versus 2 mmHg in young subjects).

Renal Impairment: Renal excretion is the major route for elimination of naratriptan. A study to compare male and female subjects with mild to moderate renal impairment (n=15; 31-58 yrs, screening creatinine clearance: median 41.2 mL/min, range 18 to 115 mL/min) to gender-matched healthy subjects (n=8, 21-47 yrs) showed a decrease in oral clearance (mean decreased by 50%) resulting in a longer mean half-life (approximately 11 hours, range 7 to 20 hours) and an increase in the mean C_{max} (approximately 40%). In this study, blood pressure measurements suggested that increased exposure in renally-impaired subjects may be associated with increases in blood pressure which are larger than those seen in healthy subjects receiving the same dose (5 mg). (see DOSAGE AND ADMINISTRATION.)

Hepatic Impairment: Liver metabolism plays a limited role in the clearance of naratriptan. The pharmacokinetics of a single 2.5 mg dose of naratriptan were determined in subjects with moderate hepatic impairment (Child-Pugh grade A or B, n=8) and gender- and age-matched healthy subjects (n=8). Subjects with hepatic impairment showed a moderate decrease in clearance (approximately 30%) resulting in increases of approximately 40% in the half-life (range 8 to 16 hours) and the area under the plasma concentration time curve (see Dosage and Administration).

Clinical Studies ***Therapeutic Clinical Trials:*** Four double-blind, placebo-controlled, dose-ranging clinical trials evaluated the safety and efficacy of AMERGE at oral doses ranging from 0.1 to 10 mg in a total of 3160 adult patients with migraine attacks characterized by moderate or severe pain. The minimal effective dose was 1.0 mg. In three of the four clinical trials, a higher overall rate of headache relief was achieved with a 2.5 mg dose. Single doses of 5 mg and higher are not recommended due to an increased incidence of adverse events. Onset of significant headache relief (defined as no or mild pain) became apparent at 60-120 minutes after these doses. AMERGE also relieved the nausea, phonophobia, and photophobia associated with migraine attacks.

The following table shows the 4 hour efficacy results obtained for the recommended doses of AMERGE in two of the four dose-ranging efficacy studies. In Study 1, patients were randomised to receive placebo or a particular dose of AMERGE for the treatment of a single migraine attack according to a parallel group design, whereas, in Study 2, patients were randomised to receive each of the treatments for separate migraine attacks according to a crossover design. In both studies, patients who achieved headache relief at 240 minutes post-dose, but experienced a worsening of severity between 4 and 24 hours post-dosing were permitted to take a second dose of double-blind medication identical to the first.

Table 2: Results at 240 Minutes Post First Dose

Parameter	Study 1			Study 2		
	Placebo (n=107)	AMERGE 1 mg (n=219)	AMERGE 2.5 mg (n=209)	Placebo (n=602)	AMERGE 1 mg (n=595)	AMERGE 2.5 mg (n=586)
Pain relief (0/1)[1]	27%	52%*	66%*M	33%	57%*	68%*M
Pain free (0)[2]	10%	26%*	43%*M	15%	33%*	45%*
Nausea free	56%	71%!	77%!	54%	69%*	75%*
Photophobia free	34%	57%!	67%!	33%	53%*	61%*
Phonophobia free	^	^	^	36%	55%*	65%*
Clinical disability[3] (0/1)	49%	62%!	72%!	50%	70%*	76%*

[1] Pain relief is defined as a reduction in headache severity from grade 3 or 2 (severe or moderate) to grade 1 or 0 (mild or no pain)
[2] Pain free is defined as a headache severity score of 0 (no pain)
[3] Clinical disability is measured on a 4-point scale (0=able to function normally, 1=ability mildly impaired, 2=ability severely impaired, 3=bed rest required)
^ photophobia and phonophobia collected as one measure
* $p<0.01$ versus placebo
M $p<0.01$ versus AMERGE 1 mg. Note: comparisons were not performed for any parameter other than pain relief and pain free in study 1 and for pain relief in study 2:
! Statistical comparisons not performed

Significant headache relief was sustained over 24 hours. Data from four placebo controlled studies (n=3160) showed that of the patients who achieved headache relief with AMERGE Tablets 2.5 mg, 72% to 83% did not experience recurrence of headache between 4 and 24 hours post-dosing. Subgroup analyses of the overall population of patients participating in the placebo-controlled trials, indicate that the efficacy of AMERGE was unaffected by migraine type (with/without aura), gender, oral contraceptive use, or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants). In a long-term, repeat dose, open study of 417 patients (all were initiated on a 2.5 mg dose of AMERGE but were given the option to titrate down to a 1 mg dose if 2.5 mg was not well tolerated) a total of 15,301 attacks were treated (mean number of treated attacks/patient=36 for the 2.5 mg dose and 8 for the 1 mg dose) over a period of up to 12 months. Headache response was sustained (as judged by the proportion of attacks treated with AMERGE resulting in headache relief). The median percentage of attacks per patient requiring a second dose for headache recurrence was 8%. Of the 417 patients treating attacks, 10 patients opted for a dosage reduction.

Indications and Clinical Use: AMERGE (naratriptan hydrochloride) Tablets are indicated for the acute treatment of migraine attacks with or without aura. AMERGE Tablets are not for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine (see CONTRAINDICATIONS). Safety and efficacy have not been established for cluster headache which is present in an older, predominantly male population.

Contraindications: AMERGE (naratriptan hydrochloride) Tablets is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular disease (e.g., atherosclerotic disease, congenital heart disease) should not receive AMERGE. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS).

Because AMERGE can give rise to increases in blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension (see WARNINGS). Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because AMERGE may also cause coronary vasospasm and these effects may be additive, the use of AMERGE within 24 hours before or after treatment with other 5-HT1 receptor agonists, or ergotamine-containing drugs or their derivatives (e.g., dihydroergotamine, methysergide) is contraindicated. AMERGE is contraindicated in patients with hemiplegic, basilar, or ophthalmoplegic migraine. AMERGE Tablets are contraindicated in patients with severe renal impairment (creatinine clearance <15 mL/min) (see ACTIONS AND CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION).

AMERGE Tablets are contraindicated in patients with severe hepatic impairment (Child-Pugh grade C) (see ACTIONS AND CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION).

AMERGE Tablets are contraindicated in patients with hypersensitivity to naratriptan or any component of the formulation.

Warnings:

AMERGE (naratriptan hydrochloride) should only be used where a clear diagnosis of migraine has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: AMERGE has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. In rare cases, the symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of another 5-HT_1 agonist. AMERGE should not be given to patients who have documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). **It is strongly recommended that AMERGE not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female who is surgically or physiologically postmenopausal, or male who is over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, AMERGE should not be administered (see CONTRAINDICATIONS).**

For patients with risk factors predictive of CAD who are considered to have a satisfactory cardiovascular evaluation, the first dose of AMERGE should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining electrocardiograms in patients with risk factors during the interval immediately following AMERGE administration on the first occasion of use. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

Intermittent long-term users of AMERGE who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluations over the course of treatment.

If symptoms consistent with angina occur after the use of AMERGE, ECG evaluation should be carried out to look for ischemic changes.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to AMERGE (naratriptan hydrochloride).

Cardiac Events and Fatalities Associated With 5-HT_1 Agonists: AMERGE can cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

Premarketing Experience With AMERGE Tablets: Among approximately 3500 patients with migraine who participated in premarketing clinical trials of AMERGE Tablets, four patients treated with single oral doses of AMERGE ranging from 1 to 10 mg experienced asymptomatic ischemic ECG changes with at least one, who took 7.5 mg, likely due to coronary vasospasm.

Cerebrovascular Events and Fatalities With 5-HT_1 Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT_1 agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA).

Special Cardiovascular Pharmacology Studies: In subjects (n=10) with suspected coronary artery disease undergoing angiography, naratriptan at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort).

Migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving subcutaneous naratriptan 1.5 mg in the absence of a migraine attack. Naratriptan was associated with a reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperemic myocardial blood flow (~10%). The relevance of these findings to the use of recommended oral doses of naratriptan is not known.

Hypersensitivity: Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as AMERGE. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS). Owing to the possibility of cross-reactive hypersensitivity reactions, AMERGE should not be used in patients having a history of hypersensitivity to sumatriptan or chemically-related 5-HT_1 receptor agonists. As AMERGE contains a sulphonamide component, there is a theoretical risk of hypersensitivity reactions in patients with known hypersensitivity to sulphonamides.

Other Vasospasm-Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of another 5-HT_1 agonist to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.

Increases in Blood Pressure: Elevations in blood pressure have been reported following use of AMERGE. At the recommended oral doses, the elevations are generally small (population average maximum increases of <5 mmHg systolic and <3 mmHg diastolic at the 2.5 mg dose). The effects may be more pronounced in the elderly and hypertensive patients. In a pharmacodynamic study conducted in normotensive patients (n=12) and in hypertensive patients controlled by antihypertensive treatment (n=12), the pressor effects of AMERGE were greater in hypertensive patients (weighted mean increases in systolic and diastolic blood pressure of 6 and 4 mmHg in hypertensive subjects versus 3 and 2 mmHg in normotensive patients receiving two 2.5 mg doses separated by a 2 hour time interval). Two hypertensive patients experienced three events of chest discomfort while receiving naratriptan. Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT_1 agonists with and without a history of hypertension. AMERGE is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS).

Precautions: Cardiovascular: Discomfort in the chest, neck, throat, and jaw (including pain, pressure, heaviness, tightness) has been reported after administration of AMERGE (naratriptan hydrochloride). Because 5-HT_1 agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following AMERGE should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following naratriptan administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS).

Neurologic Conditions: Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of AMERGE.

Seizures: Caution should be observed if AMERGE is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold.

Renal or Hepatic Impairment: AMERGE Tablets should be administered with caution to patients with impaired renal or hepatic function (see ACTIONS AND CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION).

Psychomotor Impairment: In a study of psychomotor function in healthy volunteers, single oral 5 and 10 mg doses of AMERGE were associated with sedation and decreased alertness. Although these doses are higher than those recommended for the treatment of migraine, patients should be cautioned that drowsiness may occur following treatment with AMERGE. They should be advised not to perform skilled tasks (e.g. driving or operating machinery) if drowsiness occurs.

Drug Interactions: The limited metabolism of AMERGE and the wide range of cytochrome P450 isoenzymes involved, as determined by *in vitro* studies, suggest that significant drug interactions with AMERGE are unlikely. AMERGE did not inhibit monoamine oxidase enzymes (MAO-A or MAO-B) *in vitro*. The possibility of pharmacodynamic *in vivo* interactions between AMERGE and monoamine oxidase inhibitors has not been investigated.

Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a

theoretical basis for these effects being additive, ergot-containing or ergot-type medications (like dihydroergotamine or methysergide) are contraindicated within 24 hours of AMERGE administration (see CONTRAINDICATIONS).

Other 5-HT$_1$ Agonists: The administration of AMERGE with other 5-HT$_1$ agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with co-administration of 5-HT$_1$ agonists, use of these drugs within 24 hours of each other is contraindicated.

Other Serotonergic Drugs: Rare postmarketing reports describe patients with weakness, hyperreflexia, and incoordination following the combined use of a selective serotonin reuptake inhibitor (SSRI) and 5-HT$_1$ agonists. If concomitant treatment with AMERGE and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline), tricyclic antidepressant, monoamine oxidase inhibitor, or other drug with serotonergic activity is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised.

Hormonal contraceptives: In a population pharmacokinetic study in migraine patients, hormonal contraceptive use was associated with a 32% decrease in naratriptan clearance.

Tobacco: In a population pharmacokinetic study in migraine patients, tobacco use was associated with a 29% increase in naratriptan clearance.

Alcohol and Food: Clinical studies did not reveal any pharmacokinetic interaction when naratriptan was administered together with alcohol or food.

Use in Pregnancy: The safety of AMERGE for use during human pregnancy has not been established. AMERGE Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To monitor fetal outcomes of pregnant women exposed to AMERGE, Glaxo Wellcome Inc. maintains a Naratriptan Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 722-9292, ext. 39441.

Use in Nursing Mothers: AMERGE and/or its metabolites are distributed into the milk of lactating rats (at 2 hours post oral gavage dosing, levels in milk were 3.5 times higher than maternal plasma levels). Therefore, caution should be exercised when considering the administration of AMERGE Tablets to nursing women.

Use in Pediatrics: Safety and effectiveness of AMERGE Tablets have not been studied in children under 12 years of age. Use of the drug in this age group is, therefore, not recommended.

Adolescents: The efficacy of AMERGE Tablets at single doses of 0.25, 1.0 and 2.5 mg was not demonstrated to be greater than placebo in adolescents (12-17 years). Therefore, the use of the drug in adolescents is not recommended.

Use in the Elderly: The safety and effectiveness of AMERGE has not been adequately studied in individuals over 65 years of age. AMERGE Tablets are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in elderly patients who have reduced renal function. In addition, elderly patients are more likely to have decreased hepatic function; they are at higher risk for CAD; and blood pressure increases may be more pronounced in the elderly. Clinical studies of AMERGE Tablets did not include patients over 65 years of age. Its use in this age group is, therefore, not recommended.

Drug/Laboratory Test Interactions: AMERGE Tablets are not known to interfere with commonly employed clinical laboratory tests.

Dependence Liability: In one clinical study enrolling 12 subjects, all of whom had experience using oral opiates and other psychoactive drugs, subjective responses typically associated with many drugs of abuse were produced with less intensity during treatment with AMERGE (1-5 mg) than with codeine (30 to 90 mg). Long term studies (12 months) in migraine patients using AMERGE Tablets revealed no evidence of increased drug utilization.

Melanin Binding: In pigmented rats treated with a single oral dose (10 mg/kg) of radiolabelled naratriptan, radioactivity was detected in the eyes at 3 months post-administration, a finding which suggests that the drug or its metabolites may bind to the melanin of the eye. The possible clinical significance of this finding is unknown. No systematic monitoring of ophthalmologic function was undertaken in clinical trials. Prescribers should consider the possibility of long-term ophthalmologic effects due to accumulation of naratriptan in melanin-rich tissues.

Adverse Reactions: Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT$_1$ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Experience in Controlled Clinical Trials with AMERGE

Typical 5-HT$_1$ Agonist Adverse Reactions: As with other 5-HT$_1$ agonists, AMERGE (naratriptan hydrochloride) has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb.

Acute Safety: The safety and efficacy of the 1 and 2.5 mg doses of AMERGE were investigated in four placebo-controlled clinical trials in adult migraine patients. Two of these trials were of parallel group design and involved the treatment of a single migraine attack. A third study was of crossover design and involved the treatment of one migraine attack per dose group. The fourth study was a parallel group trial in which patients treated up to 3 migraine attacks. In all studies, patients who achieved headache relief at 240 minutes post-dose, but experienced a worsening of severity between 4 and 24 hours post-dosing, were permitted to take a second dose of double-blind medication identical to the first.

The overall incidence of adverse events following doses of 1 mg or 2.5 mg AMERGE (one or two doses) were similar to placebo (28.5% and 30.2% versus 28.9% with placebo). AMERGE Tablets were generally well tolerated and most adverse reactions were mild, transient and self-limiting. The most common adverse events to occur at a higher rate than in the corresponding placebo group were malaise/fatigue (2.4% versus 0.8% with placebo) and neck/throat/jaw sensations (2.1% versus 0.3% with placebo). Table 3 lists the most common adverse events that occurred in the four large placebo-controlled clinical trials. Only events that occurred at a frequency of 1% or more in the AMERGE Tablets 2.5 mg or 1 mg group and were more frequent in that group than in the placebo group are included in Table 3. From this table, it appears that many of these adverse events are dose related.

Table 3: Treatment-Emergent Adverse Events in Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients With Migraine*

	Placebo	AMERGE 1 mg	AMERGE 2.5 mg
Number of Patients	922	1024	1016
Number of Migraine Attacks Treated	1059	1387	1368
Symptoms of Potentially Cardiac Origin			
• neck/throat/jaw sensations*	0.3%	1.7%	2.1%
• chest sensations*	1.1%	0.8%	1.2%
• upper limb sensations*	0.3%	0.5%	1.4%
Neurology			
• dizziness	1.5%	1.0%	2.2%
• drowsiness/sleepiness	0.8%	0.9%	1.7%
• paresthesia	0.8%	1.6%	1.5%
• head/face sensations*	0.5%	0.5%	1.3%
• headache	0.2%	0.4%	1.0%
Gastrointestinal			
• nausea	6.2%	5.9%	6.3%
• hyposalivation	0.3%	0.5%	1.0%
Non-Site Specific			
• malaise & fatigue	0.8%	1.6%	2.4%

*The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.

Long-Term Safety: In a long-term open study, 417 patients treated 15,301 migraine attacks with AMERGE over a period of up to 1 year. The most common adverse events in descending order of frequency were as follows: nausea (16%); malaise/fatigue (11%); drowsiness (10%); chest sensations* (8%); neck/throat/jaw sensations* (8%); paresthesia (7%); head/face sensations* (6%); vomiting (6%); and dizziness (5%). Due to the lack of a placebo arm in this study, the role of AMERGE in causation cannot be reliably determined. (*See footnote for Table 3)

Other Adverse Events Observed in Association with AMERGE: In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because some events were observed in open and uncontrolled studies, the role of AMERGE Tablets in their causation cannot be reliably determined. All reported events are included except those already listed in Table 3, those too general to be informative, and those not reasonably associated with the use of the drug. Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (N=2790) exposed to AMERGE Tablets. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare adverse events are those occurring in fewer than 1/1,000 patients.

Cardiovascular: Infrequent were palpitations, increased blood pressure, tachyarrhythmias and abnormal ECGs. Rare were bradycardia, hypotension, varicosities and heart murmur.

Ear, Nose & Throat: Frequent were ear, nose & throat infections. Infrequent were phonophobia, sinusitis, and upper respiratory inflammation. Rare were allergic rhinitis, labyrinthitis, tinnitus, ear, nose & throat haemorrhage and hearing difficulty.

Endocrine & Metabolic: Infrequent were thirst and polydipsia, dehydration and fluid retention. Rare were hypertipidemia, hypercholesterolemia, hypothyroidism, hyperglycemia, glycosuria and ketonuria and parathyroid neoplasm.

Eye: Infrequent was photophobia. Rare were eye haemorrhage, dry eyes and difficulty focusing.

Gastrointestinal: Frequent was vomiting. Infrequent were dyspeptic symptoms, diarrhea, hyposalivation, gastrointestinal discomfort & pain, gastroenteritis and constipation. Rare were abnormal liver function tests, abnormal bilirubin levels, salivary gland swelling, hemorrhoids, gastritis, esophagitis, oral itching & irritation, regurgitation & reflux and gastic ulcers.

Musculoskeletal: Infrequent were musculoskeletal/muscle pain, muscle cramps & spasms, arthralgia & articular rheumatism. Rare were joint and muscle stiffness, tightness & rigidity.

Neurology: Frequent was migraine. Infrequent were vertigo, tremors, sleep disorders, cognitive function disorders and hyperesthesia. Rare were disorders of equilibrium, decreased consciousness, confusion, sedation, coordination disorders, neuritis, dreams, altered sense of taste, motor retardation, muscle twitching & fasciculations.

Non-Site Specific: Frequent were paresthesia and heat sensations. Infrequent were chills and/or fever, descriptions of odour or taste and feelings of pressure/tightness/heaviness. Rare were allergies & allergic reactions, mobility disorders and faintness.

Psychiatry: Infrequent were anxiety and depressive disorders. Rare were aggression, agitation and detachment.

Reproduction: Rare were lumps of female reproductive tract and inflammation of the fallopian tube.

Skin: Infrequent were skin photosensitivity, skin rashes, pruritus, sweating and urticaria. Rare were skin erythema, dermatitis & dermatosis and pruritic skin rash.

Urology: Infrequent were urinary infections. Rare were urinary tract haemorrhage, urinary urgency and pyelitis.

Symptoms and Treatment of Overdosage: In clinical studies, numerous patients (n=222) and healthy subjects (n=196) have received AMERGE (naratriptan hydrochloride) Tablets at doses of 5-25 mg. In the majority of cases, no serious adverse events were reported. One patient treated with a 7.5-mg dose experienced ischemic ECG changes which were likely due to coronary vasospasm. This event was not associated with a serious clinical outcome. A patient who was mildly hypertensive experienced a significant increase in blood pressure (baseline value of 150/98 to 204/144 mmHg at 225 minutes) beginning 30 minutes after the administration of a 10 mg dose (4 times the maximum recommended single dose). The event resolved with antihypertensive treatment. Administration of
25 mg (10 times the maximum recommended single dose) in one healthy male subject increased blood pressure from 120/67 mmHg pretreatment up to 191/113 mmHg at approximately 6 hours postdose and resulted in adverse events including light-headedness, tension in the neck, tiredness, and loss of coordination. Blood pressure returned to near baseline by 8 hours after dosing without any pharmacological intervention.

The elimination half-life of naratriptan is about 5 to 8 hours (see ACTIONS AND CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with AMERGE Tablets should continue for at least 24 hours or longer if symptoms or signs persist. Standard supportive treatment should be applied as required. If the patient presents with chest pain or other symptoms consistent with angina pectoris, electrocardiogram monitoring should be performed for evidence of ischemia. Appropriate treatment (e.g., nitroglycerin or other coronary artery vasodilators) should be administered as required.

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of AMERGE.

Dosage and Administration: AMERGE (naratriptan hydrochloride) Tablets are recommended only for the acute treatment of migraine attacks. AMERGE should not be used prophylactically.

Adults: The minimal effective single adult dose of AMERGE Tablets is 1 mg. The maximum recommended single dose is 2.5 mg (see CLINICAL STUDIES).

Table 4: Percentage of Patients with Headache Relief at 4 Hours Post-Dosing?

	Placebo		AMERGE 1 mg		AMERGE 2.5 mg	
	%	(N)	%	(N)	%	(N)
Study 1	39	(91)	64	(85)	63^	(87)
Study 2	34	(122)	50*	(117)	60*^	(127)
Study 3	27	(107)	52*	(219)	66*M	(209)
Study 4	33	(602)	57*	(595)	68*M	(586)

? Pain relief is defined as a reduction in headache severity from grade 3 or 2 (severe or moderate) to grade 1 or 0 (mild or no pain)
^ Comparison between 1 mg and 2.5 mg AMERGE doses was not performed *p<0.05 versus placebo
M p<0.01 versus AMERGE 1 mg

In three of the four studies, optimal rates of headache relief were achieved with a 2.5 mg dose. As patients may vary in their dose-responsiveness, the choice of dose should be made on an individual basis, weighing the possible benefit of the 2.5 mg dose with the potential for a greater risk of adverse events.

If the migraine headache returns, or if a patient has a partial response, the initial dose may be repeated once after 4 hours, for a maximum dose of 5 mg in a 24 hour period. The safety of treating, on average, more than four headaches in a 30 day period has not been established.

AMERGE Tablets should be swallowed whole with fluids. AMERGE tablets should be taken as early as possible after the onset of a migraine headache, but are effective if taken at a later stage.

If a patient does not respond to the first dose of AMERGE Tablets, a second dose should not be taken for the same attack, as it is unlikely to be of benefit.

Renal disease/functional impairment causes prolongation of the half-life of orally administered AMERGE. Consequently, if treatment is deemed advisable in the presence of renal impairment, a maximum single dose of 1 mg should be administered. No more than a total of 2 mg should be taken in any 24 hour period. Repeated dosing in renally impaired patients has not been evaluated (see ACTIONS AND CLINICAL PHARMACOLOGY). Administration of AMERGE tablets in patients with severe renal impairment (creatinine clearance <15 mL/min) is contraindicated (see CONTRAINDICATIONS).

Hepatic disease/functional impairment causes prolongation of the half-life of orally administered AMERGE. Consequently, if treatment is deemed advisable in the presence of hepatic impairment, a maximum single dose of 1 mg should be administered. No more than a total of 2 mg should be taken in any 24 hour period (see ACTIONS AND CLINICAL PHARMACOLOGY). Administration of AMERGE Tablets in patients with severe hepatic impairment (Child-Pugh grade C) is contraindicated (see CONTRAINDICATIONS).

Hypertension: AMERGE should not be used in patients with uncontrolled or severe hypertension. Patients with mild to moderate controlled hypertension should be treated cautiously at the lowest effective dose.

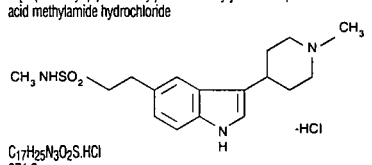
Pharmaceutical Information

Drug Substance

Proper Name: naratriptan hydrochloride

Chemical Name: 2-[3-(1-Methyl-piperidin-4-yl)-1H-indol-5-yl]-ethanesulphonic acid methylamide hydrochloride

Structural Formula:



Molecular Formula: $C_{17}H_{25}N_3O_2S.HCl$

Molecular Weight: 371.9

Physical Characteristics: white to pale yellow microcrystalline solid with a melting point of 246EC

Solubility: In water (25EC) = 35 mg/mL

pH and pKa: pKa = 9.7 (piperidinyl nitrogen)
pH (1% aqueous solution) = 6.3

Composition: AMERGE 2.5 mg Tablets contain 2.5 mg of naratriptan (base) as the hydrochloride salt and the following non-medicinal ingredients: croscarmellose sodium; hydroxypropyl methylcellulose; indigo carmine aluminium lake (FD&C Blue No. 2); iron oxide yellow; lactose; magnesium stearate; microcrystalline cellulose; titanium dioxide; and triacetin.

AMERGE 1 mg Tablets contain 1 mg of naratriptan (base) as the hydrochloride salt and the following non-medicinal ingredients: croscarmellose sodium; hydroxypropyl methylcellulose; lactose; magnesium stearate; microcrystalline cellulose; titanium dioxide; and triacetin.

Stability and Storage Recommendations: AMERGE Tablets should be stored below 30°C.

Availability of Dosage Forms: AMERGE Tablets 2.5 mg are green film-coated, D-shaped tablets embossed GXCE5 on one side, available in blister packs of 2 or 6 tablets (4 blister packs inserted into a carton), or bottles of 60 tablets.

AMERGE Tablets 1 mg are white film-coated, D-shaped tablets embossed GXCE3 on one side, available in blister packs of 2 tablets (4 blister packs inserted into a carton), or bottles of 60 tablets.

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1. Product Monograph of PrAMERGE®; Glaxo Wellcome Inc. 1998.
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Product Monograph available to health care professionals upon request.

GlaxoWellcome

Glaxo Wellcome Inc.
7333 Mississauga Road North, Mississauga, Ontario L5N 6L4

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See pages A16, A17

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 $beta_{ser17}$. 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. 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, multiclinic (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 ≤ 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 baclofen 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.

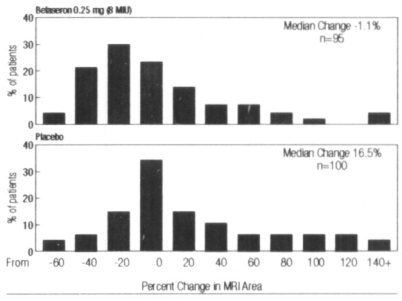
Of the first 372 patients randomized, 72 (19%) failed to complete 2 full years on their assigned treatments. The reasons given for withdrawal varied with treatment assignment. Excessive use of steroids accounted for 11 of the 26 placebo withdrawals. In contrast, among the 25 withdrawals from the 0.25 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 fall 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 demyelinization (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.

Table 1: 2-Year Study Results

Primary and Secondary Endpoints

Efficacy Parameters		Treatment Groups			Statistical Comparisons p-value		
Primary Clinical Endpoints		**Placebo (n=123)**	**0.05 mg (1.6 MIU) (n =125)**	**0.25 mg (8 MIU) (n=124)**	**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†	20	22	29	0.151	0.077	0.001
	1	32	31	39			
	2	20	28	17			
	3	15	15	14			
	4	15	7	9			
	≥5	21	16	8			
Secondary Endpoints††							
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‡ at endpoint		0.21	0.21	-0.07	0.995	0.108	0.144
Mean change in Scripps score‡‡ 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.

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.

Awareness 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/mm³. When the absolute neutrophil count had returned to a value greater than 750/mm³, 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) have 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

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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 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/mm³ (82%),
- ALT (SGPT) > 5 times baseline value (19%),
- absolute neutrophil count < 1500/mm³ (18%) (no patients had absolute neutrophil counts < 500/mm³),
- WBC < 3000/mm³ (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/mm³ (82%),
- ALT (SGPT) > 5 times baseline value (19%),
- absolute neutrophil count < 1500/mm³ (18%),
- menstrual disorder (17%),
- WBC < 3000/mm³ (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
Body as a Whole		
- 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%
Cardiovascular System		
- Migraine	7%	12%
- Palpitation*	2%	8%
- Hypertension	2%	7%
- Tachycardia	3%	6%
- Peripheral vascular disorder	2%	5%
- Hemorrhage	1%	3%
Digestive System		
- Diarrhea	29%	35%
- Constipation	18%	24%
- Vomiting	19%	21%
- Gastrointestinal disorder	3%	6%
Endocrine System		
- Goiter	0%	2%

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

Adverse Reaction	Placebo n=123	0.25 mg (8 MIU) n=124
Hemic and Lymphatic System		
- Lymphocytes < 1500/mm³	67%	82%
- ANC < 1500/mm³*	6%	18%
- WBC < 3000/mm³*	5%	16%
- Lymphadenopathy	11%	14%
Metabolic and Nutritional Disorders		
- ALT (SGPT) > 5 times baseline*	6%	19%
- 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%
Musculoskeletal System		
- Myalgia*	28%	44%
- Myasthenia	10%	13%
Nervous System		
- 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%
Respiratory System		
- Sinusitis	26%	36%
- Dyspnea*	2%	8%
- Laryngitis	2%	6%
Skin and Appendages		
- Sweating*	11%	23%
- Alopecia	2%	4%
Special Senses		
- Conjunctivitis	10%	12%
- Abnormal vision	4%	7%
Urogenital System		
- 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 nondrug 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 hemorrhage, syncope, *thrombophlebitis, thrombosis, varicose vein, vasospasm,* venous pressure increased, ventricular extrasystoles, and ventricular fibrillation;

Digestive System: aphthous stomatitis, cardiospasm, 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, periodontal abscess, proctitis, rectal hemorrhage, salivary gland enlargement, stomach ulcer, 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/mm³, 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, hypalgesia, 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, hypoventilation, 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, gynecomastia, 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).

References:

1. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. ***Neurology*** 1995;45:1277-1285. **2.** 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. **3.** Paty DW, *et al.* 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. **4.** ®Betaseron® Product Monograph, Berlex Canada Inc. 1996. **5.** Data on file, Health Canada, March 1998.

Product Monograph available to healthcare professionals upon request.

Epival®

(divalproex sodium)

PRESCRIBING INFORMATION

NAME OF DRUG: EPIVAL® (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 spinal 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_{450} isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P_{450} 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-Epoxide: 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 -epoxide 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 -epoxide 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 unimpaired 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, hypesthesia, 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. Hyperglycinemia has been reported and associated with a fatal outcome in a patient with preexisting non-ketotic hyperglycinemia.

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)
Body as a Whole		
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
Digestive System		
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
Nervous System		
Somnolence	19.1	12.4
Dizziness	12.4	4.1
Tremor	5.6	6.2
Respiratory System		
Pharyngitis	6.7	9.3
Skin and Appendages		
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.

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ONCE-A-WEEK AVONEX™ (Interferon beta-1a) IM Injection

PRESCRIBING INFORMATION

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

Description

AVONEX™ (Interferon beta-1a) is produced by recombinant DNA technology. Interferon beta-1a is a 166 amino acid glycoprotein with a predicted molecular weight of approximately 22,500 daltons. It is produced by mammalian cells (Chinese Hamster Ovary cells) into which the human interferon beta gene has been introduced. The amino acid sequence of AVONEX™ is identical to that of natural human interferon beta.

Using the World Health Organization (WHO) natural interferon beta standard, Second International Standard for Interferon, Human Fibroblast (Gb-23-902-531), AVONEX™ has a specific activity of approximately 200 million international units (IU) of antiviral activity per mg; 30 mcg of AVONEX™ contains 6 million IU of antiviral activity.

General

Interferons are a family of naturally occurring proteins and glycoproteins that are produced by eukaryotic cells in response to viral infection and other biological inducers. Interferon beta, one member of this family, is produced by various cell types including fibroblasts and macrophages. Natural interferon beta and Interferon beta-1a are similarly glycosylated. Glycosylation of other proteins is known to affect their stability, activity, biodistribution, and half-life in blood. Glycosylation also decreases aggregation of proteins. Protein aggregates are thought to be involved in the immunogenicity of recombinant proteins. Aggregated forms of interferon beta are known to have lower levels of specific activity than monomeric (non-aggregated) forms of interferon beta.

Biologic Activities

Interferons are cytokines that mediate antiviral, antiproliferative, and immunomodulatory activities in response to viral infection and other biological inducers. Three major interferons have been distinguished: alpha, beta, and gamma. Interferons alpha and beta form the Type I class of interferons and interferon gamma is a Type II interferon. These interferons have overlapping but clearly distinct biological activities.

Interferon beta exerts its biological effects by binding to specific receptors on the surface of human cells. This binding initiates a complex cascade of intracellular events that lead to the expression of numerous interferon-induced gene products and markers. These include 2', 5'-oligoadenylate synthetase, β_2-microglobulin, and neopterin. These products have been measured in the serum and cellular fractions of blood collected from patients treated with AVONEX™.

The specific interferon-induced proteins and mechanisms by which AVONEX™ exerts its effects in multiple sclerosis (MS) have not been fully defined. To understand the mechanism(s) of action of AVONEX™, studies were conducted to determine the effect of IM injection of AVONEX™ on levels of the immunosuppressive cytokine interleukin 10 (IL-10) in serum and cerebrospinal fluid (CSF) of treated patients. IL-10, or cytokine synthesis inhibitory factor, is a potent immunosuppressor of a number of pro-inflammatory cytokines such as interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-∝), interleukin 1 (IL-1), tumor necrosis factor beta (TNF- ß), and interleukin 6 (IL-6), which are secreted by T lymphocyte helper-1 (Th^1) cells and macrophages. Elevated serum IL-10 levels were seen after IM injection of AVONEX™, from 48 hours post-injection through at least 7 days. Similarly, in the Phase III study, IL-10 levels in CSF were significantly increased in patients treated with AVONEX™ compared to placebo. CSF IL-10 levels correlated with a favourable clinical treatment response to AVONEX™. Upregulation of IL-10 represents a possible mechanism of action of interferon beta in relapsing MS. IL-10 has been demonstrated to decrease relapses in acute and chronic relapsing experimental autoimmune encephalomyelitis (EAE), an animal model resembling MS. However, no relationship has been established between the absolute levels of IL-10 and the clinical outcome in MS.

CLINICAL TRIALS: EFFECTS IN MULTIPLE SCLEROSIS

The clinical effects of AVONEX™ (Interferon beta-1a) in MS were studied in a randomized, multicentre, double-blind, placebo-controlled study in patients with relapsing (stable or progressive) MS. In this study, 301 patients received either 6 million IU (30 mcg) of AVONEX™ (n=158) or placebo (n=143) by IM injection once weekly. Patients were entered into the trial over a 2 1/2 year period, received injections for up to 2 years, and continued to be followed until study completion. By design, there was staggered enrollment into the study with termination at a fixed point, leading to variable lengths of follow-up. There were 144 patients treated with AVONEX™ for more than 1 year, 115 patients for more than 18 months, and 82 patients for 2 years.

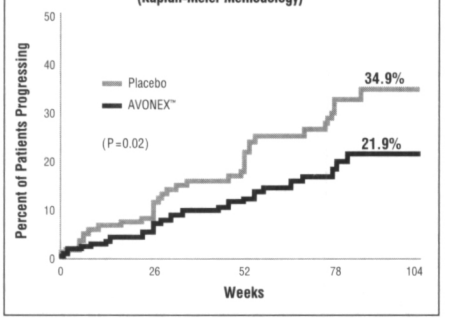
All patients had a definite diagnosis of MS of at least 1 year duration and had at least 2 exacerbations in the 3 years prior to study entry (or 1 per year if the duration of disease was less than 3 years). At entry, study participants were without exacerbation during the prior 2 months and had Kurtzke Expanded Disability Status Scale (EDSS) scores ranging from 1.0 to 3.5. The mean EDSS score at baseline was 2.3 for placebo-treated patients and 2.4 for AVONEX™-treated patients. Patients with chronic progressive multiple sclerosis were excluded from this study.

The primary outcome assessment was time to progression in disability, measured as an increase in the EDSS of at least 1.0 point that was sustained for at least 6 months. The requirement for a sustained 6 month change was chosen because this reflects permanent disability rather than a transient effect due to an exacerbation. Studies show that of the patients who progress and are confirmed after only 3 months, 18% revert back to their baseline EDSS, whereas after 6 months only 11% revert.

Secondary outcomes included exacerbation frequency and results of magnetic resonance imaging (MRI) scans of the brain including gadolinium (Gd)-enhanced lesion number and volume and T2-weighted (proton density) lesion volume. Additional secondary endpoints included upper and lower extremity function tests.

Time to onset of sustained progression in disability was significantly longer in patients treated with AVONEX™ than in patients receiving placebo (p = 0.02). The Kaplan-Meier plots of these data are presented in Figure 1. The Kaplan-Meier estimate of the percentage of patients progressing by the end of 2 years was 34.9% for placebo-treated patients and 21.9% for AVONEX™-treated patients, indicating a slowing of the disease process. This represents a significant reduction in the risk of disability progression in patients treated with AVONEX™, compared to patients treated with placebo.

FIGURE 1
Onset of Sustained Disability Progression by Time on Study (Kaplan-Meier Methodology)



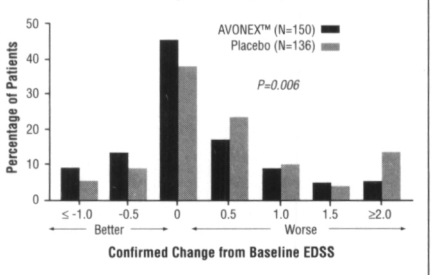
Note: Disability progression represents at least a 1.0 point increase in EDSS score sustained for at least 6 months. The value p=0.02 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given timepoint (e.g., 34.9% vs. 21.9% at Week 104.).

The distribution of confirmed EDSS change from study entry (baseline) to the end of the study is shown in Figure 2. There was a statistically significant difference between treatment groups in confirmed change for patients with at least 2 scheduled visits (136 placebo-treated and 150 AVONEX™-treated patients; p = 0.006; see Table 1). Confirmed EDSS change was calculated as the difference between the EDSS score at study entry and 1 of the scores determined at the last 2 scheduled visits. Further analyses using more rigorous measures of progression of disability were performed. When the requirement for sustained EDSS change was increased from 6 months to 1 year, a significant benefit in favour of AVONEX™ recipients persisted (p=0.002). When treatment failure was defined as 2.0 points or greater increase in EDSS sustained for 6 months, 18.3% of placebo-treated patients worsened compared to 6.1% of AVONEX™-treated patients. Additionally, significantly fewer AVONEX™ recipients progressed to EDSS milestones of 4.0 (14% vs. 5%, p=0.014) or 6.0 (7% vs. 1%, p=0.028).

The rate and frequency of exacerbations were determined as secondary outcomes (see Table 1). AVONEX™ treatment significantly decreased the frequency of exacerbations in patients who were enrolled in the study for at least 2 years, from 0.90 in the placebo-treated group to 0.61 in the AVONEX™-treated group (p=0.002). This represents a 32% reduction.

Additionally, placebo-treated patients were twice as likely to have 3 or more exacerbations during the study when compared to AVONEX™-treated patients (32% vs. 14%).

FIGURE 2
Confirmed EDSS Change from Study Entry to End of Study



Gd-enhanced and T2-weighted (proton density) MRI scans of the brain were obtained in most patients at baseline and at the end of 1 and 2 years of treatment. Gd-enhancing lesions seen on brain MRI scans represent areas of breakdown of the blood brain barrier thought to be secondary to inflammation. Patients treated with AVONEX™ demonstrated significantly lower Gd-enhanced lesion number after 1 and 2 years of treatment ($p \leq 0.05$; see Table 1). The mean number of Gd-enhanced lesions for patients treated with AVONEX™ was 3.2 at baseline and 0.8 at Year 2, compared to 2.3 at baseline and 1.6 at Year 2 for the placebo-treated patients. The volume of Gd-enhanced lesions was also analyzed and showed similar treatment effects ($p \leq 0.03$). Percentage change in T2-weighted lesion volume from study entry to Year 1 was significantly lower in AVONEX™-treated than placebo-treated patients (p = 0.02). A significant difference in T2-weighted lesion volume change was not seen between study entry and Year 2. Treatment with AVONEX™ resulted in a significant decrease in the number of active (new and enlarging) T2 lesions over 2 years (p = 0.002).

The exact relationship between MRI findings and the clinical status of patients is unknown.

Of the limb function tests, only 1 demonstrated a statistically significant difference between treatment groups (favoring AVONEX™).

Twenty-three of the 301 patients (8%) discontinued treatment prematurely. Of these, 1 patient treated with placebo (1%) and 6 patients treated with AVONEX™ (4%) discontinued treatment due to adverse events. Of these 23 patients, 13 remained on study and were evaluated for clinical endpoints.

A summary of the effects of AVONEX™ on the primary and major secondary endpoints of this study is presented in Table 1.

Table 1
MAJOR CLINICAL ENDPOINTS

Endpoint	Placebo	AVONEX™	P-Value
PRIMARY ENDPOINT:			
Time to sustained progression in disability (N: 143, 158)[1]	- See Figure 1 -		0.02[2]
Percentage of patients progressing in disability at 2 years (Kaplan-Meier estimate)[1]	34.9%	21.9%	
SECONDARY ENDPOINTS:			
DISABILITY			
Mean confirmed change in EDSS from study entry to end of study (N: 136, 150)[1]	0.50	0.20	0.006[3]
EXACERBATIONS FOR PATIENTS COMPLETING 2 YEARS:			
Number of exacerbations (N: 87, 85)			
0	26%	38%	0.03[3]
1	30%	31%	
2	11%	18%	
3	14%	7%	
≥ 4	18%	7%	
Percentage of patients exacerbation-free (N: 87, 85)	26%	38%	0.10[4]
Annual exacerbation rate (N: 87, 85)	0.90	0.61	0.002[5]
MRI			
Number of Gd-enhanced lesions:			
At study entry (N: 132, 141)			
Mean (Median)	2.3 (1.0)	3.2 (1.0)	
Range	0-23	0-56	
Year 1 (N: 123, 134)			
Mean (Median)	1.6 (0)	1.0 (0)	0.02[3]
Range	0-22	0-28	
Year 2 (N: 82, 83)			
Mean (Median)	1.6 (0)	0.8 (0)	0.05[3]
Range	0-34	0-13	
T2 lesion volume:			
Percentage change from study entry to Year 1 (N: 116, 123)			
Median	-3.3%	-13.1%	0.02[3]
Percentage change from study entry to Year 2 (N: 83, 81)			
Median	-6.5%	-13.2%	0.36[3]
Number of new and enlarging lesions at Year 2 (N: 80, 78)			
Median	3.0	2.0	0.002[6]

Note: (N: ,) denotes the number of evaluable placebo and AVONEX™ (Interferon beta-1a) patients, respectively.

[1] Patient data included in this analysis represent variable periods of time on study.
[2] Analyzed by Mantel-Cox (logrank) test.
[3] Analyzed by Mann-Whitney rank-sum test.
[4] Analyzed by Cochran-Mantel-Haenszel test.
[5] Analyzed by likelihood ratio test.
[6] Analyzed by Wilcoxon rank-sum test.

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INDICATIONS AND CLINICAL USE

AVONEX™ (Interferon beta-1a) is indicated for the treatment of relapsing forms of multiple sclerosis to slow the progression of disability, decrease the frequency of clinical exacerbations, and reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans. Safety and efficacy have not been evaluated in patients with chronic progressive multiple sclerosis.

CONTRAINDICATIONS

AVONEX™ (Interferon beta-1a) is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation.

WARNINGS

AVONEX™ (Interferon beta-1a) should be used with caution in patients with depression. Depression and suicide have been reported to occur in patients receiving other interferon compounds. Depression and suicidal ideation are known to occur at an increased frequency in the MS population. A relationship between the occurrence of depression and/or suicidal ideation and the use of AVONEX™ has not been established. An equal incidence of depression was seen in the placebo-treated and AVONEX™-treated patients in the placebo-controlled relapsing MS study. Patients treated with AVONEX™ should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, antidepressant therapy or cessation of AVONEX™ therapy should be considered.

PRECAUTIONS

General

Caution should be exercised when administering AVONEX™ (Interferon beta-1a) to patients with pre-existing seizure disorder. In the placebo-controlled study, 4 patients receiving AVONEX™ experienced seizures, while no seizures occurred in the placebo group. Of these 4 patients, 3 had no prior history of seizure. It is not known whether these events were related to the effects of MS alone, to AVONEX™, or to a combination of both. For patients with no prior history of seizure who developed seizures during therapy with AVONEX™, an etiologic basis should be established and appropriate anti-convulsant therapy instituted prior to considering resumption of AVONEX™ treatment. The effect of AVONEX™ administration on the medical management of patients with seizure disorder is unknown.

Patients with cardiac disease, such as angina, congestive heart failure, or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation of therapy with AVONEX™. AVONEX™ does not have any known direct-acting cardiac toxicity; however, symptoms of flu syndrome seen with AVONEX™ therapy may prove stressful to patients with severe cardiac conditions.

Laboratory Tests

In addition to those laboratory tests normally required for monitoring patients with MS, complete blood cell counts and white blood cell differential, platelet counts, and blood chemistries, including liver and thyroid function tests, are recommended during AVONEX™ therapy. During the placebo-controlled study, complete blood cell counts and white blood cell differential, platelet counts, and blood chemistries were performed at least every 6 months. There were no significant differences between the placebo and AVONEX™ groups in the incidence of thyroid abnormalities, liver enzyme elevation, leukopenia, or thrombocytopenia (these are known to be dose-related laboratory abnormalities associated with the use of interferons). Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Drug Interactions

No formal drug interaction studies have been conducted with AVONEX™. In the placebo-controlled study, corticosteroids or ACTH were administered for treatment of exacerbations in some patients concurrently receiving AVONEX™. In addition, some patients receiving AVONEX™ were also treated with anti-depressant therapy and/or oral contraceptive therapy. No unexpected adverse events were associated with these concomitant therapies.

Other interferons have been noted to reduce cytochrome P-450 oxidase-mediated drug metabolism. Formal hepatic drug metabolism studies with AVONEX™ in humans have not been conducted. Hepatic microsomes isolated from AVONEX™-treated rhesus monkeys showed no influence of AVONEX™ on hepatic P-450 enzyme metabolism activity.

As with all interferon products, proper monitoring of patients is required if AVONEX™ is given in combination with myelosuppressive agents.

Use in Pregnancy

If a woman becomes pregnant or plans to become pregnant while taking AVONEX™, she should be informed of the potential hazards to the fetus, and it should be recommended that the woman discontinue therapy. The reproductive toxicity of AVONEX™ has not been studied in animals or humans. In pregnant monkeys given interferon beta at 100 times the recommended weekly human dose (based upon a body surface area comparison), no teratogenic or other adverse effects on fetal development were observed. Abortifacient activity was evident following 3 to 5 doses at this level. No abortifacient effects were observed in monkeys treated at 2 times the recommended weekly human dose (based upon a body surface area comparison). Although no teratogenic effects were seen in these studies, it is not known if teratogenic effects would be observed in humans. There are no adequate and well-controlled studies with interferons in pregnant women.

Nursing Mothers

It is not known whether AVONEX™ is excreted in human milk. Because of the potential of serious adverse reactions in nursing infants, a decision should be made to either discontinue nursing or to discontinue AVONEX™.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients *below the age of 18 years.*

Information to Patients

Patients should be informed of the most common adverse events associated with AVONEX™ administration, including symptoms associated with flu syndrome (see **Adverse Events** and **Information for the Patient**). Symptoms of flu syndrome are most prominent at the initiation of therapy and decrease in frequency with continued treatment. In the placebo-controlled study, patients were instructed to take 650 mg acetaminophen immediately prior to injection and for an additional 24 hours after each injection to modulate acute symptoms associated with AVONEX™ administration.

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

When a physician determines that AVONEX™ can be used outside of the physician's office, persons who will be administering AVONEX™ should receive instruction in reconstitution and injection, including the review of the injection procedures (see **Information for the Patient**). If a patient is to self-administer, the physical ability of that patient to self-inject intramuscularly should be assessed. If home use is chosen, the first injection should be performed under the supervision of a qualified health care professional. A puncture-resistant container for disposal of needles and syringes should be used. Patients should be instructed in the technique and importance of proper syringe and needle disposal and be cautioned against reuse of these items.

ADVERSE EVENTS

The safety data describing the use of AVONEX™ (Interferon beta-1a) in MS patients are based on the placebo-controlled trial in which 158 patients randomized to AVONEX™ were treated for up to 2 years (see **Clinical Trials**).

The 5 most common adverse events associated (at $p<0.075$) with AVONEX™ treatment were flu-like symptoms (otherwise unspecified), muscle ache, fever, chills, and asthenia. The incidence of all 5 adverse events diminished with continued treatment.

One patient in the placebo group attempted suicide; no AVONEX™-treated patients attempted suicide. The incidence of depression was equal in the 2 treatment groups. However, since depression and suicide have been reported with other interferon products, AVONEX™ should be used with caution in patients with depression (see **Warnings**).

In the placebo-controlled study, 4 patients receiving AVONEX™ experienced seizures, while no seizures occurred in the placebo group. Of these 4 patients, 3 had no prior history of seizure. It is not known whether these events were related to the effects of MS alone, to AVONEX™, or to a combination of both (see **Precautions**).

Table 2 enumerates adverse events and selected laboratory abnormalities that occurred at an incidence of 2% or more among the 158 patients *with relapsing MS treated with 30 mcg of AVONEX™ once weekly by* IM injection. Reported adverse events have been classified using standard COSTART terms. Terms so general as to be uninformative or more common in the placebo-treated patients have been excluded.

AVONEX™ has also been evaluated in 290 patients with illnesses other than MS. The majority of these patients were enrolled in studies to evaluate AVONEX™ treatment of chronic viral hepatitis B and C, in which the doses studied ranged from 15 mcg to 75 mcg, given subcutaneously (SC), 3 times a week, for up to 6 months. The incidence of common adverse events in these studies was generally seen at a frequency similar to that seen in the placebo-controlled MS study. In these non-MS studies, inflammation at the site of the SC injection was seen in 52% of treated patients. In contrast, injection site inflammation was seen in 3% of MS patients receiving AVONEX™, 30 mcg by IM injection. SC injections were also associated with the following local reactions: injection site necrosis, injection site atrophy, injection site edema, and injection site hemorrhage. None of the above was observed in the MS patients participating in the placebo-controlled study.

Table 2
Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study

Adverse Event	Placebo (N = 143)	AVONEX™ (N = 158)
Body as a Whole		
Headache	57%	67%
Flu-like symptoms (otherwise unspecified)*	40%	61%
Pain	20%	24%
Fever*	13%	23%
Asthenia	13%	21%
Chills*	7%	21%
Infection	6%	11%
Abdominal pain	6%	9%
Chest pain	4%	6%
Injection site reaction	1%	4%
Malaise	3%	4%
Injection site inflammation	0%	3%
Hypersensitivity reaction	0%	3%
Ovarian cyst	0%	3%
Ecchymosis injection site	1%	2%
Cardiovascular System		
Syncope	2%	4%
Vasodilation	1%	4%
Digestive System		
Nausea	23%	33%
Diarrhea	10%	16%
Dyspepsia	7%	11%
Anorexia	6%	7%
Hemic and Lymphatic System		
Anemia*	3%	8%
Eosinophils ≥ 10%	4%	5%
HCT (%) ≤ 32 (females) or ≤ 37 (males)	1%	3%
Metabolic and Nutritional Disorders		
SGOT ≥ 3 x ULN	1%	3%
Musculoskeletal System		
Muscle ache*	15%	34%
Arthralgia	5%	9%
Nervous System		
Sleep difficult	16%	19%
Dizziness	13%	15%
Muscle spasm	6%	7%
Suicidal tendency	1%	4%
Seizure	0%	3%
Speech disorder	0%	3%
Ataxia	0%	2%
Respiratory System		
Upper respiratory tract infection	28%	31%
Sinusitis	17%	18%
Dyspnea	3%	6%
Skin and Appendages		
Urticaria	2%	5%
Alopecia	1%	4%
Nevus	0%	3%
Herpes zoster	2%	3%
Herpes simplex	1%	2%
Special Senses		
Otitis media	5%	6%
Hearing decreased	0%	3%
Urogenital		
Vaginitis	2%	4%

* Significantly associated with AVONEX™ treatment ($p \leq 0.05$).

Other events observed during premarket evaluation of AVONEX™, administered either SC or IM in all patient populations studied, are listed in the paragraph that follows. Because most of the events were observed in open and uncontrolled studies, the role of AVONEX™ in their causation cannot be reliably determined. **Body as a Whole:** abscess, ascites, cellulitis, facial edema, hernia, injection site fibrosis, injection site hypersensitivity, lipoma, neoplasm, photosensitivity reaction, sepsis, sinus headache, toothache; **Cardiovascular System:** arrhythmia, arteritis, heart arrest, hemorrhage, hypotension, palpitation, pericarditis, peripheral ischemia, peripheral vascular disorder, postural hypotension, pulmonary embolus, spider angioma, telangiectasia, vascular disorder; **Digestive System:** blood in stool, colitis, constipation, diverticulitis, dry mouth, gallbladder disorder, gastritis, gastrointestinal hemorrhage, gingivitis, gum hemorrhage, hepatoma, hepatomegaly, increased appetite, intestinal perforation, intestinal obstruction, periodontal abscess, periodontitis, proctitis, thirst, tongue disorder, vomiting; **Endocrine System:** hypothyroidism; **Hemic and Lymphatic System:** coagulation time increased, ecchymosis, lymphadenopathy, petechia; **Metabolic and Nutritional Disorders:** abnormal healing, dehydration, hypoglycemia, hypomagnesemia, hypokalemia; **Musculoskeletal System:** arthritis, bone pain, myasthenia, osteonecrosis, synovitis; **Nervous System:** abnormal gait, amnesia,

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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 antiepileptic 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		
kg	lb		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	125	0	125
25-39.9	55-87.9	500	250	0	250
40-59.9	88-131.9	750	250	250	250
60-74.9	132-164.9	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® (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

Tradename: EPIVAL®

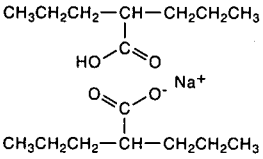
Proper Name: Divalproex sodium

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:* $C_{16}H_{31}NaO_4$

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® 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, Howel 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. Monopharmacy 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 DH. Side effects of valproate. *Am J Med* 1988;84 Suppl 1A:34-41. **7.** Epival Product Monograph. Abbott Laboratories, Limited.

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anxiety, Bell's Palsy, clumsiness, depersonalization, drug dependence, facial paralysis, hyperesthesia, increased libido, neurosis, psychosis; **Respiratory System:** emphysema, hemoptysis, hiccup, hyperventilation, laryngitis, pharyngeal edema, pneumonia; **Skin and Appendages:** basal cell carcinoma, blisters, cold clammy skin, contact dermatitis, erythema, furunculosis, genital pruritus, nevus, rash, seborrhea, skin ulcer, skin discolouration; **Special Senses:** abnormal vision, conjunctivitis, earache, eye pain, labyrinthitis, vitreous floaters; **Urogenital:** breast fibroadenosis, breast mass, dysuria, epididymitis, fibrocystic change of the breast, fibroids, gynecomastia, hematuria, kidney calculus, kidney pain, leukorrhea, menopause, nocturia, pelvic inflammatory disease, penis disorder, Peyronies Disease, polyuria, post menopausal hemorrhage, prostatic disorder, pyelonephritis, testis disorder, urethral pain, urinary urgency, urinary retention, urinary incontinence, vaginal hemorrhage.

Serum Neutralizing Antibodies

MS patients treated with AVONEX™ may develop neutralizing antibodies specific to interferon beta. Analyses conducted on sera samples from 2 separate clinical studies of AVONEX™ suggest that the plateau for the incidence of neutralizing antibodies formation is reached at approximately 12 months of therapy. Data furthermore demonstrate that at 12 months, **approximately 6% of patients treated with AVONEX™ develop neutralizing antibodies.**

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage is unlikely to occur with use of AVONEX™ (Interferon beta-1a). In clinical studies, overdosage was not seen using Interferon beta-1a at a dose of 75 mcg given SC 3 times per week.

DOSAGE AND ADMINISTRATION

The recommended dosage of AVONEX™ (Interferon beta-1a) for the treatment of relapsing forms of multiple sclerosis is 30 mcg injected intramuscularly once a week.

AVONEX™ is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in IM injection technique.

PHARMACEUTICAL INFORMATION

Composition:

AVONEX™ is supplied as a sterile white to off-white lyophilized powder in a single-use vial containing 33 mcg (6.6 million IU) of Interferon beta-1a, 16.5 mg Albumin Human, USP, 6.4 mg Sodium Chloride, USP, 6.3 mg Dibasic Sodium Phosphate, USP, and 1.3 mg Monobasic Sodium Phosphate, USP, and is preservative-free. Diluent is supplied in a single-use vial (Sterile Water for Injection, USP, preservative-free).

Reconstitution:

AVONEX™ is reconstituted by adding 1.1 mL (cc) of diluent (approximate pH 7.3) to the single-use vial of lyophilized powder; 1.0 mL (cc) is withdrawn for administration.

Stability and Storage:

Vials of AVONEX™ must be stored in a 2-8°C (36-46°F) refrigerator. Should refrigeration be unavailable, AVONEX™ can be stored at up to 25°C (77°F) for a period of up to 30 days. DO NOT EXPOSE TO HIGH TEMPERATURES. DO NOT FREEZE. Do not use beyond the expiration date stamped on the vial. Following reconstitution, it is recommended the product be used as soon as possible but within 6 hours stored at 2-8°C (36-46°F).
DO NOT FREEZE RECONSTITUTED AVONEX™.

AVAILABILITY OF DOSAGE FORMS

AVONEX™ (Interferon beta-1a) is available as:

Package (Administration Pack) containing 4 Administration Dose Packs (each containing one vial of AVONEX™, one 10 mL (10 cc) diluent vial, three alcohol wipes, one 3 cc syringe, one Micro Pin®, one needle, and one adhesive bandage).

REFERENCES:
1. AVONEX Product Monograph, March 31, 1998.
2. Data on file, PRB#8154-1, Biogen, Inc., November 20, 1997.
3. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol. 1996;39:285-294.
4. Herndon RM, et al. Ongoing efficacy and safety analysis of interferon beta-1a (AVONEX™) in patients with Multiple Sclerosis. 122nd Annual Meeting ANA, San Diego, CA. 1997.

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TOPAMAX®
topiramate

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 $GABA_A$ 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 (Cmax) of 1.5 µg/mL was achieved within 2 to 3 hours (Tmax). The mean extent of absorption from a 100 mg oral dose of ^{14}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 Cmax 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 ^{14}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 ^{14}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

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

Comparisons with placebo: [a] $p = 0.051$; [b] $p < 0.05$; [c] $p \leq 0.01$; [d] $p \leq 0.001$; [e] $p = 0.053$; [f] $p = 0.065$

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 hypercalciuria. 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 dichlorphenamide, 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).

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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 dichlorphenamide, 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 [a,b]

(Events that occurred in ≥ 2% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

	TOPAMAX® Dosage (mg/day)		
Body System/ Adverse Event	**Placebo** (N=216)	**200-400** (N=113)	**600-1,000** (N=414)
Body as a Whole			
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 Flushes	1.9	2.7	0.7
Nervous System			
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
Gastrointestinal System			
Nausea	7.4	11.5	12.1
Dyspepsia	6.5	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
Metabolic and Nutritional			
Weight Decrease	2.8	7.1	12.8
Neuropsychiatric			
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
Reproductive, Female	(N=59)	(N=24)	(N=128)
Breast Pain, Female	1.7	8.3	0
Dysmenorrhea	6.8	8.3	3.1
Menstrual Disorder	0	4.2	0.8
Reproductive, Male	(N=157)	(N=89)	(N=286)
Prostatic Disorder	0.6	2.2	0
Respiratory System			
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
Skin and Appendages			
Pruritus	1.4	1.8	3.1
Vision			
Diplopia	5.6	14.2	10.4
Vision Abnormal	2.8	14.2	10.1
White Cell and RES			
Leukopenia	0.5	2.7	1.2

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to **TOPAMAX** or placebo.

[b] 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®** 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.

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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 overdosage 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 overdosage 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^2), 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)-ß-D-fructopyranose sulfamate

Molecular Formula: $C_{12}H_{21}NO_8S$

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:

1. Faught E et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. *Neurology* 1996; 46:1684-90. **2.** TOPAMAX (topiramate) Product Monograph. Janssen-Ortho Inc., 1997. **3.** Walker MC and Sander JWAS. Topiramate: a new antiepileptic drug for refractory epilepsy. *Seizure* 1996; 5: 199-203. **4.** Shorvan SD. Safety of topiramate: adverse events and relationships to dosing. *Epilepsia* 1996; 37(Suppl) 2): S18-22.

JANSSEN-ORTHO Inc.
19 Green Belt Drive
North York, Ontario M3C 1L9

TOPAMAX
topiramate

OVERDOSAGE

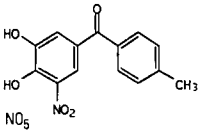
The highest dose of 'Tasmar' (tolcapone) administered to humans was 800 mg t.i.d., with and without levodopa coadministration. This was in a one week study in elderly, healthy volunteers. The peak plasma concentrations of tolcapone at this dose were on average 30 µg/ml (compared to 3 and 6 µg/ml with 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: $C_{14}H_{11}NO_5$
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. 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.

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See page A9

TASMAR®
TOLCAPONE

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 (Cmax) and the time of its occurrence (tmax) 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 (Cmax-Cmin). 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 Cmax 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 tmax 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 (Vss) 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 >99.9% over the concentration range of 0.32 to 30 µg/ml. At clinical doses, mean Cmax 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 ^{14}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 Cmax 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 digitoxin (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 microsome 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 phamacokinetics 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; 200 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 tumor 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 (80/20 mg/kg/day), produced an increased incidence of fetal malformations (primarily external and skeletal digit defects) compared to 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/m² 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/m² 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-methyldopa, 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 premarketing 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% (48/296) 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%, 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 N=298 %	'Tasmar' t.i.d. 100 mg N=296 %	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 Discoloration	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	9.7	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 headedness 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 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, hypertonia, euphoria; Gastrointestinal System: flatulence, abdominal discomfort; Cardiovascular System: hypotension, 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 discolouration; Rare: appetite disturbances, tongue dryness. Cardiovascular System: Infrequent: hypertension, vasodilation, angina pectoris, heart failure, atrial fibrillation, tachycardia, aortic stenosis, arrythmia, arteriospasm, bradycardia, cerebral hemorrhage, coronary artery disorder, heart arrest, myocardial infarct, myocardial ischemia, pulmonary embolus; Rare: arteriosclerosis, cardiovascular disorder, pericar dial 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 discolouration, 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.

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2101 - 32nd St.
Vernon, BC V1T 5L2
Ph: (250) 545-2211
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In accordance with its employment equity policy, the University of Toronto encourages applications from qualified women and men, members of visible minorities, aboriginal persons and persons with disabilities. In accordance with the Canadian Immigration requirements, this advertisement is directed to Canadian Citizens and permanent residents.
Please send curriculum vitae and letter of application to:

Dr. Catherine Zahn
Head, Division of Neurology
The Toronto Hospital and The Mount Sinai Hospital
8EC-034
399 Bathurst Street
Toronto, Ontario M5B 1W8
Tel: (416) 603-5580
Fax: (416) 603-5768

University of Toronto
The Toronto Hospital/Mount Sinai Hospital
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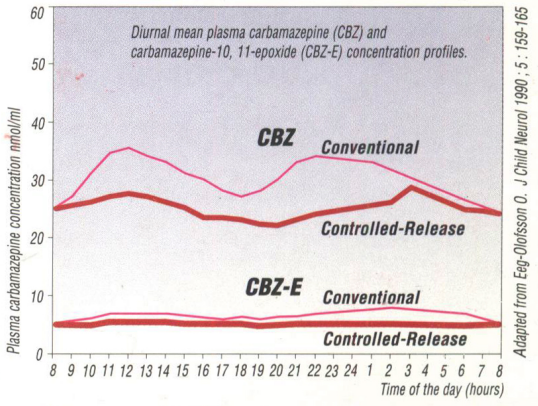

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