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

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 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. 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). 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. Table 1 lists adverse events that occurred at an incidence of 2% 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. The Adverse Reactions section has been condensed. See full Product Monograph for the complete information.

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. 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

TABLE 1

Adverse events with incidence ≥2% 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	4	–
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
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
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)	–	–	9.8	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
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
Saliva Increased	–	–	2.4	0.8
Dysphagia	1.3	0.0	2.4	0.8
Heart Rate and Rhythm				
Palpitation	3.2	2.0	2.9	2.5
Metabolic and Nutritional				
Alkaline Phosphate Increased	2.5	1.4	1.0	0.0
Weight Decrease	–	–	2.4	0.8
Musculoskeletal System				
Arthralgia	–	–	6.7	5.0
Arthritis	–	–	2.9	0.8
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
Red Blood Cell				
Anemia	–	–	2.4	0.0
Reproductive Male				
Impotence	2.5	1.4	–	–
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	–	–
Urinary System				
Urinary Tract Infection	5.1	4.1	6.3	2.5
Vascular Extracardiac				
Peripheral Ischemia	2.5	0.0	–	–
Vision				
Vision Abnormal	5.7	3.4	–	–
Eye Abnormality	3.2	1.4	–	–

–: Incidence of adverse event <1%.

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. 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.

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 – green imprinted with SB and 4892; 2.0 mg – pale pink imprinted with SB and 4893; 5.0 mg – 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:

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4. Schrag AE, *et al.* The Safety of Ropinirole, a selective non-ergoline dopamine agonist in patients with Parkinson's disease. *Clin Neuropharmacol* 1998;21:169-175.

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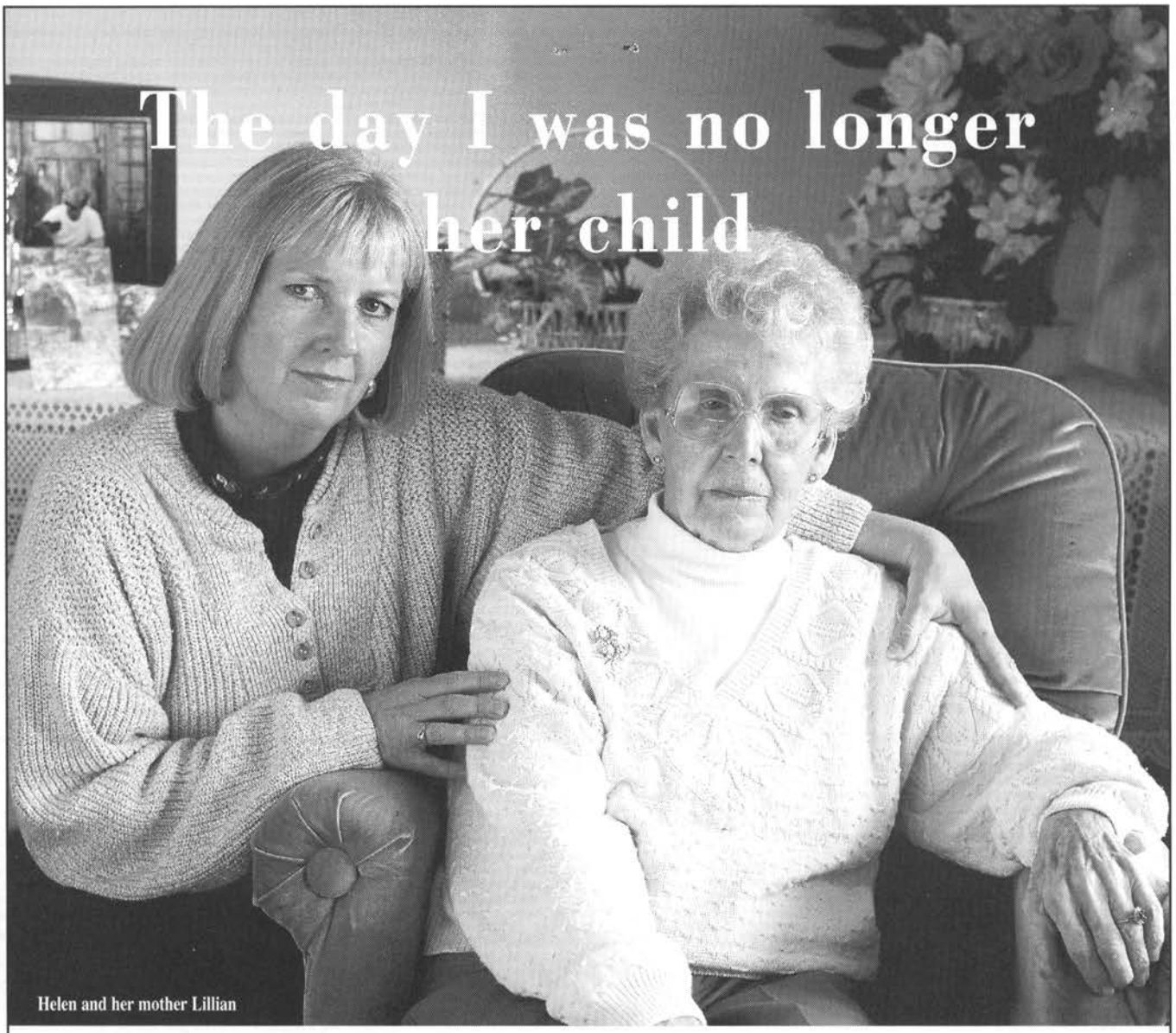

Helen and her mother Lillian

Growing up, she did her best to care for me. Today, our roles have reversed. I do my best to care for her, though she can no longer even enjoy the simple pleasures of living. She was taken from me by an unforgiving disease.

Alzheimer Disease attacks more than just memory. In time, it deteriorates personality and motor functions until the body simply shuts down. Today, 1 in 13 Canadians over 65 are affected by Alzheimer Disease and related dementias*.

Canada is a research leader in finding the cause and cure. Progress has been made. But resources continue to be scarce. Many critical projects are underfunded or unfunded.

As a major source of research funding and support, the Alzheimer Society needs your gift to continue to provide help and hope to those affected by Alzheimer Disease and their families. For more information, contact your local Alzheimer Society or visit our Web site at www.alzheimer.ca

Alzheimer *Society*

Help for Today. Hope for Tomorrow.

* Canadian Study of Health and Aging

See IFC

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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-HT_1 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 hi;gher 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 hyperlipidemia, 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).

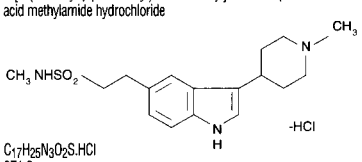
Table 4: Percentage of Patients with Headache Relief at 4 Hours Post-Dosing[?]

	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 246°C
Solubility: In water (25°C) = 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.

References:
1. Product Monograph of PrAMERGE® (naratriptan hydrochloride); Glaxo Wellcome Inc. April 1998.
2. Mathew NT, Asgharnejad M, Peykamian M et al. Naratriptan is effective and well tolerated in the acute treatment of migraine: results of a double-blind, placebo-controlled, crossover study. Neurology 1997;49:1485-1490.
3. Klassen A, Elkind A, Asgharnejad M et al. Naratriptan is effective and well tolerated in the acute treatment of migraine: results of a double-blind, placebo-controlled, parallel-group study. Headache 1997;37:640-645.
4. Bomhof MAM, Heywood J, Pradalier A et al. Tolerability and efficacy of naratriptan tablets with long-term treatment (6 months). Cephalalgia 1998;18:33-37.

Product Monograph available to health care professionals upon request.

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

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 pharmacodynamic 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_T/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_T/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 38% were men. The racial distribution was as follows: white: 95%, black: 3%, and other races: 2%.

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

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

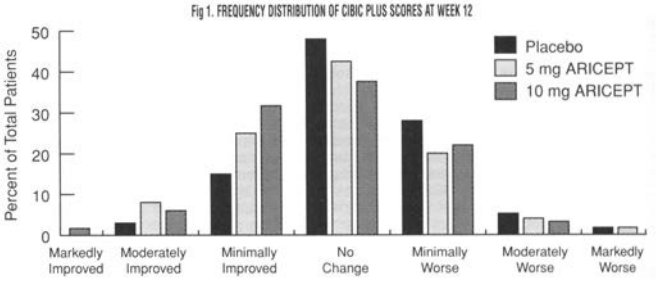
The data shown below for the two primary outcome measures in donepezil clinical trials were obtained from the Intent-To-Treat population (ITT analysis, i.e., all patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete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

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

Effects on ADAS-cog: Patients treated with donepezil showed significant improvements in ADAS-cog score from baseline, and when compared with placebo. The 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 0.28 ± 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

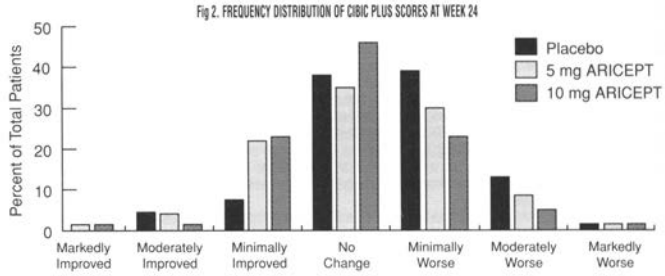


Thirty-Week Study (24 weeks of treatment + 6-week placebo washout): In this study, 473 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of donepezil for 24 weeks of double-blind active treatment followed by a 6-week single-blind placebo washout period. As in the 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 nonsteroidal 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 Ki 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 1700 individuals for various lengths of time during clinical trials worldwide. Approximately 1200 patients have been treated for at least 3 months, and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 550 patients treated for 3 months, 475 patients treated for 6 months and 115 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days.

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

Postintroduction Reports: Voluntary reports of adverse events temporally associated with **ARICEPT** that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block, hemolytic anemia, hyponatremia, pancreatitis, and rash.

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 ≥ 65 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 tablets and in blister strips boxed as 28 tablets (combination of 2 strips of 14 tablets).

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5. IMS Global Services-Year 1997.

Full product monograph available upon request.

Pr Zanaflex®
(tizanidine hydrochloride)

Zanaflex®
(tizanidine HCl)
equivalent to 4 mg tizanidine
Antispastic Agent

PRODUCT MONOGRAPH

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION[1,2,3]

Tizanidine is an agonist at α_2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

The imidazoline chemical structure of tizanidine is related to that of the anti-hypertensive drug clonidine and other α_2-adrenergic agonists. Pharmacological studies in animals show similarities between the two compounds, but tizanidine was found to have one-tenth to one-fiftieth (1/50) of the potency of clonidine in lowering blood pressure.

PHARMACOKINETICS

Following oral administration, tizanidine is essentially completely absorbed and has a half-life of approximately 2.5 hours (coefficient of variation [CV] = 33%). Following administration of tizanidine peak plasma concentrations occurred at 1.5 hours (CV = 40%) after dosing. Food increases C_{max} by approximately one-third and shortens time to peak concentration by approximately 40 minutes, but the extent of tizanidine absorption is not affected. Tizanidine has linear pharmacokinetics over a dose of 1 to 20 mg. The absolute oral bioavailability of tizanidine is approximately 40% (CV = 24%), due to extensive first-pass metabolism in the liver; approximately 95% of an administered dose is metabolized. Tizanidine metabolites are not known to be active; their half-lives range from 20 to 40 hours. Tizanidine is widely distributed throughout the body; mean steady state volume of distribution is 2.4 L/kg (CV = 21%) following intravenous administration in healthy adult volunteers.

Following single and multiple oral dosing of ^{14}C-tizanidine, an average of 60% and 20% of total radioactivity was recovered in the urine and feces, respectively.

Tizanidine is approximately 30% bound to plasma proteins, independent of concentration over the therapeutic range.

SPECIAL POPULATIONS

Age Effects: No specific pharmacokinetic study was conducted to investigate age effects. Cross study comparison of pharmacokinetic data, following single dose administration of 6 mg Zanaflex® (tizanidine HCl) showed that younger subjects cleared the drug four times faster than the elderly subjects. Zanaflex has not been evaluated in children (see PRECAUTIONS).

Hepatic Impairment: Pharmacokinetic differences due to hepatic impairment have not been studied (see WARNINGS).

Renal Impairment: Zanaflex clearance is reduced by more than 50% in elderly patients with renal insufficiency (creatinine clearance < 25 mL/min) compared to healthy elderly subjects; this would be expected to lead to a longer duration of clinical effect. Zanaflex should be used with caution in renally impaired patients (see PRECAUTIONS).

Gender Effects: No specific pharmacokinetic study was conducted to investigate gender effects. Retrospective analysis of pharmacokinetic data, however, following single and multiple dose administration of 4 mg Zanaflex showed that gender had no effect on the pharmacokinetics of Zanaflex.

Race Effects: Pharmacokinetic differences due to race have not been studied.

Drug interactions -Oral Contraceptives: No specific pharmacokinetic study was conducted to investigate interaction between oral contraceptives and Zanaflex. Retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg Zanaflex, however, showed that women concurrently taking oral contraceptives had 50% lower clearance of Zanaflex compared to women not on oral contraceptives (see PRECAUTIONS).

CLINICAL STUDIES

The capacity of Zanaflex (tizanidine HCl) to reduce increased muscle tone associated with spasticity was demonstrated in two adequate and well controlled studies in patients with multiple sclerosis or spinal injury.

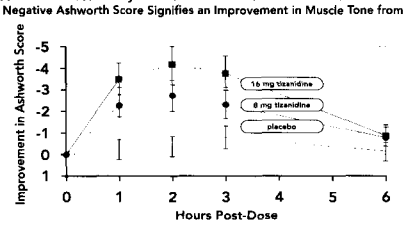
In one study, patients with multiple sclerosis were randomized to receive single oral doses of drug or placebo.[4] Patients and assessors were blind to treatment assignment and efforts were made to reduce the likelihood that assessors would become aware indirectly of treatment assignment (e.g., they did not provide direct care to patients and were prohibited from asking questions about side effects). In all, 140 patients received either placebo, 8 mg or 16 mg of Zanaflex.

Response was assessed by physical examination; muscle tone was rated on a 5 point scale (Ashworth score), with a score of 0 used to describe normal muscle tone. A score of 1 indicated a slight spastic catch while a score of 2 indicated more marked muscle resistance. A score of 3 was used to describe considerable increase in tone, making passive movement difficult. A muscle immobilized by spasticity was given a score of 4. Spasm counts were also collected.

Assessments were made at 1, 2, 3 and 6 hours after treatment. A statistically significant reduction of the Ashworth score for Zanaflex compared to placebo was detected at 1, 2 and 3 hours after treatment. Figure 1 below shows a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale. The greatest reduction in muscle tone was 1 to 2 hours after treatment. By 6 hours after treatment, muscle tone in the 8 and 16 mg tizanidine groups was indistinguishable from muscle tone in placebo treated patients. Within a given patient, improvement in muscle tone was correlated with plasma concentration. Plasma concentrations were variable from patient to patient at a given dose. Although 16 mg produced a larger effect, adverse events including hypotension were more common and more severe than in the 8 mg group. There were no differences in the number of spasms occurring in each group.

In a multiple dose study, 118 patients with spasticity secondary to spinal cord injury were randomized to either placebo or Zanaflex.[5] Steps similar to those taken in the first study were employed to ensure the integrity of blinding.

FIGURE 1: Single Dose Study - Mean Change in Muscle Tone from Baseline as Measured by the Ashworth Scale ± 95% Confidence Interval
(A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)



Patients were titrated over 3 weeks up to a maximum tolerated dose or 36 mg daily given in three unequal doses (e.g., 10 mg given in the morning and afternoon and 16 mg given at night). Patients were then maintained on their maximally tolerated dose for 4 additional weeks (i.e., maintenance phase). Throughout the maintenance phase, muscle tone was assessed on the Ashworth scale within a period of 2.5 hours following either the morning or afternoon dose and counts of spasms were collected by patient diary.

At endpoint (the protocol-specified time of outcome assessment), there were statistically significant reductions in muscle tone and spasms in the Zanaflex treated group compared to placebo. The reduction in muscle tone was not associated with a reduction in muscle strength (a desirable outcome) but also did not lead to any consistent advantage of Zanaflex treated patients on measures of activities of daily living. Figures 2 and 3 below show a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale and a comparison of the mean change in daytime spasms as recorded in patient diaries, respectively.

FIGURE 2: Multiple Dose Study - Mean Change in Muscle Tone 0.5-2.5 Hours after Dosing as Measured by the Ashworth Scale ± 95% Confidence Interval
(A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)

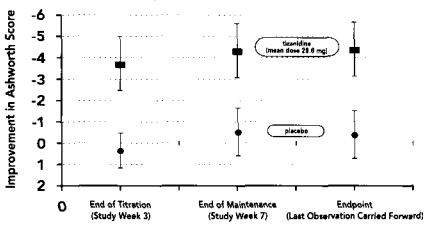
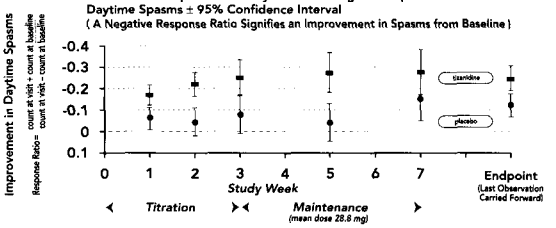


FIGURE 3: Multiple Dose Study - Mean Change in Response Ratio of Daytime Spasms ± 95% Confidence Interval
(A Negative Response Ratio Signifies an Improvement in Spasms from Baseline)



In a second multiple dose study, 187 patients with spasticity secondary to multiple sclerosis were randomized to either placebo or Zanaflex.[6] Patients were titrated over 3 weeks up to a maximum tolerated dose or 36 mg daily given in three equal doses. Patients were then maintained on their maximally tolerated dose for 9 additional weeks (i.e., maintenance phase). Throughout the maintenance phase, muscle tone was assessed on the Ashworth scale and global efficacy was assessed by both patient and investigator.

There was a statistically significant reduction in muscle tone in the Zanaflex treated group as compared to placebo at the last maintenance phase measurement of muscle tone (the protocol-specified time of outcome assessment) and throughout the maintenance phase. The reduction in muscle tone was not associated with a reduction in muscle strength.

INDICATIONS AND CLINICAL USE

Zanaflex (tizanidine HCl) is a short-acting drug for the management of spasticity.

CONTRAINDICATIONS

Zanaflex (tizanidine HCl) is contraindicated in patients with known hypersensitivity to Zanaflex or its ingredients.

WARNINGS

HYPOTENSION

Tizanidine HCl is an α_2-adrenergic agonist (like clonidine) and can produce hypotension. In a single dose study where blood pressure was monitored closely after dosing, two-thirds of patients treated with 8 mg of Zanaflex had a 20% reduction in either the diastolic or systolic BP. The reduction was seen within 1 hour after dosing, peaked 2 to 3 hours after dosing and was associated, at times, with bradycardia, orthostatic hypotension, lightheadedness/dizziness and rarely syncope. The hypotensive effect is dose related and has been measured following single doses of ≥ 2 mg.

The chance of significant hypotension may possibly be minimized by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to a fixed upright position may be at increased risk for hypotensive and orthostatic effects.

Caution is advised when Zanaflex is to be used in patients who have a history of orthostatic hypotension or labile blood pressure or who are receiving concurrent antihypertensive therapy. Zanaflex should not be used with other α_2-adrenergic agonists.

RISK OF LIVER INJURY

Zanaflex use occasionally causes drug induced liver injury, most often hepatocellular in type. In controlled clinical studies, approximately 5% of patients treated with Zanaflex had elevations of liver function tests (ALT/SGPT, AST/SGOT) to greater than 3 times the upper limit of normal (or 2 times if baseline levels were elevated). The patients usually remain asymptomatic despite increased aminotransferases. In occasional symptomatic cases, nausea, vomiting, anorexia and jaundice have been reported. The onset of the elevated liver enzymes typically occurred within the first 6 months of treatment with Zanaflex and most resolved rapidly upon drug withdrawal with no reported residual problems. In postmarketing experience, three deaths associated with liver failure have been reported in patients treated with tizanidine, including one case of fatal fulminant hepatitis.

Monitoring of aminotransferase levels is recommended during the first 6 months of treatment (e.g., baseline, 1, 3 and 6 months) and periodically thereafter, based on clinical status. Because of the potential toxic hepatic effect of tizanidine, the drug should be used only with extreme caution in patients with impaired hepatic function.

SEDATION

In the multiple dose, controlled clinical studies, 48% of patients receiving any dose of Zanaflex reported sedation as an adverse event. In 10% of these cases, the sedation was rated as severe compared to <1% in the placebo treated patients. Sedation may interfere with every day activity.

The effect appears to be dose related. In a single dose study, 92% of the patients receiving 16 mg, when asked, reported that they were drowsy during the 6 hour study. This compares to 76% of the patients on 8 mg and 35% of the patients on placebo. Patients began noting this effect 30 minutes following dosing. The effect peaked 1.5 hours following dosing. Of the patients who received a single dose of 16 mg, 51% continued to report drowsiness 6 hours following dosing compared to 13% in the patients receiving placebo or 8 mg of Zanaflex.

In the multiple dose studies, the prevalence of patients with sedation peaked following the first week of titration and then remained stable for the duration of the maintenance phase of the study.

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HALLUCINATIONS

Zanaflex use has been associated with hallucinations. Formed, visual hallucinations or delusions have been reported in 5 of 170 patients (3%) in two North American controlled clinical studies. Most of the patients were aware that the events were unreal. One patient developed psychoses in association with the hallucinations. One patient continued to have problems for at least 2 weeks following discontinuation of Zanaflex. Dosage reduction or discontinuation should be considered for patients who experience hallucinations while receiving Zanaflex. Particular caution should be observed if Zanaflex is administered to patients with a prior history of psychotic illness.

LIMITED DATABASE FOR CHRONIC USE OF SINGLE DOSES ABOVE 8 MG AND MULTIPLE DOSES ABOVE 24 MG PER DAY

Clinical experience with long-term use of Zanaflex at single doses of 8 to 16 mg or total daily doses of 24 to 36 mg is limited. Approximately 75 patients have been exposed to individual doses of 12 mg or more for at least one year and approximately 80 patients have been exposed to total daily doses of 30 to 36 mg/day for at least one year. There is essentially no long-term experience with single, daytime doses of 16 mg. Because long-term clinical study experience at high doses is limited, only those adverse events with a relatively high incidence are likely to have been identified.

PRECAUTIONS

GENERAL

Zanaflex (tizanidine HCl) should be used with caution in patients for whom spasticity is used to obtain increased function, such as maintenance of upright posture and balance in locomotion.

CARDIOVASCULAR

Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses equal to the maximum human dose on a mg/m^2 basis. ECG evaluation was not performed in the controlled clinical studies. Reduction in pulse rate has been noted in association with decreases in blood pressure in the single dose controlled study (see WARNINGS).

OPHTHALMIC

Dose-related retinal degeneration and corneal opacities have been found in animal studies at doses equivalent to approximately the maximum recommended dose on a mg/m^2 basis. There have been no reports of corneal opacities or retinal degeneration in the clinical studies.

USE IN ELDERLY

Zanaflex should be used with caution in elderly patients because clearance is decreased four-fold.

USE IN CHILDREN

There are no adequate and well-controlled studies to document the safety and efficacy of Zanaflex in children under 18 years in age.

USE IN OBSTETRICS

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

Reproduction studies performed in rats at a dose of 3 mg/kg, equal to the maximum recommended human dose on a mg/m^2 basis and in rabbits at 30 mg/kg, 16 times the maximum recommended human dose on a mg/m^2 basis did not show evidence of teratogenicity. Tizanidine at doses that are equal to and up to 8 times the maximum recommended human dose on a mg/m^2 basis increased gestation duration in rats. Prenatal and postnatal pup loss was increased and developmental retardation occurred. Postimplantation loss was increased in rabbits at doses of 1 mg/kg or greater, equal to or greater than 0.5 times the maximum recommended human dose on a mg/m^2 basis. Zanaflex has not been studied in pregnant women. Zanaflex should be given to pregnant women only if clearly needed.

NURSING MOTHERS

It is not known whether Zanaflex is excreted in human milk, although as a lipid soluble drug, it might be expected to pass into breast milk.

PATIENTS WITH SPECIAL DISEASES AND CONDITIONS

USE IN RENALLY IMPAIRED PATIENTS

Zanaflex should be used with caution in patients with renal insufficiency (Clcr <25 mL/min), as clearance is reduced by more than 50%. In these patients, during titration, the individual doses should be reduced. If higher doses are required, individual doses rather than dosing frequency should be increased. These patients should be monitored closely for onset or increase in severity of the common adverse events (dry mouth, somnolence, asthenia and dizziness) as indicators of potential overdose.

USE IN WOMEN TAKING ORAL CONTRACEPTIVES

Zanaflex should be used with caution in women taking oral contraceptives; as clearance of tizanidine is reduced by approximately 50% in such patients. In these patients, during titration, the individual doses should be reduced.

DEPENDENCE LIABILITY

Monkeys were shown to self-administer tizanidine in a dose-dependent manner, and abrupt cessation of tizanidine produced transient signs of withdrawal at doses > 35 times the maximum recommended human dose on a mg/m^2 basis. These transient withdrawal signs (increased locomotion, body twitching, and aversive behavior toward the observer) were not reversed by naloxone administration.

DRUG INTERACTIONS

In vitro studies of cytochrome P450 isoenzymes using human liver microsomes indicate that neither tizanidine nor its major metabolites are likely to affect the metabolism of other drugs metabolized by cytochrome P450 isoenzymes.

Acetaminophen: Zanaflex delayed the T_{max} of acetaminophen by 16 minutes. Acetaminophen did not affect the pharmacokinetics of Zanaflex.

Alcohol: Alcohol increased the AUC of Zanaflex by approximately 20% while also increasing its C_{max} by approximately 15%. This was associated with an increase in side effects of Zanaflex. The CNS depressant effects of Zanaflex and alcohol are additive.

Oral Contraceptives: No specific pharmacokinetic study was conducted to investigate interaction between oral contraceptives and Zanaflex, but retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg Zanaflex showed that women concurrently taking oral contraceptives had 50% lower clearance of Zanaflex than women not on oral contraceptives.

Antihypertensives: In placebo-controlled clinical trials, Zanaflex has been administered concomitantly with antihypertensive medications in 30 patients. The addition of Zanaflex to antihypertensive therapy was associated with a 20-30% increase in the incidence of clinically significant decreases in systolic or diastolic blood pressure compared with both placebo plus antihypertensive (N=36) and Zanaflex alone (N=226).

Concurrent use of antihypertensive and Zanaflex therapy also resulted in an increase in reports of orthostatic hypotension. Lower initial doses and cautious dose titration should be considered when Zanaflex is to be administered to patients receiving antihypertensive therapy or if antihypertensive therapy is to be initiated in a patient receiving Zanaflex.

INFORMATION TO BE PROVIDED TO THE PATIENTS

Patients should be advised of the limited clinical experience with Zanaflex both in regard to duration of use and the higher doses required to reduce muscle tone (see WARNINGS).

Because of the possibility of Zanaflex lowering blood pressure, patients should be warned about the risk of clinically significant orthostatic hypotension (see WARNINGS).

Because of the possibility of sedation, patients should be warned about performing activities requiring alertness, such as driving a vehicle or operating machinery (see WARNINGS). Patients should also be instructed that the sedation may be additive when Zanaflex is taken in conjunction with drugs (baclofen, benzodiazepines) or substances (e.g., alcohol) that act as CNS depressants.

ADVERSE REACTIONS

In multiple dose, placebo-controlled clinical studies, 264 patients were treated with Zanaflex (tizanidine HCl) and 261 with placebo. Adverse events, including severe adverse events, were more frequently reported with Zanaflex than with placebo.

COMMON ADVERSE EVENTS LEADING TO DISCONTINUATION

Forty-five of 264 (17%) patients receiving Zanaflex and 13 of 261 (5%) patients receiving placebo in three multiple dose, placebo-controlled clinical studies discontinued treatment for adverse events. When patients withdrew from the study, they frequently had more than one reason for discontinuing. The adverse events most frequently leading to withdrawal of Zanaflex treated patients in the controlled clinical studies were asthenia (weakness, fatigue and/or tiredness) (3%), somnolence (3%), dry mouth (3%), increased spasm or tone (2%) and dizziness (2%).

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF TIZANIDINE

In multiple dose, placebo-controlled clinical studies involving 264 patients with spasticity, the most frequent adverse events were dry mouth, somnolence/sedation, asthenia (weakness, fatigue and/or tiredness) and dizziness. Three quarters of the patients rated the events as mild to moderate and one quarter of the patients rated the events as being severe. These events appeared to be dose related.

ADVERSE EVENTS REPORTED IN CONTROLLED STUDIES

The events cited reflect experience gained under closely monitored conditions of clinical studies in a highly selected patient population. In actual clinical practice or in other clinical studies, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 1 lists treatment emergent signs and symptoms that were reported in greater than 2% of patients in three multiple dose, placebo-controlled studies who received Zanaflex where the frequency in the Zanaflex group was at least as common as in the placebo group. These events are not necessarily related to Zanaflex treatment. For comparison purposes, the corresponding frequency of the event (per 100 patients) among placebo treated patients is also provided.

TABLE 1: Multiple Dose, Placebo-Controlled Studies - Frequent (> 2%) Adverse Events Reported for Which Zanaflex Incidence is Greater Than Placebo

Event	Placebo N = 261 %	Zanaflex N = 264 %
Dry mouth	10	49
Somnolence	10	48
Asthenia*	16	41
Dizziness	4	16
UTI	7	10
Infection	5	6
Constipation	1	4
Liver function tests abnormal	<1	3
Vomiting	0	3
Speech disorder	0	3
Amblyopia (blurred vision)	<1	3
Urinary frequency	2	3
Flu syndrome	2	3
SGPT/ALT increased	<1	3
Dyskinesia	0	3
Nervousness	<1	3
Pharyngitis	1	3
Rhinitis	2	3

* weakness, fatigue and/or tiredness

In the single dose, placebo-controlled study involving 142 patients with spasticity, the patients were specifically asked if they had experienced any of the four most common adverse events dry mouth, somnolence (drowsiness), asthenia (weakness, fatigue and/or tiredness), and dizziness. In addition, hypotension and bradycardia were observed. The occurrence of these adverse events are summarized in Table 2. Other events were, in general, reported at a rate of 2% or less.

TABLE 2: Single Dose, Placebo-Controlled Study - Common Adverse Events Reported

Event	Placebo N = 48 %	Zanaflex 8 mg N = 45 %	Zanaflex 16 mg N = 49 %
Somnolence	31	78	92
Dry mouth	35	76	88
Asthenia*	40	67	78
Dizziness	4	22	45
Hypotension	0	16	33
Bradycardia	0	2	10

* weakness, fatigue and/or tiredness

OTHER ADVERSE EVENTS OBSERVED DURING THE EVALUATION OF TIZANIDINE

Zanaflex was administered to 1187 patients in additional clinical studies where adverse event information was available. The conditions and duration of exposure varied greatly, and included (in overlapping categories) double-blind and open-label studies, uncontrolled and controlled studies, inpatient and outpatient studies, and titration studies. Untoward events associated with this exposure 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 untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 1187 patients exposed to Zanaflex who experienced an event of the type cited on at least one occasion while receiving tizanidine. All reported events are included except those already listed in Table 1. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with Zanaflex, they were not necessarily caused by it.

Events are further 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 (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients.

BODY AS A WHOLE: *Frequent:* fever; *Infrequent:* allergic reaction, moniliasis, malaise, abscess, neck pain, sepsis, cellulitis, death, overdose; *Rare:* carcinoma, congenital anomaly, suicide attempt.

CARDIOVASCULAR SYSTEM: *Infrequent:* vasodilatation, postural hypotension, syncope, migraine, arrhythmia; *Rare:* angina pectoris, coronary artery disorder, heart failure, myocardial infarct, phlebitis, pulmonary embolus, ventricular extrasystoles, ventricular tachycardia.

DIGESTIVE SYSTEM: *Frequent:* abdomen pain, diarrhea, dyspepsia; *Infrequent:* dysphagia, cholelithiasis, fecal impaction, flatulence, gastrointestinal hemorrhage, hepatitis, melena; *Rare:* gastroenteritis, hematemesis, hepatoma, intestinal obstruction, liver damage.

HEMIC AND LYMPHATIC SYSTEM: *Infrequent:* ecchymosis, hypercholesteremia, anemia, hyperlipemia, leukopenia, leukocytosis, sepsis; *Rare:* petechia, purpura, thrombocythemia, thrombocytopenia.

METABOLIC AND NUTRITIONAL SYSTEM: *Infrequent:* edema, hypothyroidism, weight loss; *Rare:* adrenal cortex insufficiency, hyperglycemia, hypokalemia, hyponatremia, hypoproteinemia, respiratory acidosis.

MUSCULOSKELETAL SYSTEM: *Frequent:* myasthenia, back pain; *Infrequent:* pathological fracture, arthralgia, arthritis, bursitis.

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NERVOUS SYSTEM: *Frequent:* depression, anxiety, paresthesia; *Infrequent:* tremor, emotional lability, convulsion, paralysis, thinking abnormal, vertigo, abnormal dreams, agitation, depersonalization, euphoria, migraine, stupor, dysautonomia, neuralgia; *Rare:* dementia, hemiplegia, neuropathy.

RESPIRATORY SYSTEM: *Infrequent:* sinusitis, pneumonia, bronchitis; *Rare:* asthma.

SKIN AND APPENDAGES: *Frequent:* rash, sweating, skin ulcer; *Infrequent:* pruritus, dry skin, acne, alopecia, urticaria; *Rare:* exfoliative dermatitis, herpes simplex, herpes zoster, skin carcinoma.

SPECIAL SENSES: *Infrequent:* ear pain, tinnitus, deafness, glaucoma, conjunctivitis, eye pain, optic neuritis, otitis media, retinal hemorrhage, visual field defect; *Rare:* iritis, keratitis, optic atrophy.

UROGENITAL SYSTEM: *Infrequent:* urinary urgency, cystitis, menorrhagia, pyelonephritis, urinary retention, kidney calculus, uterine fibroids enlarged, vaginal moniliasis, vaginitis; *Rare:* albuminuria, glycosuria, hematuria, metrorrhagia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

One significant overdosage of Zanaflex (tizanidine HCl) has been reported. Attempted suicide by a 46 year-old male with multiple sclerosis resulted in coma very shortly after the ingestion of one hundred 4 mg Zanaflex tablets. Pupils were not dilated and nystagmus was not present. The patient had marked respiratory depression with Cheyne-Stokes respiration. Gastric lavage and forced diuresis with furosemide and mannitol were instituted. The patient recovered several hours later without sequelae. Laboratory findings were normal.

Should overdosage occur, basic steps to ensure the adequacy of an airway and the monitoring of cardiovascular and respiratory systems should be undertaken. For the most recent information concerning the management of overdose, contact a poison control centre.

DOSAGE AND ADMINISTRATION

A single oral dose of 8 mg of Zanaflex (tizanidine HCl) reduces muscle tone in patients with spasticity for a period of several hours. The effect peaks at approximately 1 to 2 hours and dissipates between 3 to 6 hours. Zanaflex dosing should be scheduled such that the peak effect coincides with activities for which relief of spasticity is most desirable. Effects are dose-related.

Although single doses of less than 8 mg have not been demonstrated to be effective in controlled clinical studies, the dose-related nature of Zanaflex's common adverse events, particularly blood pressure reduction, make it prudent to begin treatment with single oral doses of 4 mg. Increase the dose gradually (2 to 4 mg steps) to optimum effect (satisfactory reduction of muscle tone at a tolerated dose).

The dose can be repeated at 6 to 8 hour intervals, as needed, to a maximum of three doses in 24 hours. The total daily dose should not exceed 36 mg.

Experience with single doses exceeding 8 mg and daily doses exceeding 24 mg is limited. There is essentially no experience with repeated, single, daytime doses greater than 12 mg or total daily doses greater than 36 mg (see WARNINGS).

PHARMACEUTICAL INFORMATION

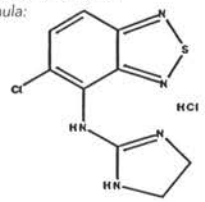
DRUG SUBSTANCE

Proper name: tizanidine HCl (USAN)

Chemical name: 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiodiazole hydrochloride

Molecular formula: $C_9H_8Cl_2N_5S$

Structural formula:



Molecular weight: 290.2

Appearance: white to off-white, fine crystalline powder, odorless or faint characteristic odor

Solubility: approximately 5% soluble in water and methanol; solubility in water decreases as the pH increases

pK_a value: 7.35 determined potentiometrically

pH: 4.3 - 5.3

Partition coefficient: 3.6:1

Melting point: 288 - 290°C

COMPOSITION

Zanaflex (tizanidine HCl) tablets are composed of the active ingredient, tizanidine hydrochloride (4.576 mg equivalent to 4 mg tizanidine base), and the inactive ingredients, silicon dioxide colloidal, stearic acid, microcrystalline cellulose and anhydrous lactose.

STABILITY AND STORAGE RECOMMENDATIONS

The product should be stored at 15-30°C (58-86°F). Dispense in containers with child resistant closure.

AVAILABILITY OF DOSAGE FORMS

Zanaflex is supplied as 4 mg white tablets for oral administration, embossed with the Athena logo and "594" on one side and cross-scored on the other. Zanaflex is available in 75 cc white, square, wide mouth high density polyethylene (HDPE) bottles of 150 tablets.

REFERENCES: 1. Nance PW, Bugaresti J, Shellenberger K, *et al.* Efficacy and safety of tizanidine in the treatment of spasticity in patients with spinal cord injury. *Neurology.* 1994;44(Suppl 9):S44-S52. 2. Wagstaff AJ. And Bryson HM. Tizanidine – A Review of its Pharmacology, Clinical Efficacy and Tolerability in the Management of Spasticity Associated with Cerebral and Spinal Disorders. *Drugs* 1997; 53(3):435-452. 3. Lataste X, Emre M, Davis C, Groves L. Comparative profile of tizanidine in the management of spasticity. *Neurology* 1994;44(Suppl 9):S53-S59. 4. Coward DM. Tizanidine: Neuropharmacology and Mechanism of Action. *Neurology* 1994;44(Suppl 9):S6-S11. 5. Zanaflex Product Monograph.

Full Product Monograph available upon request.

DRAXIS

DRAXIS HEALTH INC.
6870 Goreway Drive,
Mississauga, Ontario L4V 1P1

Zanaflex® (tizanidine hydrochloride)

Relief. Strength. Flexibility.

®Zanaflex is a registered trademark of Elan Pharmaceuticals Inc.
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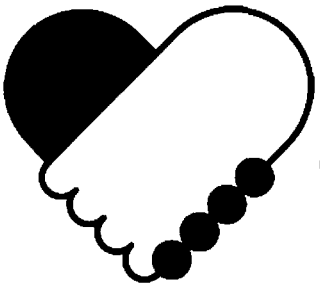
PAAB
CCPP

See page A-3

https://doi.org/10.1017/S0317167100049659 Published online by Cambridge University Press

If you have an interest in Neurological Sciences – you should be a partner . . .



CANADIAN CONGRESS OF NEUROLOGICAL SCIENCES PARTNERS PROGRAM

The CCNS **PARTNERS PROGRAM** is intended to provide a forum which will bring together all the professional societies, volunteer agencies, and commercial organizations in Canada which show a common interest in disorders affecting the nervous system. These include conditions such as Alzheimer's Disease, Stroke, Multiple Sclerosis, Epilepsy, ALS, Parkinson's Disease, Spinal Cord and Head Injuries.

Through a number of joint programs and initiatives, the goals will be to increase public awareness of neurologic disorders, to improve the well-being of people with these disorders, and to promote and encourage the development of new strategies for treatment and prevention of these conditions.

A website is being developed that will act as the core of communication for the **PARTNERS PROGRAM**. This site will act as a resource for information for the Partners, CCNS members, and individuals interested in gaining more information about neurological disorders.

A national Angus Reid telephone survey, aimed at the Canadian public to assess their general knowledge of neurological disorders, has recently been completed by the **PARTNERS**. The results strongly reinforce the need for a coalition of organizations involved in neurosciences. Details of the survey are available to the **PARTNERS**.

We are actively encouraging all those interested to join the **PARTNERS PROGRAM** and to develop this initiative.

THE PARTNERS ARE COMPRISED OF THE CCNS SOCIETIES AND AFFILIATE GROUPS, FOR-PROFIT AND NON-PROFIT ORGANIZATIONS WITH AN INTEREST IN CANADIAN NEUROSCIENCES.

Only by uniting Neurological Sciences in Canada will we achieve our goals.

FOR MORE INFORMATION REGARDING THE CCNS PARTNERSHIP PROGRAM

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Zomig®

zolmitriptan tablets 2.5 mg

PHARMACOLOGICAL CLASSIFICATION
5-HT_1 Receptor Agonist

THERAPEUTIC CLASSIFICATION
Migraine Therapy

ACTIONS AND CLINICAL PHARMACOLOGY
ZOMIG® (zolmitriptan) is a selective 5-hydroxytryptamine$_1$ (5-$HT_{1B/1D}$) receptor agonist. It exhibits a high affinity at human recombinant 5-HT_{1B} and 5-HT_{1D} receptors and modest affinity for 5-HT_{1A} receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-HT_2, 5-HT_3, 5-HT_4, alpha$_{1}$, alpha$_{2}$, or beta$_1$, -adrenergic; H_1, H_2, histaminic; muscarinic; dopamine$_1$, or dopamine$_2$, receptors. The N-desmethyl metabolite of zolmitriptan also has high affinity for 5-$HT_{1B/1D}$ and modest affinity for 5-HT_{1A} receptors.

It has been proposed that symptoms associated with migraine headaches arise from the activation of the trigemino-vascular system, which results in local cranial vasodilation and neurogenic inflammation involving the antidromic release of sensory neuropeptides [Vaso-active Intestinal Peptide (VIP), Substance P and calcitonin gene related peptide (CGRP)]. The therapeutic activity of zolmitriptan for the treatment of migraine headache is thought to be attributable to its agonist effects at 5-$HT_{1B/1D}$ receptors on the intracranial blood vessels, including the arterio-venous anastamoses, and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

Pharmacokinetics
Absorption and Bioavailability: In man, zolmitriptan is rapidly and well absorbed (at least 64%) after oral administration with peak plasma concentrations occurring in 2 hours. The mean absolute bioavailability of the parent compound is approximately 40%. Food has no significant effect on the bioavailability of zolmitriptan.

During a moderate to severe migraine attack in male and female patients, mean AUC_{0-4} and C_{max} for zolmitriptan were decreased by 40% and 25%, respectively and mean t_{max} was delayed by one-half hour compared to the same patients during a migraine free period.

Plasma Kinetics and Disposition: When given as a single dose to healthy volunteers, zolmitriptan displayed linear kinetics over the dose range of 2.5 to 50 mg.

The mean apparent volume of distribution is 7.0 L/kg. Plasma protein binding of zolmitriptan over the concentration range of 10 - 1000 ng/L is 25%.

There is no evidence of accumulation on multiple dosing with zolmitriptan up to doses of 10 mg.

Biotransformation and Elimination: Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. The enzymes responsible for the metabolism of zolmitriptan remain to be fully characterized. The mean elimination half-life of zolmitriptan is approximately 2.5 to 3 hours. Mean total plasma clearance of zolmitriptan is 31.5 mL/min/kg, of which one-sixth is renal clearance. The renal clearance is greater than the glomerular filtration rate suggesting renal tubular secretion.

In a study in which radiolabeled zolmitriptan was administered orally to healthy volunteers, 64% and 30% of the administered ^{14}C-zolmitriptan dose was excreted in the urine and feces, respectively. About 8% of the dose was recovered in the urine as unchanged zolmitriptan. The indole acetic acid and N-oxide metabolites, which are inactive, accounted for 31% and 7% of the dose, respectively, while the active N-desmethyl metabolite accounted for 4% of the dose.

Conversion of zolmitriptan to the active N-desmethyl metabolite occurs such that metabolite concentrations are approximately two thirds that of zolmitriptan. Because the 5-$HT_{1B/1D}$ potency of the N-desmethyl metabolite is 2 to 6 times that of the parent, the metabolite may contribute a substantial portion of the overall effect after zolmitriptan administration. The half-life of the active N-desmethyl metabolite is 3 hours and the t_{max} is approximately 2 to 3 hours.

Special Populations:

Adolescents (12 - 17 years of age): In a single dose pharmacokinetic study of 5 mg ZOMIG®, systemic exposure to the parent compound was not found to differ significantly between adolescents and adults. However, plasma levels of the active metabolite were significantly greater (40 - 50%) in adolescents than adults.

Elderly: Zolmitriptan pharmacokinetics in healthy elderly non-migraineur (non-migraine sufferers) volunteers (age 65 - 76) were similar to those in younger non-migraineur volunteers (age 18 - 39).

Gender: Mean plasma concentrations of zolmitriptan were up to 1.5-fold greater in females than in males.

Renal Impairment: In patients with severe renal impairment (ClCr ≥5 - ≤25 mL/min) clearance of zolmitriptan was reduced by 25% compared to normal (ClCr ≥ 70 mL/min). There was no significant change observed in the clearance of zolmitriptan in patients with moderate renal impairment (ClCr ≥26 - ≤50 mL/min).

Hepatic Impairment: A study to evaluate the effect of liver disease on the pharmacokinetics of zolmitriptan showed that the AUC and C_{max} were increased by 94% and 50% respectively in patients with moderate liver disease and by 226% and 47% in patients with severe liver disease compared with healthy volunteers. Exposure to the metabolites, including the active N-desmethyl metabolite, was decreased. For the N-desmethyl metabolite, AUC and C_{max} were reduced by 33% and 44% in patients with moderate liver disease and by 82% and 90% in patients with severe liver disease.

The plasma half-life (t 1/2) of zolmitriptan was 4.7 hours in healthy volunteers, 7.3 hours in patients with moderate liver disease and 12 hours in those with severe liver disease. The corresponding t 1/2 values for the N-desmethyl metabolite were 5.7 hours, 7.5 hours and 7.8 hours respectively.

Seven out of 27 patients with hepatic impairment (4 with moderate and 3 with severe liver disease) experienced 20 to 80 mmHg elevations in systolic and/or diastolic blood pressure after a 10 mg dose. Zolmitriptan should be administered with caution in subjects with moderate or severe liver disease (see WARNINGS and DOSAGE and ADMINISTRATION).

Hypertension: No differences in the pharmacokinetics of zolmitriptan were noted in mild to moderate hypertensive volunteers compared to normotensive controls. In this study involving a limited number of patients, small dose-dependent increases in systolic and diastolic blood pressure (approximately 3 mmHg) did not differ between mild/moderate hypertensives and normotensive controls.

Race: The effect of race on the pharmacokinetics of zolmitriptan has not been systematically evaluated. Retrospective analysis of pharmacokinetic data between Japanese and Caucasian subjects revealed no significant differences.

Therapeutic Clinical Trials
The efficacy of ZOMIG® tablets in the acute treatment of migraine attacks was evaluated in five randomized, double-blind, placebo-controlled studies, of which 2 utilized the 1 mg dose, 2 utilized the 2.5 mg dose and 4 utilized the 5 mg dose. In all studies, the effect of zolmitriptan was compared to placebo in the treatment of a single migraine attack. All studies used the marketed formulation. Study 1 was a single-center study in which patients treated their headaches in a clinic setting. In the other studies, patients treated their headaches as outpatients. In Study 4, patients who had previously used sumatriptan were excluded, whereas in the other studies no such exclusion was applied. Patients enrolled in these five studies were predominantly female (82%) and Caucasian (97%) with a mean age of 40 years (range 12-65). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed at 1, 2, and, in most studies, 4 hours after dosing. Associated symptoms such as nausea, photophobia and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours post dose. A second dose of ZOMIG® tablets or other medication was allowed 2 to 24 hours after the initial dose, to treat persistent and recurrent headache. The frequency and time to use of these additional treatments were also recorded.

Table 1 shows efficacy results for ZOMIG® in 5 placebo-controlled trials, 4 of which were multicenter. The percentage of patients with pain relief (grade 1/0) at 2 hours after treatment (the primary endpoint measure) was significantly greater among patients receiving ZOMIG® at all doses compared to those on placebo. In Study 3, which directly compared the 1 mg, 2.5 mg and 5 mg doses, there was a statistically significant greater proportion of patients with headache response at 2 and 4 hours in the higher dose groups (2.5 mg or 5 mg) than in the 1 mg group. There was no statistically significant difference between the 2.5 mg and 5 mg dose groups for the primary endpoint measure of pain relief (1/0) at 2 hours, or at any other time point measured.

Table 1: Percentage of Patients with Pain Relief (1/0)* at 1, 2 and 4 hours - Intent to Treat Population

Study	Hour Post-dose	Placebo	Zomig® Dose (mg) 1	2.5	5
		%	%	%	%
1	1	15	9	-	24
	2	15	27	-	62†
	4	70	68	-	71
		(N=20)	(N=22)	-	(N=21)
2	1	18	-	-	42†
	2	21	-	-	61†
		(N=99)	-	-	(N=213)
3	1	24	33	43†	44†
	2	32	50†	63†**	65†**
	4	31	58†	74†	75†
		(N=140)	(N=141)	(N=298)	(N=280)
4	1	21	-	-	34†
	2	44	-	-	59*
	4	60	-	-	80†
		(N=56)	-	-	(N=498)
5	1	26	-	35	-
	2	36	-	62†	-
	4	35	-	71†	-
		(N=101)	-	(N=200)	-

*p≤0.05 in comparison with placebo. **p≤0.01 in comparison with 1 mg
†p≤0.01 in comparison with placebo - = Not studied

* 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).

The proportion of patients pain free at 2 hours was statistically significantly greater for patients receiving ZOMIG® tablets at doses of 1, 2.5 and 5 mg compared with placebo in Study 3.

For patients with migraine associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of ZOMIG® as compared to placebo (see Table 2).

Table 2. Improvement in Non-Headache Symptoms*

Symptom	Patients free of non-headache symptoms at 2 hours, % (Percentage improvement over baseline) Placebo	Zomig® Dose (mg) 1	2.5	5
Nausea	61 (16)	70 (23)	72 (20)	73 (26)
Photophobia	36 (18)	48 (23)	57 (39)	63 (43)
Phonophobia	46 (16)	61 (34)	67 (40)	67 (40)

*combined data from Studies 1,2,3 and 5

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The probability of taking a second ZOMIG® dose or other medication for migraine over 24 hours following the initial dose of study treatment was lower for ZOMIG® treated groups as compared to placebo. For the 1 mg dose, the probability of taking a second dose was similar to placebo and greater than with either the 2.5 or 5 mg dose.

The efficacy of ZOMIG® was not affected by the presence of aura and was independent of headache duration pre-treatment, relationship to menses, gender, age or weight of the patient, pre-treatment nausea and concomitant use of common migraine prophylactic drugs.

In an open label study conducted to evaluate long-term safety, patients treated multiple migraine headaches with 5 mg doses of zolmitriptan for up to 1 year. A total of 31,579 migraine attacks were treated during the course of the study (mean number of headaches treated per patient was 15). An analysis of patients who treated at least 30 migraine attacks of moderate or severe intensity (n = 233) suggests that the 2 hour headache response rate is maintained with repeated use of zolmitriptan.

INDICATIONS AND CLINICAL USE
ZOMIG® (zolmitriptan) is indicated for the acute treatment of migraine attacks with or without aura.

ZOMIG® is not intended 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
ZOMIG (zolmitriptan) 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 diseases (e.g., atherosclerotic disease, congenital heart disease) should not receive ZOMIG®. Ischemic cardiac syndromes include, but are not restricted 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 ZOMIG® can give rise to increases in blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension (see WARNINGS).

ZOMIG® should not be used within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

ZOMIG® is contraindicated in patients with hemiplegic, basilar or ophthalmoplegic migraine.

Concurrent administration of MAO inhibitors or use of zolmitriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see PRECAUTIONS, Drug Interactions).

ZOMIG® is contraindicated in patients with hypersensitivity to zolmitriptan or any component of the formulation.

WARNINGS
ZOMIG® (zolmitriptan) 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: ***ZOMIG® has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. Following the use of other 5-HT_1 agonists, in rare cases these 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 5-HT_1 agonists, including ZOMIG®. ZOMIG® should not be given to patients who have documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS).*** **It is strongly recommended that ZOMIG® 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, ZOMIG® 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 ZOMIG® 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 ZOMIG® 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 ZOMIG® 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 ZOMIG®, 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 ZOMIG®.

Cardiac Events and Fatalities Associated With 5-HT_1 Agonists: In special cardiovascular studies (see below), another 5-HT_1 agonist has been shown to cause coronary vasospasm. ZOMIG® has not been tested under similar conditions, however, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described below should be considered for all agents of this class. Serious adverse cardiac events, including acute myocardial infarction, life threatening disturbance 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.

Patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive ZOMIG®.

Premarketing Experience with ZOMIG Tablets: Among the more than 2,500 patients with migraine who participated in premarketing controlled clinical trials of ZOMIG® tablets, no deaths or serious cardiac events were reported.

Cerebrovascular Events and Fatalities With 5-HT_1 Agonists: Cerebral haemorrhage, subarachnoid haemorrhage, 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 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, haemorrhage, TIA).

Special Cardiovascular Pharmacology Studies With Another 5-HT_1 Agonist: In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT_1 agonist 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). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.

In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperaemic myocardial blood flow (~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT_1 agonist is not known.

Similar studies have not been done with ZOMIG®. However, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.

Hypersensitivity: Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as ZOMIG®. 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. Owing to the possibility of cross-reactive hypersensitivity reactions, ZOMIG® should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists.

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: In pharmacodynamic studies, an increase of 1 and 5 mmHg in the systolic and diastolic blood pressure, respectively, was seen in volunteers with 5 mg ZOMIG®. In the headache trials, vital signs were measured only in a small, single-center inpatient study, and no effect on blood pressure was seen. In a study of patients with moderate to severe liver disease, 7 of 27 patients experienced 20 to 80 mmHg elevations in systolic or diastolic blood pressure after a 10 mg ZOMIG® dose. Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension who received 5-HT_1 agonists. ZOMIG® is contraindicated in patients with uncontrolled or severe hypertension.

PRECAUTIONS
Cardiovascular: Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) have been reported after administration of ZOMIG® (zolmitriptan). Because 5-HT_1 agonists may cause coronary vasospasm, patients who experience signs or symptoms suggestive of angina following ZOMIG® 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 ZOMIG® 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 neurological 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 ZOMIG®.

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

Hepatic Impairment: ZOMIG® should be administered with caution to patients with moderate or severe hepatic impairment, using a dose lower than 2.5 mg (see ACTIONS AND CLINICAL PHARMACOLOGY, WARNINGS, and DOSAGE AND ADMINISTRATION).

Psychomotor Effect: Although ZOMIG® did not interfere with psychomotor performance in healthy volunteers, some patients in clinical trials experienced sedation with ZOMIG®. Patients should thus be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that ZOMIG® does not affect them adversely.

Drug Interactions:

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 ZOMIG® administration (see CONTRAINDICATIONS).

Other 5-HT$_1$ Agonists: The administration of ZOMIG® 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 coadministration of 5-HT$_1$ agonists, use of these drugs within 24 hours of each other is contraindicated.

All drug interaction studies with drugs listed below were performed in healthy volunteers using a single 10 mg dose of ZOMIG® and a single dose of the other drug, except where otherwise noted.

MAO Inhibitors: In a limited number of subjects, following one week administration of 150 mg b.i.d moclobemide, a specific MAO-A inhibitor, there was an increase of approximately 26% in both AUC and C_{max} for zolmitriptan and a 3-fold increase in the AUC and C_{max} of the active N-desmethyl metabolite. Administration of selegiline, a selective MAO-B inhibitor, at a dose of 10 mg/day for one week, had no effect on the pharmacokinetic parameters of zolmitriptan and the active N-desmethyl metabolite. The specificity of selegiline diminishes with higher doses and varies between patients. Therefore, coadministration of zolmitriptan in patients taking MAO inhibitors is contraindicated (see CONTRAINDICATIONS).

Cimetidine and other 1A2 Inhibitors: Following administration of cimetidine, a general P450 inhibitor, the half life and AUC of zolmitriptan and its active metabolite were approximately doubled. Patients taking cimetidine should not exceed a dose of 5 mg ZOMIG in any 24 hour period. Based on the overall interaction profile, an interaction with specific inhibitors of CYP 1A2 cannot be excluded. Therefore, the same dose reduction is recommended with compounds of this type, such as fluvoxamine and the quinolones (e.g., ciprofloxacin). Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

Oral Contraceptives: Retrospective analysis of pharmacokinetic data across studies indicated that mean plasma concentrations of zolmitriptan were generally greater in females taking oral contraceptives compared to those not taking oral contraceptives. Mean C_{max} and AUC of zolmitriptan were found to be higher by 30% and 50%, respectively, and t_{max} was delayed by 30 minutes in females taking oral contraceptives. The effect of ZOMIG® on the pharmacokinetics of oral contraceptives has not been studied.

Propranolol: Propranolol, at a dose of 160 mg/day for 1 week increased the C_{max} and AUC of zolmitriptan by 1.5-fold. C_{max} and AUC of the N-desmethyl metabolite were reduced by 30% and 15%, respectively. There were no interactive effects on blood pressure or pulse rate following administration of propranolol with zolmitriptan.

Selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, paroxetine,fluvoxamine, sertraline): SSRIs have been reported, rarely, to cause weakness, hyper-reflexia, and incoordination when co-administered with 5-HT$_1$ agonists. If concomitant treatment with ZOMIG® and an SSRI is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised.

The pharmacokinetics and effects of ZOMIG® on blood pressure were unaffected by 4-week pre-treatment with oral fluoxetine (20 mg/day). The effects of zolmitriptan on fluoxetine metabolism were not assessed.

Acetaminophen: After concurrent administration of single 10 mg doses of ZOMIG® and 1 g acetaminophen, there was no significant effect on the pharmacokinetics of ZOMIG®. ZOMIG® reduced the AUC and C_{max} of acetaminophen by 11% and 31% respectively and delayed the t_{max} of acetaminophen by 1 hour.

Metoclopramide: Metoclopramide (single 10 mg dose) had no effect on the pharmacokinetics of ZOMIG® or its metabolites.

Use in Pregnancy: The safety of ZOMIG® for use during human pregnancy has not been established. ZOMIG® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers: It is not known whether zolmitriptan and/or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when considering the administration of ZOMIG® to nursing women. Lactating rats dosed with zolmitriptan had milk levels equivalent to maternal plasma levels at 1 hour and 4 times higher than plasma levels at 4 hours.

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

Use in Adolescents (12-17 years of age): Systemic exposure to the parent compound does not differ significantly between adolescents and adults, however exposure to the active metabolite is greater in adolescents (see ACTIONS AND CLINICAL PHARMACOLOGY). Safety and efficacy of ZOMIG® have not been established in patients 12-17 years of age. The use of ZOMIG® in adolescents is, therefore, not recommended.

Use in the Elderly: The safety and effectiveness of ZOMIG® have not been studied in individuals over 65 years of age. The risk of adverse reactions to this drug may be greater in elderly patients as they are more likely to have decreased hepatic function, be at higher risk for CAD, and experience blood pressure increases that may be more pronounced. Clinical studies did not include patients over 65 years of age. Its use in this age group is, therefore, not recommended.

Drug/Laboratory Test Interactions: Zolmitriptan is not known to interfere with commonly employed clinical laboratory tests.

Dependence Liability: The abuse potential of ZOMIG® has not been assessed in clinical trials.

Binding to Melanin-Containing Tissues: When pigmented rats were given a single oral dose of 10 mg/kg of radiolabeled zolmitriptan, the radioactivity in the eye after 7 days, the latest time point examined, was still 75% of the values measured after 4 hours. This suggests that zolmitriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that zolmitriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with zolmitriptan were noted in any of the toxicity studies. No systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, however, prescribers should be aware of the possibility of long-term ophthalmologic effects.

ADVERSE EVENTS

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 ZOMIG® (zolmitriptan)

Typical 5-HT$_1$ Agonist Adverse Reactions: As with other 5-HT$_1$ agonists, ZOMIG® 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. In very rare cases, as with other 5-HT$_1$ agonists, angina pectoris and myocardial infarction have been reported.

Acute Safety: In placebo-controlled migraine trials, 1,673 patients received at least one dose of ZOMIG®. The following table (Table 3) lists adverse events that occurred in placebo-controlled clinical trials in migraine patients. Events that occurred at an incidence of 1% or more in any one of the ZOMIG® 1 mg, 2.5 mg or 5 mg dose groups and that occurred at a higher incidence than in the placebo group are included. The events cited reflect experience gained under closely monitored conditions in 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.

Several of the adverse events appear dose related, notably paresthesia, sensation of heaviness or tightness in chest, neck, jaw and throat, dizziness, somnolence, and possibly asthenia and nausea.

Table 3: Treatment Emergent Adverse Events in Five Single-Attack Placebo-Controlled Migraine Trials, Reported by ≥ 1% Patients Treated With ZOMIG®

Number of patients	Placebo 491	Zomig® 1 mg 163	Zomig® 2.5 mg 498	Zomig® 5 mg 1012
	% incidence			
Symptoms of potential cardiac origin:				
neck/throat/jaw sensations*	3.0	6.1	7.0	10.9
chest/thorax sensations*	1.2	1.8	3.4	3.8
upper limb sensations*	0.5	2.4	4.2	4.1
palpitations	0.7	0	0.2	2.2
Other Body Systems:				
Neurological:				
dizziness	4.0	5.5	8.4	9.5
nervousness	0.2	0	1.4	0.7
somnolence	3.0	4.9	6.0	7.7
thinking abnormal	0.5	0	1.2	0.3
tremor	0.7	0.6	1.0	0.7
vertigo	0	0	0	1.5
hyperesthesia	0	0	0.6	1.1
Digestive:				
diarrhea	0.5	0.6	1.0	0.6
dry mouth	1.7	4.9	3.2	3.2
dyspepsia	0.5	3.1	1.6	1.0
dysphagia	0	0	0	1.8
nausea	3.7	3.7	9.0	6.2
vomit	2.5	0.6	1.4	1.5
Miscellaneous:				
asthenia	3.2	4.9	3.2	8.8
limb sensations (upper & lower)*	0.7	0.6	0.4	1.6
limb sensations (lower)*	0.7	1.2	0.4	1.8
sensations - location unspecified*	5.2	4.9	5.8	9.2
abdominal pain	1.7	1.2	0.6	1.3
reaction aggravated	1.0	1.2	1.0	0.7
head/face sensations*	1.7	6.7	8.6	10.9
myalgia	0.2	0	0.2	1.3
myasthenia	0.2	0	0.6	1.9
dyspnea	0.2	0.6	0.2	1.2
rhinitis	0.2	1.2	1.2	0.9
sweating	1.2	0	1.6	2.5
taste perversion	0.5	2.5	0.6	0.7

* The term sensation encompasses adverse events described as pain, discomfort, pressure, heaviness, tightness, heat/burning sensations, tingling and paresthesia

ZOMIG® is generally well tolerated. Across all doses, most adverse events were mild to moderate in severity as well as transient and self-limiting. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age of patients; use of prophylactic medications; or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse events.

Long-Term Safety: In a long-term open label study in which patients were allowed to treat multiple migraine attacks for up to one year, 8% (167 of 2,058) of patients withdrew from the study due to an adverse experience. In this study, migraine headaches could be treated with either a single 5 mg dose of ZOMIG®, or an initial 5 mg dose followed by a second 5 mg dose if necessary (5+5 mg). The most common adverse events (defined as occurring at an incidence of at least 5%) recorded for the 5 mg and 5+5 mg doses, respectively, were little different and comprised, in descending order of frequency: neck/throat sensations* (16%, 15%), *head/face sensations** (15%, 14%), *asthenia* (14%, 14%), *sensations** location unspecified (12%, 11%), limb sensations* (11%, 11%), nausea (12%, 8%), dizziness (11%, 9%), somnolence (10%, 10%), chest/thorax sensations* (7%, 7%), dry mouth (4%, 5%), and hyperesthesia (5%, 4%). Due to the lack of a placebo arm in this study, the role of ZOMIG® in causation cannot be reliably determined. (*See footnote for Table 3.) The long-term safety of a 2.5 mg dose was not assessed in this study. Long-term safety information on the 2.5 mg dose is not yet available.

Other Events: In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of ZOMIG® in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used ZOMIG® (n=4,027) and reported an event divided by the total number of patients exposed to ZOMIG®. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: infrequent adverse events are those occurring in 1/100 to 1/1,000 patients and rare adverse events are those occurring in fewer than 1/1,000 patients.

Atypical sensation: Infrequent was hyperesthesia.

General: Infrequent were allergy reaction, chills, facial edema, fever, malaise and photosensitivity.

Cardiovascular: Infrequent were arrhythmias, hypertension and syncope. Rare were bradycardia, extrasystoles, postural hypotension, QT prolongation, tachycardia and thrombophlebitis.

Digestive: Infrequent were increased appetite, tongue edema, esophagitis, gastroenteritis, liver function abnormality and thirst. Rare were anorexia, constipation, gastritis, hematemesis, pancreatitis, melena and ulcer.

Hemic: Infrequent was ecchymosis. Rare were cyanosis, thrombocytopenia, eosinophilia and leukopenia.

Metabolic: Infrequent was edema. Rare were hyperglycemia and alkaline phosphatase increased.

Musculoskeletal: Infrequent were back pain, leg cramps and tenosynovitis. Rare were arthritis, tetany and twitching.

Neurological: Infrequent were agitation, anxiety, depression, emotional lability and insomnia. Rare were akathesia, amnesia, apathy, ataxia, dystonia, euphoria, hallucinations, cerebral ischemia, hyperkinesia, hypotonia, hypertonia and irritability.

Respiratory: Infrequent were bronchitis, bronchospasm, epistaxis, hiccup, laryngitis and yawn. Rare were apnea and voice alteration.

Skin: Infrequent were pruritus, rash and urticaria.

Special Senses: Infrequent were dry eye, eye pain, hyperacusis, ear pain, parosmia, and tinnitus. Rare were diplopia and lacrimation.

Urogenital: Infrequent were hematuria, cystitis, polyuria, urinary frequency, urinary urgency. Rare were miscarriage and dysmenorrhea.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no experience with clinical overdose. Volunteers receiving single 50 mg oral doses of ZOMIG® (zolmitriptan) commonly experienced sedation.

The elimination half-life of zolmitriptan is 2.5 - 3 hours (see ACTIONS & CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with ZOMIG® should continue for at least 15 hours or while symptoms or signs persist.

There is no specific antidote to zolmitriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

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

DOSAGE AND ADMINISTRATION

ZOMIG® (zolmitriptan) is recommended only for the acute treatment of migraine attacks. ZOMIG® should not be used prophylactically.

Adults: The minimal effective single adult dose of ZOMIG® is 1 mg. The recommended single dose is 2.5 mg. The 1 mg dose can be approximated by manually breaking a 2.5 mg tablet in half.

In controlled clinical trials, single doses of 1 mg, 2.5 mg or 5 mg ZOMIG® were shown to be effective in the acute treatment of migraine headaches. In the only direct comparison of the 2.5 and 5 mg doses, there was little added benefit from the higher dose, while side effects increased with 5 mg ZOMIG® (see Therapeutic Clinical Trials, Table 1, and ADVERSE EVENTS, Table 3).

If the headache returns, the dose may be repeated after 2 hours. A total cumulative dose of 10 mg should not be exceeded in any 24 hour period. Controlled trials have not established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating more than 3 migraine headaches with ZOMIG® in a one month period remains to be established.

Hepatic Impairment: Patients with moderate to severe hepatic impairment have decreased clearance of zolmitriptan and significant elevation in blood pressure was observed in some patients. Use of a low dose (<2.5 mg) with blood pressure monitoring is recommended (see ACTIONS AND CLINICAL PHARMACOLOGY, and WARNINGS).

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

Cimetidine and other 1A2 inhibitors: Patients taking cimetidine and other 1A2 inhibitors should not exceed a dose of 5 mg ZOMIG® in any 24 hour period (see PRECAUTIONS, Drug Interactions).

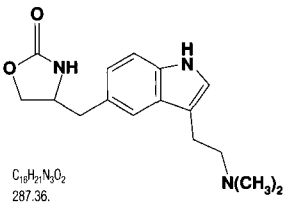
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Zolmitriptan

Chemical name: (S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone

Structural Formula:



Molecular Formula: $C_{16}H_{21}N_3O_2$

Molecular Weight: 287.36.

Physical Form: White to almost white powder

Solubility: slightly soluble in water (1.3 mg/mL at 25°C), 0.1M hydrochloric acid (33 mg/mL at 25°C).

pKa : 9.64 ± 0.01

Partition co-efficient: octanol-1-ol/water partition log K_D=-1.0.

Melting point: 136°C.

Composition Inactive ingredients: anhydrous lactose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400 and 8000, sodium starch glycolate, titanium dioxide, yellow iron oxide (2.5 mg).

Stability and Storage Recommendations Store at room temperature between 15 and 30°C.

AVAILABILITY OF DOSAGE FORMS

ZOMIG® (zolmitriptan) 2.5 mg tablets are yellow, round biconvex film-coated tablets intagliated 'Z' on one side. Available in blister packs of 3 and 6 tablets.

Product Monograph available on request.

Zomig® (zolmitriptan) is a registered trademark of the AstraZeneca group of companies.

References: **1.** Rapoport AM et al. Optimizing the dose of zolmitriptan (Zomig, *311C90) for the acute treatment of migraine. A multicenter, double-blind, placebo-controlled, dose range-finding study. *Neurology* 1997;49(5):1210-1218. **2.** Zomig® (zolmitriptan) Product Monograph, AstraZeneca. **3.** Saper J et al. Zomig is consistently effective in the acute treatment of migraine. *Headache* 1998;(38):400. **4.** Zagami AS. 311C90: Long-term efficacy and tolerability profile for the acute treatment of migraine. *Neurology* 1997;48(Suppl 3):S25-S28. **5.** Edmeads JG, Millson DS. Tolerability profile of zolmitriptan (Zomig™; 311C90), a novel dual central and peripherally acting 5-HT$_{1B/D}$ agonist. *Cephalalgia* 1997;17(Suppl 18):41-52. **6.** Tepper SJ et al. A Long-term study to maximise migraine relief with zolmitriptan. *Curr Med Res Opin* 1999;15(4).

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See pages A-26

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.

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 efficacy of 8 MIU BETASERON, administered subcutaneously every other day, has been studied in one placebo-controlled clinical trial in relapsing-remitting MS patients (n=124) and a placebo-controlled trial in secondary-progressive MS patients (n=360).

1. Relapsing-Remitting MS: 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.

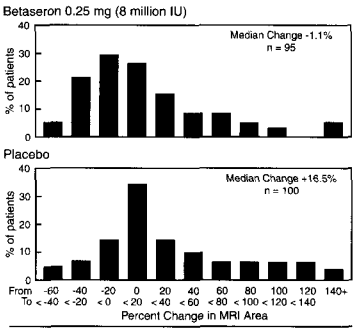
Over the 2-year period, there were 25 MS-related hospitalizations in the 0.25 mg (8 MIU) BETASERON-treated group compared to 48 hospitalizations in the placebo group. In comparison, non-MS hospitalizations were evenly distributed between the groups, with 16 in the 0.25 mg (8 MIU) BETASERON group and 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 fell into each of these intervals. The median percent change in MRI area for the 0.25 mg (8 MIU) group was -1.1% which was significantly smaller than the 16.5% observed for the placebo group (p=0.0001).

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

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"

Figure 1: Distribution of Change in MRI Area



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.

2. Secondary-Progressive MS: The effectiveness of BETASERON administered subcutaneously at a dose of 0.25 mg (8 MIU) every other day for 3 years was studied in a European multicenter (32 sites), randomized, double-blind, placebo-controlled trial in patients with secondary-progressive MS.

The study included patients between 18 and 55 years of age who had clinically definite or laboratory-supported definite MS for not less than one year. Disease had to be in the secondary-progressive phase and deterioration could not be exclusively related to incomplete recovery from relapses. EDSS score at study entry was between 3.0 and 6.5 and patients had to have a history of at least two clearly identified relapses, or deterioration of at least 1 EDSS point (or 0.5 points between EDSS scores of 6.0 to 7.0) within the preceding 24 months.

The primary efficacy endpoint was time to confirmed progression in disability, as determined by an increase by one point on the EDSS from baseline if the entry score was 3.0 to 5.5, or 0.5 points on the EDSS if the baseline score was 6.0 or 6.5. The increased score had to be maintained for three months before progression was confirmed. Secondary efficacy endpoints included time to becoming wheelchair-bound (EDSS 7.0) and annual relapse rate.

Although the study was designed with a treatment duration of three years, a prospectively planned interim analysis of efficacy was performed after all patients had completed 2 years in the study. This resulted in a decision by an independent Advisory Board to terminate the study early. Approximately 85% of all EDSS data for the three year study duration were available for the interim analysis of the primary endpoint. The primary analysis of efficacy was based on all patients randomized to treatment (Intent to Treat). The primary statistical method for the primary endpoint was a non-parametric analysis of covariance with stratification for centre and adjustment for baseline EDSS.

Results presented below are for the dataset at study termination.

During the study, assessment of the EDSS was performed by a physician not otherwise involved in the treatment of the patient. All EDSS physicians were regularly trained to guarantee a maximally standardized assessment of the EDSS. All efforts were undertaken to maintain the blinding, e.g., standard clothing to cover injection sites was obligatory.

A total of 718 patients (358 on placebo and 360 on BETASERON) were enrolled. In both treatment groups, the proportion of female patients exceeded that of males (Placebo: 64.2% vs. 35.8%; BETASERON: 58.1% vs. 41.9%), but this difference was not statistically significant. The mean time on treatment was 886 days for placebo and 909 days for BETASERON. Eighty-eight (88) patients were lost to follow-up; the remainder were followed up until the end of study irrespective of continuation of study drug. Over the 3-year study period, treatment was discontinued prematurely by 117 (32.7%) placebo patients and 103 (29.6%) BETASERON patients. Lack of efficacy, adverse events and non-compliance were the most common reasons for ending treatment in 15.6%, 6.4% and 7.5% of the placebo group and in 7.5%, 14.2% and 3.3% of the BETASERON group, respectively. The treatment groups were well-balanced for all relevant baseline values, including EDSS at baseline, and time since evidence of secondary-progressive disease.

There was a statistically significant difference in time to confirmed progression in disability in favour of BETASERON (p=0.0046), as shown in Table 2. The delay in progression in disability became apparent after 9 months of treatment and was statistically significant from month 12 onwards. The proportion of patients with confirmed progression in disability was reduced from 60.9% in the placebo group to 51.9% in the BETASERON group (p=0.0245).

The treatment effect was consistent across all baseline EDSS levels studied; however, the difference in the proportion of patients having confirmed progression in disability between BETASERON and placebo-treated patients was lower for patients with study entry EDSS values of ≥6.0, compared to the other EDSS categories (EDSS ≤3.5: 15.0%; EDSS 4.0-5.5: 11.3% and EDSS ≥6.0: 3.5%). Although the proportion of male patients in the BETASERON group with confirmed progression in disability was slightly higher than that of female patients, piecewise logistic regression analysis did not reveal any significant treatment by gender interaction (p=0.4335).

Kaplan-Meier plots (post-hoc analysis) of the data are shown in Figure 2. The Kapian-Meier estimate of the percentage of patients progressing by the end of 3 years was 53.9% for placebo and 45.3% for BETASERON-treated patients.

The time to becoming wheelchair-bound (EDSS = 7.0) was also significantly prolonged (p=0.0047) and the proportion of patients becoming wheelchair-bound was reduced from 28.5% in the placebo group to 18.6% in the BETASERON group (p=0.0069).

BETASERON reduced the relapse rate by 26.3% over the entire study period (p=0.0034). The proportion of patients with moderate or severe relapses was reduced from 54.2% in the placebo group to 47.2% in the BETASERON group (p=0.0508). The mean annual rate of moderate or severe relapses was 0.44 and 0.31 in the placebo and the BETASERON group, respectively (p=0.0037).

The incidence of hospitalizations due to MS was reduced: 44.4% of placebo patients required hospitalization due to MS vs. 36.1% in the BETASERON group (p=0.0003). The number of patients with steroid courses was 73.2% and 62.5% of patients in the placebo and BETASERON group respectively (p=0.0010).

In addition to clinical measures, annual magnetic resonance imaging (MRI) was performed. All patients underwent a T2-weighted MRI scanning at baseline and yearly thereafter, while a subgroup of patients (Placebo, n = 61; BETASERON, n = 64) underwent monthly scans in months 1-6 and 19-24 in addition to the annual scans scheduled for the general study population. Results of secondary and tertiary MRI endpoints showed significant differences between treatment groups in favor of BETASERON (see Table 2). The exact relationship between MRI findings and the clinical status of patients is unknown.

Serum samples were collected throughout the study to test for the development of neutralizing antibodies (NAB) against interferon beta-1b. Analyses were performed to assess the association between NAB status (measured by an MxA neutralization assay) and treatment response as measured by clinical and MRI outcome measures. Confirmed NAB titers of 1:20, 1:100 and 1:400 were observed in 28%, 14% and 8% of patients, respectively. Despite continued therapy with BETASERON, 50% of the NAB-positive patients were found to have negative titers subsequent to the first development of confirmed quantifiable titers. The relationship between antibody formation and clinical efficacy is not 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.

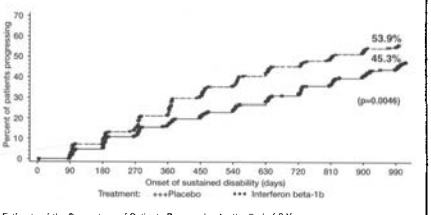
†† Sequelae and Functional Neurologic Status, both required by protocol, were not analyzed individually but are included as a function of the EDSS.

‡ 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.

Figure 2

Onset of Progression in Disability by Time in Study.
(Kaplan-Meier Methodology: Post-hoc Analysis).



Estimate of the Percentage of Patients Progressing by the End of 3 Years.
Note: The p value of 0.0046 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given timepoint.

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Table 2
Secondary-Progressive MS Study Results
Summary of Key Efficacy Endpoints

	Treatment Groups		p-value
	Placebo (n=358)	Betaseron 0.25 mg (8 MIU) (n=360)	
Primary Endpoints			
Time to Confirmed Progression in Disability[1]			0.0046
Year 1	0.70	0.81	0.0032
Year 2	0.53	0.64	0.0013
Month 33	0.44	0.53	0.0066
Secondary Clinical Endpoints			
Time to becoming wheelchair-bound[2]			0.0047
Year 1	0.90	0.96	0.0139
Year 2	0.81	0.86	0.0096
Month 36	0.69	0.80	0.0047
Proportion of patients becoming wheelchair-bound	28.5%	18.6%	0.0069
Mean annual relapse rate	0.57	0.42	0.0034
MRI: *mean percent change* in T2 *lesion volume* (baseline to last scan)	15.4	-2.1	<0.0001
MRI: mean number of newly active lesions (months 1-6)	10.24 (n=61)	3.57 (n=64)	<0.0001
Tertiary Endpoints			
Proportion of patients with confirmed progression	60.9%	51.9%	0.0245
Mean endpoint EDSS	5.93	5.58	0.0065
Median time to first relapse (days)	385	644	0.0088
MRI: mean number of persistently enhancing lesions (months 1-6)	3.10 (n=61)	1.02 (n=64)	0.0009
MRI: mean number of persistently enhancing lesions (months 19-24)	3.04 (n=53)	0.36 (n=56)	0.0004

[1]Probability of remaining progression-free during the interval.
[2]Probability of not becoming wheelchair-bound during the interval.

INDICATIONS AND CLINICAL USE

BETASERON (interferon beta-1b) is indicated for:

- the reduction of the frequency of clinical exacerbations in ambulatory patients with relapsing-remitting multiple sclerosis. Relapsing-remitting MS is characterized by *recurrent attacks of neurologic dysfunction followed by* complete or incomplete recovery.
- the slowing of progression in disability and the reduction of the frequency of clinical exacerbations in patients with secondary-progressive multiple sclerosis.

The safety and efficacy of BETASERON in primary progressive MS have 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

The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of systemic capillary leak syndrome with shock-like symptoms and fatal outcome.

In the RR-MS clinical trial, 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. In the SP-MS study there were 5 suicide attempts in the placebo group and 3 in the BETASERON group including one patient in each group who committed suicide. 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: Rare cases of cardiomyopathy have been reported. If this occurs, and a relationship to BETASERON (interferon beta-1b) is suspected, treatment should be discontinued.

Rare cases of thyroid dysfunction (hyper- as well as hypothyroidism) associated with the use of BETASERON have been reported.

Symptoms of flu syndrome observed with BETASERON therapy may prove stressful to patients with severe cardiac conditions. Patients with cardiac disease such as angina, congestive heart failure or arrhythmia should be monitored closely for worsening of their clinical conditions.

Information to be Provided to the Patient: Patients should be instructed in injection techniques to assure the safe self-administration of BETASERON. (See below and the **BETASERON® INFORMATION FOR THE PATIENT** section.)

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® INFORMATION FOR THE PATIENT** section 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.

Overall, 80% of patients in the two controlled clinical trials 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 trials, 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 trials, patients were monitored every 3 months. The study protocol stipulated that BETASERON therapy be discontinued in the event the absolute neutrophil count fell below 750/mm^3. When the absolute neutrophil count had returned to a value greater than 750/mm^3, 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 evaluated. Although studies designed to examine drug interactions have not been done, it was noted that BETASERON patients (n=180) have received corticosterold or ACTH treatment of relapses for periods of up to 28 days.

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

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when BETASERON is administered in combination with agents that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance.

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 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 4 patients who participated in the BETASERON RR-MS clinical trial, whereas there was one induced abortion in each of the placebo and BETASERON groups in the SP-MS 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 reliable contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking BETASERON, the patient should discontinue therapy. It is not known if interferons alter the efficacy of oral contraceptives.

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

The following adverse events were observed in placebo-controlled clinical studies of BETASERON (interferon beta-1b), at the recommended dose of 0.25 mg (8 MIU), in patients with relapsing-remitting MS (n=124) and secondary-progressive MS (n=360):

1. Relapsing-remitting MS: 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, compared to placebo. Only inflammation, pain, and necrosis were reported as severe events. The incidence rate for injection site reactions was calculated over the course of 3 years. This incidence rate decreased over time, with 79% of patients experiencing the event during the first 3 months of treatment compared to 47% during the last 6 months. The median time to the first occurrence of an injection site reaction was 7 days. Patients with injection site reactions reported these events 183.7 days per year. Three patients withdrew from the 0.25 mg (8 MIU) BETASERON-treated group for injection site pain.

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

Laboratory abnormalities included:

- lymphocyte count < 1500/mm^3 (82%),
- ALT (SGPT) > 5 times baseline value (19%),
- absolute neutrophil count < 1500/mm^3 (18%) (no patients had absolute neutrophil counts <500/mm^3),
- WBC < 3000/mm^3 (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 childbearing age treated with placebo reported menstrual disorders. All reports were of mild to moderate severity and included: intermenstrual bleeding and spotting, early or delayed menses, decreased days of menstrual flow, and clotting and spotting during menstruation.

Mental disorders such as depression, anxiety, emotional lability, depersonalization, suicide attempts and confusion were observed in this study. Two patients withdrew for confusion. One suicide and four attempted suicides were also reported. It is not known whether these symptoms may be related to the underlying neurological basis of MS, to BETASERON treatment, or to a combination of both. Some similar symptoms have been noted in patients receiving interferon alpha and both interferons are thought to act through the same receptor. Patients who experience these symptoms should be monitored closely and cessation of therapy should be considered.

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

- injection site reaction (85%),
- lymphocyte count < 1500/mm^3 (82%),
- ALT (SGPT) > 5 times baseline value (19%),
- absolute neutrophil count < 1500/mm^3 (18%),
- menstrual disorder (17%),
- WBC < 3000/mm^3 (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 3. In the following table, terms so general as to be uninformative, and those events where a drug cause was remote have been excluded.

Table 3: Adverse Events and Laboratory Abnormalities

Adverse Event	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 3: Adverse Events and Laboratory Abnormalities

Adverse Event	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 (p<0.05)

It should be noted that the figures cited in Table 3 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.

2. Secondary-progressive MS: The incidence of adverse events that occurred in at least 2% of patients treated with 8 MIU BETASERON or placebo for up to three years, or where an adverse event was reported at a frequency at least 2% higher with BETASERON than that observed for placebo-treated patients in the secondary-progressive study, is presented in Table 4. Adverse events significantly associated with BETASERON compared to placebo (p<0.05) are also indicated in Table 4.

Table 4: Incidence of Adverse Events ≥ 2% or > 2% Difference (BETASERON vs. Placebo) in the Secondary Progressive MS Study

Adverse Event	Placebo n=358	0.25 mg (8 MIU) n=360
Body as a Whole		
– Asthenia	58%	63%
– Flu syndrome*	40%	61%
– Pain	25%	31%
– Fever*	13%	40%
– Back pain	24%	26%
– Accidental injury	17%	14%
– Chills*	7%	23%
– Pain in Extremity	12%	14%
– Infection	11%	13%
– Abdominal pain*	6%	11%
– Malaise	5%	8%
– Neck pain	6%	5%
– Abscess*	2%	4%
– Laboratory test abnormal	1%	3%
– Allergic reaction	3%	2%
– Chills and fever*	0%	3%
– Thorax pain	2%	1%
Cardiovascular System		
– Vasodilatation	4%	6%
– Peripheral vascular disorder	5%	5%
– Chest pain	4%	5%
– Migraine	3%	4%
– Hypotension	4%	2%
– Hypertension*	2%	4%
– Palpitation	3%	2%
– Syncope	3%	2%
– Hemorrhage	2%	2%
– Tachycardia	1%	2%
Digestive System		
– Nausea	13%	13%
– Constipation	12%	12%
– Diarrhea	10%	7%
– Gastroenteritis	5%	6%
– Vomiting	6%	4%
– Dysphagia	5%	4%
– Gastrointestinal disorder	5%	4%
– Tooth disorder	4%	4%
– Dyspepsia	4%	4%
– Anorexia	2%	4%
– Fecal incontinence	3%	2%
– Liver function test abnormal	1%	3%
– Gastritis	2%	2%
– Flatulence	1%	3%
– Sore throat	1%	2%
– Colitis	2%	0%
– Gastrointestinal pain	0%	2%
– Gingivitis	0%	2%
Hemic and Lymphatic System		
– Leukopenia*	5%	10%
– Anemia	5%	2%
– Ecchymosis	2%	1%
– Lymphadenopathy	1%	3%
Injection Site		
– Injection site reaction*	10%	46%
– Injection site inflammation*	4%	48%
– Injection site pain	5%	9%
– Injection site necrosis*	0%	5%
– Injection site hemorrhage	2%	2%
Metabolic and Nutritional Disorders		
– Peripheral edema	7%	7%
– Weight loss	3%	2%
– SGPT increased	2%	2%
– Hypercholesteremia	2%	1%
Musculoskeletal System		
– Myasthenia	40%	39%
– Arthralgia	20%	20%
– Myalgia*	9%	23%
– Bone fracture (not spontaneous)	5%	3%
– Muscle cramps	3%	3%
– Spontaneous bone fracture	3%	3%
– Arthritis	1%	2%
– Joint disorder	1%	2%
Nervous System		
– Headache	41%	47%
– Neuropathy	41%	38%
– Paresthesia	39%	35%
– Hypertonia*	31%	41%
– Abnormal gait	34%	34%
– Depression	31%	27%
– Ataxia	23%	19%
– Dizziness	14%	14%
– Incoordination	13%	11%
– Insomnia	8%	12%
– Vertigo	12%	8%
– Emotional lability	11%	8%
– Paralysis	10%	8%
– Somnolence	8%	8%
– Tremor	9%	6%
– Sweating increased	6%	6%
– Neuralgia	7%	5%
– Movement disorder	6%	5%
– Sleep disorder	5%	6%
– Anxiety	5%	6%
– Hypesthesia	4%	6%
– Nervousness	3%	4%
– Speech disorder	5%	2%
– Dysarthria	4%	2%
– Spastic paralysis	1%	3%
– Convulsion	2%	2%
– Hyperesthesia	2%	2%
– Amnesia	3%	1%
– Dry mouth	2%	1%
– Hemiplegia	2%	1%
– Thinking abnormal	2%	1%
– Myoclonus	2%	0%
Respiratory System		
– Rhinitis	32%	28%
– Pharyngitis	20%	16%
– Bronchitis	12%	9%
– Cough increased	10%	5%
– Sinusitis	6%	6%
– Pneumonia	5%	5%
– Dyspnea	2%	3%
– Upper respiratory tract infection	2%	3%
– Asthma	2%	1%
– Voice alteration	2%	1%
Skin and Appendages		
– Rash*	12%	20%
– Pruritus	6%	6%
– Skin disorder	4%	4%
– Eczema	4%	2%
– Herpes simplex	2%	3%
– Alopecia	2%	2%
– Acne	2%	2%
– Dry skin	3%	1%
– Subcutaneous hematoma	3%	1%
– Breast pain	2%	1%
– Herpes zoster	2%	1%
– Seborrhea	2%	1%
Special Senses		
– Abnormal vision	15%	11%
– Amblyopia	10%	7%
– Diplopia	9%	7%
– Eye pain	5%	4%
– Otitis media	3%	2%
– Conjunctivitis	3%	2%
– Eye disorder	2%	3%
– Deafness	3%	1%
– Optic neuritis	2%	2%
– Ear disorder	2%	1%
– Tinnitus	2%	1%
Urogenital System		
– Urinary tract infection	25%	22%
– Urinary incontinence	15%	8%
– Urinary tract disorder	10%	7%
– Cystitis	9%	7%
– Urinary urgency	7%	8%
– Menstrual disorder	13%	9%
– Increased urinary frequency	5%	6%
– Metrorrhagia	6%	12%
– Urinary retention	6%	4%
– Vaginitis	4%	3%
– Amenorrhea	4%	3%
– Dysuria	2%	2%
– Impotence	4%	7%
– Menopause	4%	2%
– Menorrhagia	4%	2%
– Nocturia	1%	2%
– Vaginal moniliasis	2%	2%
– Kidney pain	2%	0%
– Pyelonephritis	0%	2%
– Prostatic disorder	1%	2%

*significantly associated with BETASERON treatment (p<0.05)

Seventy-four (74) patients discontinued treatment due to adverse events (23 on placebo and 51 on BETASERON). Injection site reactions were significantly associated with early termination of treatment in the BETASERON group compared to placebo (p<0.05). The highest frequency of adverse events leading to discontinuation involved the nervous system, of which depression (7 on placebo and 11 on BETASERON) was the most common.

Significantly more patients on active therapy (14.4% vs. 4.7% on placebo) had elevated ALT (SGPT) values (>5 times baseline value). Elevations were also observed in AST (SGOT) and gamma-GT values in the BETASERON group throughout the study. In the BETASERON group, most ALT (SGPT) abnormalities resolved spontaneously with continued treatment whereas some resolved upon dose reduction or temporary discontinuation of treatment.

Lymphopenia (<1500/mm³) was observed in 90.9% of BETASERON patients compared to 74.3% of placebo patients and neutropenia (<1400/mm³) was noted in 18.0% BETASERON and 5.1% placebo patients.

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

BETASERON (interferon beta-1b) should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Multiple Sclerosis.

The recommended dose of BETASERON for both relapsing-remitting and secondary-progressive MS patients is 0.25 mg (8 MIU) injected subcutaneously every other day. Limited data regarding the activity of a lower dose in relapsing-remitting MS patients are presented above (see **ACTION AND CLINICAL PHARMACOLOGY, Clinical Trials**).

In the secondary-progressive MS study, patients initiated treatment with half the dose (4 MIU s.c. every other day) for a period of 2 weeks prior to escalating to the recommended dose of 8 MIU (s.c. every other day).

Efficacy of treatment for longer than 2 years has not been substantially demonstrated in relapsing-remitting multiple sclerosis. For secondary-progressive multiple sclerosis, safety and efficacy data beyond 3 years are not available.

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 **BETASERON® [interferon beta-1b] INFORMATION FOR THE PATIENT** section for **SELF-INJECTION PROCEDURE**.)

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. Product Monograph of PBETASERON® (interferon beta-1b), Berlex Canada, June 1999.
2. 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 randomised controlled trial. *Neurology* 1995;45:1227-1285.

Product Monograph available upon request.

Member PAAB R&D

See pages A-9, A-10, A-11, A-17, A-18, A-19

Lamictal® Antiepileptic

Do not exceed the recommended initial dose and subsequent dose escalations of LAMICTAL. More rapid initial titration has been associated with an increased incidence of serious dermatological reactions (see WARNINGS).

Lamotrigine Tablets (25, 100, and 150 mg Tablets; 5 mg Chewable/Dispersible Tablets)

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 adult 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.

The effectiveness of lamotrigine adjunctive therapy has also been shown in pediatric and adult patients with Lennox-Gastaut syndrome. A significant reduction in major motor seizures, drop attacks, and tonic-clonic seizures was seen following lamotrigine treatment compared with placebo treated patients. Improvements in cognitive skills (speech, nonverbal communication, alertness, attention, intellectual capacity), behaviour, and fine coordination have been seen with lamotrigine treatment in these patients.

Studies have also been conducted using lamotrigine monotherapy in adult 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 adult patients (any seizure type) can be converted to lamotrigine monotherapy from polytherapy with significant numbers of patients maintaining or improving seizure control. Efficacy was maintained during long-term treatment (up to 152 weeks).

Pharmacokinetics

Adults: LAMICTAL is rapidly and completely absorbed following oral administration, reaching peak plasma concentrations 1.4 to 4.8 hours (T_{max}) post-dosing. When administered with food, the rate of absorption is slightly reduced, but the extent remains unchanged. Following single LAMICTAL doses of 50-400 mg, peak plasma concentration (C_{max}≈0.6-4.6 µg/mL) and the area under the plasma concentration-versus-time curve (AUC=29.9-211 h•µg/mL) increase linearly with dose. The time-to-peak concentration, elimination half-life ($t_{½}$), and volume of distribution (Vd/F) are independent of dose. The $t_{½}$ 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 $t_{½}$ decreased by an average of 26% (mean steady state $t_{½}$ 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 ß-glucuronidase. Approximately 70% of an oral LAMICTAL dose is recovered in urine as this metabolite.

Table 1 Mean pharmacokinetic parameters in adult patients with epilepsy or healthy volunteers

		Healthy young volunteers		Patients with epilepsy		
	LAMICTAL administered	LAMICTAL	LAMICTAL +Valproic acid*	LAMICTAL +Enzyme-inducing AEDs	LAMICTAL +Valproic acid	LAMICTAL +Valproic acid +Enzyme-inducing AEDs
T_{max} (hrs)	Single dose	2.2 (0.25-12.0)†	1.8 (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
$t_{½}$	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

*Valproic acid administered chronically (Multiple-dose study) or for 2 days (Single-dose study). ND=Not done
†Range of individual values across studies.

Pediatrics: Lamotrigine was rapidly absorbed in children, with a T_{max} ranging from 1 to 6 hours. The mean Vd/F of lamotrigine in children aged 5 to 11 years (1.3 to 1.4 L/kg) was similar to that seen in adults (0.9 to 1.4 L/kg) but was larger in younger children (1.8 to 2.3 L/kg). As with adults, the elimination of lamotrigine in pediatric patients was similarly affected by concomitant AEDs. While the CL/F was higher and $t_{½}$ was shorter in younger children than in older children, the mean CL/F was higher and mean $t_{½}$ was shorter in both pediatric groups than in adults. Population analysis results showed that the estimated apparent plasma clearances in patients aged 13 to 18 years were similar to those found in adult patients.

Table 2 Mean pharmacokinetic parameters in pediatric patients with epilepsy

Pediatric study population	Number of subjects	T_{max} (h)	$t_{½}$ (h)	CL/F (mL/min/kg)
10 months to 5.3 years of age				
Patients taking EIAEDs	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking AEDs with no known effect on drug-metabolizing enzymes	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking VPA only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
5 to 11 years of age				
Patients taking EIAEDs	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking EIAEDs plus VPA	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking VPA only*	3	4.5 (3.0-6.0)	55.4 (24.3-73.7)	0.31 (0.20-0.54)
13 to 18 years of age				
Patients taking EIAEDs	11	†	†	1.3
Patients taking EIAEDs plus VPA	8	†	†	0.5
Patients taking VPA only	4	†	†	0.3

*Two subjects were included in the calculation for mean T_{max}. EIAEDs=Enzyme-inducing antiepileptic drugs; VPA=Valproic acid
†Parameter not estimated.

Elderly: The pharmacokinetics of lamotrigine in 12 healthy elderly volunteers (≥65 years) who each received a single oral dose of LAMICTAL (150 mg) was not different from the one 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) was 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 has 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 $t_{½}$ to 13 hours. Concomitant administration of LAMICTAL with valproic acid significantly increases $t_{½}$ and decreases the clearance of lamotrigine, whereas concomitant administration of LAMICTAL with valproic acid plus enzyme-inducing AEDs can prolong $t_{½}$ up to approximately 27 hours. Chronic administration of acetaminophen was shown to slightly decrease the $t_{½}$ and increase the clearance of a single dose of lamotrigine. The key lamotrigine parameters for adult patients and healthy volunteers are summarized in Table 1, and for pediatric patients in Table 2.

INDICATIONS AND CLINICAL USE

LAMICTAL (lamotrigine) is indicated: as adjunctive therapy for the management of adult patients with epilepsy who are not satisfactorily controlled by conventional therapy; for use as monotherapy in adults following withdrawal of concomitant antiepileptic drugs; as adjunctive therapy for the management of the seizures associated with Lennox-Gastaut syndrome in pediatric and adult patients.

CONTRAINDICATIONS

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

WARNINGS

SERIOUS RASHES ASSOCIATED WITH HOSPITALIZATION HAVE OCCURRED WITH THE USE OF LAMICTAL (lamotrigine). THE INCIDENCE OF THESE RASHES IN CLINICAL TRIALS WAS 1% (1/100) IN PEDIATRIC PATIENTS (AGE <16 YEARS) AND 0.3% (3/1000) IN ADULTS. THE INCIDENCE OF SERIOUS RASH REPORTED AS STEVENS-JOHNSON SYNDROME (SJS) IN CLINICAL TRIALS WAS 0.5% (1/200) IN PEDIATRIC PATIENTS AND 0.1% (1/1000) IN ADULTS. IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR DEATH ASSOCIATED WITH RASH HAVE BEEN REPORTED, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.

A HIGHER INCIDENCE OF SERIOUS DERMATOLOGIC EVENTS (see PRECAUTIONS, **Skin-related events**, Tables 3 and 4; see also DOSAGE AND ADMINISTRATION) HAS BEEN ASSOCIATED WITH MORE RAPID INITIAL TITRATION (EXCEEDING THE RECOMMENDED INITIAL DOSE OR EXCEEDING THE RECOMMENDED DOSE ESCALATION) AND USE OF CONCOMITANT VALPROIC ACID. NEARLY ALL CASES OF RASH 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.

Table 3 Effect of concomitant AEDs on rash associated with LAMICTAL in all adult 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*	1788	9.2%	1.8%	0.1%
Enzyme-inducing AEDs + VPA	318	8.8%	3.5%	0.9%
VPA±Non-enzyme-inducing AEDs†	159	20.8%	11.9%	2.5%
Non-enzyme-inducing AEDs	27	18.5%	0.0%	0.0%

*Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.
†Non-enzyme-inducing AEDs include clonazepam, clobazam, ethosuximide, methsuximide, vigabatrin, and gabapentin.

Table 4 Effect of the initial daily dose* of LAMICTAL, in the presence of concomitant AEDs, on the incidence of rash leading to withdrawal of treatment in adult add-on clinical trials

AED group	Enzyme-inducing AEDs†		Enzyme-inducing AEDs+VPA		VPA±Non-enzyme-inducing AEDs‡	
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

*Average daily dose in week 1.
†Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.
‡Non-enzyme-inducing AEDs include clonazepam, clobazam, ethosuximide, methsuximide, vigabatrin, and gabapentin.

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 (i.e., rash) 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 adult 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 adult 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 3 and 4; see also WARNINGS and DOSAGE AND ADMINISTRATION).

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**.

The net effects of co-administration of LAMICTAL with phenytoin, carbamazepine or valproic acid are summarized in Table 5.

Table 5 Summary of AED interactions with LAMICTAL

AED	AED plasma concentration with adjunctive LAMICTAL*	Lamotrigine plasma concentration with adjunctive AEDs†
Phenytoin (PHT)	No significant effect	↓50%
Carbamazepine (CBZ)	No significant effect	↓40%
CBZ epoxide‡	Conflicting data	
Valproic acid (VPA)	Decreased	↑200%
VPA + PHT and/or CBZ	Not evaluated	No significant effect

*From adjunctive clinical trials and volunteer studies.

†Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteer studies.

‡Not administered, but an active metabolite of carbamazepine.

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 and Cardiac conduction abnormalities**).

Drug/laboratory test interactions: LAMICTAL has not been associated with any assay interferences in clinical laboratory tests.

Use in pediatrics

Safety and efficacy in patients below the age of 16 years, other than those with Lennox-Gastaut syndrome, have not been established.

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 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 trial data indicate that lamotrigine has no effect on blood folate concentrations in adults; however, its effects during human fetal development are unknown.

To facilitate monitoring fetal outcomes of pregnant women exposed to lamotrigine, physicians are encouraged to register patients, before fetal outcome (e.g., ultrasound, results of amniocentesis, birth, etc.) is known, in the Antiepilpetic Drug Pregnancy Registry by calling 1 800 336-2176 (toll free).

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. ALTHOUGH THE MAJORITY RECOVER FOLLOWING DRUG WITHDRAWAL, SOME PATIENTS EXPERIENCE IRREVERSIBLE SCARRING AND THERE HAVE BEEN RARE CASES OF ASSOCIATED DEATH (see WARNINGS).

Adverse experiences in patients receiving LAMICTAL (lamotrigine) were generally mild, occurred within the first two weeks of therapy, and resolved without discontinuation of the drug.

Commonly observed

The most commonly observed adverse experiences associated with the use of adjunctive therapy with LAMICTAL (incidence of at least 10%) were dizziness, headache, diplopia, somnolence, ataxia, nausea, and asthenia.

Dizziness, diplopia, ataxia, and blurred vision were dose-related and occurred more commonly in patients receiving carbamazepine in combination with LAMICTAL than in patients receiving other enzyme-inducing AEDs with LAMICTAL. Reduction of the daily dose and/or alteration of the timing of doses of concomitant antiepileptic drugs and/or LAMICTAL may reduce or eliminate these symptoms. Clinical data suggest a higher incidence of rash in patients who are receiving concomitant valproic acid, or non-inducing AEDs (see WARNINGS; see also PRECAUTIONS, **Skin-related events**, Table 3).

Adverse events associated with discontinuation of treatment

Across all adult 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 3501 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 adult 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 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 4).

Adult controlled add-on clinical studies

Table 6 enumerates adverse experiences that occurred with an incidence of 2% or greater among refractory patients with epilepsy treated with LAMICTAL.

Table 6 Treatment-emergent adverse experience incidence in adult placebo-controlled clinical studies*

Body system/ Adverse experience†		Percent of patients receiving LAMICTAL (and other AEDs) (n=711)	Percent of patients receiving placebo (and other AEDs) (n=419)
BODY AS A WHOLE	Headache	29.1	19.1
	Accidental injury	9.1	8.6
	Asthenia	8.6	8.8
	Flu syndrome	7.0	5.5
	Pain	6.2	2.9
	Back pain	5.8	6.2
	Fever	5.5	3.6
	Abdominal pain	5.2	3.6
	Infection	4.4	4.1
	Neck pain	2.4	1.2
	Malaise	2.3	1.9
	Seizure exacerbation	2.3	0.5
DIGESTIVE	Nausea	18.6	9.5
	Vomiting	9.4	4.3
	Diarrhea	6.3	4.1
	Dyspepsia	5.3	2.1
	Constipation	4.1	3.1
	Tooth disorder	3.2	1.7
MUSCULOSKELETAL	Myalgia	2.8	3.1
	Arthralgia	2.0	0.2
NERVOUS	Dizziness	38.4	13.4
	Ataxia	21.7	5.5
	Somnolence	14.2	6.9
	Incoordination	6.0	2.1
	Insomnia	5.6	1.9
	Tremor	4.4	1.4
	Depression	4.2	2.6
	Anxiety	3.8	2.6
	Convulsion	3.2	1.2
	Irritability	3.0	1.9
	Speech disorder	2.5	0.2
	Memory decreased	2.4	1.9
RESPIRATORY	Rhinitis	13.6	9.3
	Pharyngitis	9.8	8.8
	Cough increased	7.5	5.7
	Respiratory disorder	5.3	5.5
SKIN AND APPENDAGES	Rash	10.0	5.0
	Pruritus	3.1	1.7
SPECIAL SENSES	Diplopia	27.6	6.7
	Blurred vision	15.5	4.5
	Vision abnormality	3.4	1.0
UROGENITAL		**(n=365)**	**(n=207)**
(Female patients)	Dysmenorrhea	6.6	6.3
	Menstrual disorder	5.2	5.8
	Vaginitis	4.1	0.5

*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.

†Adverse experiences reported by at least 2% of patients treated with LAMICTAL are included.

Other events observed during clinical studies

During clinical testing, multiple doses of LAMICTAL were administered to 3501 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 reported adverse experiences 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 6.)

Adult 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%).

Adjunctive therapy in Lennox-Gastaut syndrome

In 169 adult and pediatric patients with Lennox-Gastaut syndrome, 3.8% of patients on LAMICTAL and 7.8% of patients on placebo discontinued due to adverse experiences. The most commonly reported adverse experiences that led to discontinuation were rash for patients treated with LAMICTAL, and deterioration of seizure control for patients treated with placebo. Fever and infection occurred at least 10% more frequently in patients ≤12 years of age than in patients >12 years of age on LAMICTAL. Rash occurred at least 10% more frequently in female patients than male patients on LAMICTAL. Table 7 lists adverse events that occurred in at least 1% of 79 adult and pediatric patients who received LAMICTAL up to 15 mg/kg per day or a maximum of 400 mg per day.

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 in Tables 6 and 7 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.

Table 7 Treatment-emergent adverse experience incidence in placebo-controlled add-on trial in adult and pediatric patients with Lennox-Gastaut syndrome*

Body system/ Adverse experience		Percent of patients receiving LAMICTAL (n=79)	Percent of patients receiving placebo (n=90)
BODY AS A WHOLE	Infection	13	8
	Accidental injury	9	7
	Flu syndrome	5	0
	Asthenia	3	1
	Abdominal pain	3	0
	Back pain	1	0
	Edema of the face	1	0
	Lab test abnormal	1	0
	Pain	1	0
CARDIOVASCULAR	Hemorrhage	3	0
DIGESTIVE	Vomiting	9	7
	Constipation	5	2
	Diarrhea	4	2
	Nausea	4	1
	Anorexia	3	1
	Stomatitis aphthosa	1	0
	Tooth disorder	1	0
ENDOCRINE	Cushing's syndrome	1	0
	Hypothyroidism	1	0
HEMIC AND LYMPHATIC	Lymphadenopathy (enlarged cervical nodes)	1	0
NERVOUS SYSTEM	Ataxia	4	1
	Convulsions	4	1
	Tremor	3	0
	Agitation	1	0
	Coordination	1	0
	Dizziness	1	0
	Emotional lability	1	0
	Nervousness	1	0
	Vertigo	1	0
RESPIRATORY	Pharyngitis	14	10
	Bronchitis	9	7
	Pneumonia	3	0
	Dyspnea	1	0
SKIN	Rash	9	7
	Eczema	4	0
	Nail disorder	1	0
SPECIAL SENSES	Blepharitis	1	0
	Conjunctivitis	1	0
	Keratitis	1	0
	Ear pain	1	0
	Eye pain	1	0
UROGENITAL	Urinary tract infection	3	0
	Balanitis	2	0
	Penis disorder	2	0

* The most frequently reported adverse reactions in children ≤12 years of age in both treatment groups were pharyngitis, fever, and infection.

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 4000 and 5000 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. Among patients ≤16 years of age, the two highest known single doses of LAMICTAL have been 3000 mg by a 14-year old female and approximately 1000 mg by a 4-year old male. The 14-year old female was taking marketed LAMICTAL; after the dose, she lost consciousness and was admitted to the hospital for supportive therapy, where she recovered fully (time to recovery not reported). The 4-year old male was drowsy and agitated when found, and his condition worsened to coma level II after hospitalization. He was given supportive therapy, and his condition improved rapidly with full recovery in 3 days.

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

General

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 Tables 8 through 11.

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 (i.e., rash) require a more rapid withdrawal (see WARNINGS and 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.

Adults and children over 12 years of age

Do not exceed the recommended initial dose and subsequent dose escalations of LAMICTAL. More rapid initial titration has been associated with an increased incidence of serious dermatological reactions (see WARNINGS). For patients taking AEDs whose pharmacokinetic interactions with LAMICTAL are currently unknown, follow the titration schedule for concomitant VPA and non-enzyme-inducing AEDs.

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, Tables 3 and 4; see also WARNINGS). The potential medical benefits of the 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 should proceed with extreme caution, especially during the first six weeks of treatment.

Table 8 LAMICTAL added to VPA with enzyme-inducing AEDs* in patients over 12 years of age

		For Information† Patients taking valproic acid *only* or VPA and non-EIAEDs
Weeks 1 + 2	25 mg once a day	*25 mg every other day*
Weeks 3 + 4	25 mg twice a day	*25 mg once a day*
Usual maintenance	To achieve maintenance, doses may be increased by 25-50 mg every 1 to 2 weeks. Usual dose is between 50-100 mg twice a day.	To achieve maintenance, doses may be increased by 25-50 mg every 1 to 2 weeks. *Usual dose is between 50-100 mg twice a day.*

*Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.
†*Column reflects dosage recommendations in the U.K. and is provided for information.*

Table 9 LAMICTAL added to enzyme-inducing AEDs* (without VPA) in patients over 12 years of age

Weeks 1 + 2	50 mg once a day
Weeks 3 + 4	50 mg twice a day
Usual maintenance	To achieve maintenance, doses may be increased by 100 mg every 1 to 2 weeks. Usual dose is between 150-250 mg twice a day.

*Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.

Withdrawal of concomitant AEDs in adults

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 $t_{½}$ 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 $t_{½}$ of lamotrigine and may require an increase in the dose of LAMICTAL.

Pediatric dosing

Do not exceed the recommended initial dose and subsequent dose escalations of LAMICTAL. More rapid initial titration has been associated with an increased incidence of serious dermatological reactions (see WARNINGS). Safety and efficacy in patients below the age of 16 years, other than those with Lennox-Gastaut syndrome, have not been established.

Table 10 Pediatric dosing with LAMICTAL for patients receiving valproic acid with or without enzyme-inducing AEDs*

Weight range		Weeks 1 + 2 0.15 mg/kg once a day	Weeks 3 + 4 0.3 mg/kg once a day	Weeks 5 and onwards to usual maintenance dose† To achieve maintenance, doses may be increased by 0.3 mg/kg every 1-2 weeks, to a maximum of 200 mg/day. Usual dose is between 1-5 mg/kg once a day.‡
<17 kg	<37 lbs	Do not take LAMICTAL because therapy cannot be initiated with currently available tablet strengths.		
17-33 kg	37-73 lbs	5 mg every other day	5 mg/day	Increase dose by no more than 5 mg/day every 1-2 weeks.
34-49 kg	75-108 lbs	5 mg /day	10 mg/day	Increase dose by no more than 10 mg/day every 1-2 weeks.
≥50 kg§	≥110 lbs	5 mg/day	15 mg/day	Increase dose by no more than 15 mg/day every 1-2 weeks.

*Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.
†It may take several weeks to months to achieve an individualized maintenance dose.
‡Can be given as two divided doses.
§Insufficient data are available to be able to support the mg/kg dosing in patients weighing more than 50 kg.

Table 11 Pediatric dosing with LAMICTAL for patients receiving enzyme-inducing AEDs*,†,‡ without valproic acid

Weight range		Weeks 1 + 2 0.3 mg/kg twice a day	Weeks 3 + 4 0.6 mg/kg twice a day	Weeks 5 and onwards to usual maintenance dose§ To achieve maintenance, doses may be increased by 1.2 mg/kg every 1-2 weeks, to a maximum of 400 mg/day. Usual dose is between 2.5-7.5 mg/kg twice a day.
<9 kg	<20 lbs	Do not take LAMICTAL because therapy cannot be initiated with currently available tablet strengths		
9-12 kg	20-26 lbs	5 mg/day	10 mg/day	Increase dose by no more than 10 mg/day every 1-2 weeks.
13-16 kg	29-35 lbs	5 mg/day	15 mg/day	Increase dose by no more than 15 mg/day every 1-2 weeks.
17-20 kg	37-44 lbs	10 mg/day	20 mg/day	Increase dose by no more than 20 mg/day every 1-2 weeks.
21-24 kg	46-53 lbs	10 mg/day	25 mg/day	Increase dose by no more than 25 mg/day every 1-2 weeks.
25-29 kg	55-64 lbs	15 mg/day	30 mg/day	Increase dose by no more than 30 mg/day every 1-2 weeks.
30-33 kg	66-73 lbs	15 mg/day	35 mg/day	Increase dose by no more than 35 mg/day every 1-2 weeks.
34-37 kg	75-81 lbs	20 mg/day	40 mg/day	Increase dose by no more than 40 mg/day every 1-2 weeks.
38-41 kg	84-90 lbs	20 mg/day	45 mg/day	Increase dose by no more than 45 mg/day every 1-2 weeks.
42-45 kg	92-99 lbs	25 mg/day	50 mg/day	Increase dose by no more than 50 mg/day every 1-2 weeks.
46-49 kg	101-108 lbs	25 mg/day	55 mg/day	Increase dose by no more than 55 mg/day every 1-2 weeks.
50-54 kg	110-119 lbs	30 mg/day	60 mg/day	Increase dose by no more than 60 mg/day every 1-2 weeks.
55-58 kg	121-128 lbs	30 mg/day	65 mg/day	Increase dose by no more than 65 mg/day every 1-2 weeks.
≥59 kg¶	≥130 lbs	35 mg/day	70 mg/day	Increase dose by no more than 70 mg/day every 1-2 weeks.

*Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.
†Can be given as two divided doses.
‡Total daily dose can be divided.
§It may take several weeks to months to achieve an individualized maintenance dose.
¶Insufficient data are available to be able to support the mg/kg dosing in patients weighing more than 59 kg.

The starting doses and dose escalations listed above are different than those used in clinical trials, however, the maintenance doses are the same as those used in clinical trials. Smaller starting doses and slower dose escalations than those used in clinical trials are recommended because of concern that the risk of serious rash may be greater with higher initial doses and more rapid dose escalation. Consequently, it may take several weeks to months to

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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- β), and interleukin 6 (IL-6), which are secreted by T lymphocyte helper-1 (Th1) 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.

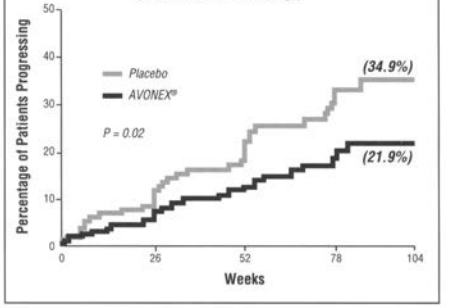
All patients had a definite diagnosis of MS of at least 1 year duration and had at least 2 exacerbations in the 3 years prior to study entry (or 1 per year if the duration of disease was less than 3 years). At entry, study participants were without exacerbation during the prior 2 months and had Kurtzke 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)



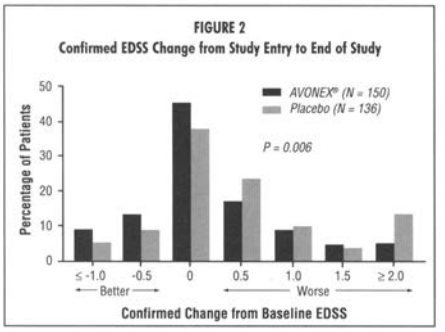
Note: Disability progression represents at least a 1.0 point increase in EDSS score sustained for at least 6 months. The value p=0.02 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given timepoint (e.g., 34.9% vs. 21.9%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

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, anxiety, Bell's Palsy, clumsiness, depersonalization, drug dependence, facial paralysis, hyperesthesia, increased libido, neurosis, psychosis; **Respiratory System:** emphysema, hemoptysis, hiccup, hyperventilation, laryngitis, pharygeal edema, pneumonia; **Skin and Appendages:** basal

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BRIEF PRESCRIBING INFORMATION

TOPAMAX
topiramate

PrTOPAMAX*
(topiramate)
25, 100 and 200 mg Tablets
15 and 25 mg Sprinkle Capsules

THERAPEUTIC CLASSIFICATION
Antiepileptic

INDICATIONS AND CLINICAL USE
TOPAMAX topiramate is indicated as adjunctive therapy for the management of patients (adults and children two years and older) 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. In adults, 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: 27/1,092 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. In the pediatric patients studied, there were no kidney stones observed.

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 topiramate, 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 therapy. These events were usually intermittent and mild, and not necessarily related to the dosage of topiramate.

Weight Loss in Pediatrics
Topiramate administration is associated with weight loss in some children that generally occurs early in therapy. Of those pediatric subjects treated in clinical trials for at least a year who experienced weight loss, 96% showed a resumption of weight gain within the period tested. In 2-4 year olds, the mean change in weight from baseline at 12 months (n=25) was +0.7 kg (range -1.1 to 3.2); at 24 months (n=14), the mean change was +2.2 (range -1.1 to 6.1). In 5-10 year olds, the mean change in weight from baseline at 12 months (n=88) was +0.7 kg (range -6.7 to 11.8); at 24 months (n=67), the mean change was +3.3 (range -8.6 to 20.0). Weight decreases, usually associated with anorexia or appetite changes, were reported as adverse events for 9% of topiramate-treated pediatric patients. The long term effects of reduced weight gain in pediatric patients is not known.

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 ($CL_{CR} \leq 60$ mL/min) or with end-stage renal disease receiving hemodialysis treatments may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function. As with all patients, the titration schedule should be guided by clinical outcome (i.e. seizure control, avoidance of side effects) with the knowledge that patients with known renal impairment may require a longer time to reach steady-state at each dose. (See **DOSAGE AND ADMINISTRATION**.)

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

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

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

Drug Interactions
Antiepileptic 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 1:

Table 1
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.

On occasion, the addition of TOPAMAX therapy to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX topiramate may require adjustment of the dose of TOPAMAX topiramate.

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

Oral Contraceptives: In a pharmacokinetic interaction study with oral contraceptives using a combination product containing norethindrone plus ethinyl estradiol, TOPAMAX topiramate 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 topiramate, 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 topiramate 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 topiramate 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 topiramate 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 topiramate on labour and delivery in humans is unknown.

Pediatric Use
Safety and effectiveness in children under 2 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 topiramate.

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
Adults
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 in adults 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 2).

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 3).

Table 2
Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials in ADULTS[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 topiramate 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 3
Dose-Related Adverse Events From
Placebo-Controlled, Add-On Trials in ADULTS

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 six 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.

Pediatrics

Adverse events associated with the use of topiramate at dosages of 5 to 9 mg/kg/day in worldwide pediatric clinical trials that were seen at greater frequency in topiramate-treated patients were: fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease.

Table 4 lists treatment-emergent adverse events that occurred in at least 2% of children treated with 5 to 9 mg/kg/day topiramate in controlled trials that were numerically more common than in patients treated with placebo.

Table 4
Incidence (%) of Treatment-Emergent Adverse Events in Worldwide Pediatric Clinical Trials Experience (2-16 years of Age)[a,b]
(Events that Occurred in ≥ 2% of Topiramate-Treated Patients and Occurred More Frequently in Topiramate-Treated Than Placebo-Treated Patients)

Body System/ Adverse Event	Placebo (N=101)	Topiramate (N=98)
Body as a Whole – General Disorders		
Fatigue	5	16.3
Injury	12.9	14.3
Allergic Reaction	1	2
Central & Peripheral Nervous System Disorders		
Gait Abnormal	5	8.2
Ataxia	2	6.1
Hyperkinesia	4	5.1
Dizziness	2	4.1
Speech Disorders/Related Speech Problems	2	4.1
Convulsions Aggravated	3	3.1
Hyporeflexia	0	2
Gastrointestinal System Disorders		
Nausea	5	6.1
Saliva Increased	4	6.1
Constipation	4	5.1
Gastroenteritis	2	3.1
Metabolic and Nutritional Disorders		
Weight Decrease	1	9.2
Thirst	1	2
Platelet, Bleeding, & Clotting Disorders		
Purpura	4	8.2
Epistaxis	1	4.1
Nervous Disorders		
Somnolence	15.8	25.5
Anorexia	14.9	24.5
Nervousness	6.9	14.3
Personality Disorder (Behavior Problems)	8.9	11.2
Difficulty with Concentration/Attention	2	10.2
Aggressive Reaction	4	9.2
Insomnia	6.9	8.2
Mood Problems	6.9	7.1
Difficulty with Memory NOS	0	5.1
Emotional Lability	5	5.1
Confusion	3	4.1
Psychomotor Slowing	2	3.1
Reproductive Disorders, Female		
Leukorrhea	0.0	2.3
Resistance Mechanism Disorders		
Infection Viral	3.0	7.1
Infection	3.0	3.1
Respiratory System Disorders		
Upper Respiratory Tract Infection	36.6	36.7
Pneumonia	1.0	5.1
Skin and Appendages Disorders		
Skin Disorder	2.0	3.1
Alopecia	1.0	2.0
Dermatitis	0.0	2.0
Hypertrichosis	1.0	2.0
Rash Erythematous	0.0	2.0
Urinary System Disorders		
Urinary Incontinence	2.0	4.1
Vision Disorders		
Eye Abnormality	1.0	2.0
Vision Abnormal	1.0	2.0
White Cell and RES Disorders		
Leukopenia	0.0	2.0

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

None of the pediatric patients who received topiramate adjunctive therapy at 5 to 9 mg/kg/day in controlled clinical trials discontinued due to adverse events. In open extensions of the controlled clinical trials, approximately 9% of the 303 pediatric patients who received topiramate at dosages up to 30 mg/kg/day discontinued due to adverse events. Adverse events associated with discontinuing therapy included aggravated convulsions (2.3%), language problems (1.3%), and difficulty with concentration/attention (1.3%).

In adult and pediatric patients, 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 topiramate as adjunctive therapy in both double-blind and open-label trials (1,446 adults and 303 children) was analyzed, a similar pattern of adverse events emerged.

Post-Marketing Adverse Reactions

The most frequently reported adverse events in spontaneous post-marketing reports on topiramate include:
Psychiatric: somnolence or sedation, hallucination(s), depression, anorexia, aggressive reaction, psychosis, thinking abnormal, paranoid reaction, insomnia, emotional lability, suicide attempt, delusion
Central and Peripheral Nervous System: confusion, convulsions aggravated, paresthesia, agitation, speech disorder, ataxia, dizziness, convulsions, amnesia, headache, hyperkinesia
Metabolic and Nutritional: weight decrease
Autonomic Nervous System: vomiting
Vision: vision abnormal
Gastrointestinal: nausea, diarrhea, abdominal pain, constipation
Body as a Whole – General Disorders: fatigue
Urinary System: renal calculus
Skin and Appendages: rash

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.

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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

General
TOPAMAX Tablets or Sprinkle Capsules can be taken without regard to meals. Tablets should not be broken. TOPAMAX Sprinkle Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

Adults (Age 17 years and older)
It is recommended that TOPAMAX topiramate as adjunctive therapy be initiated at 50 mg/day, followed by titration as needed and tolerated to an effective dose. At weekly intervals, the dose may be increased by 50 mg/day and taken in two divided doses. Some patients may benefit from lower initial doses, e.g. 25 mg and/or a slower titration schedule. Some patients may achieve efficacy with once-a-day dosing.

The recommended total daily maintenance dose is 200 mg-400 mg/day in two divided doses. 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.

Children (Ages 2-16 years)
It is recommended that TOPAMAX topiramate as adjunctive therapy be initiated at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week followed by titration as needed and tolerated to an effective dose. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses). Some patients may benefit from lower initial doses and/or a slower titration schedule.

The recommended total daily maintenance dose is approximately 5 to 9 mg/kg/day in two divided doses. Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

Geriatrics
See **PRECAUTIONS** section.

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 antiseizure 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, 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.

AVAILABILITY OF DOSAGE FORMS

TOPAMAX may be given as Tablets or Sprinkle Capsules.

TOPAMAX Tablets are available in three strengths containing 25, 100 or 200 mg topiramate per tablet. The 25 mg tablets are white, round and coated; the 100 mg tablets are light yellow, round and coated; the 200 mg tablets are salmon-coloured, round and coated. Each strength is available in bottles containing 60 tablets with desiccant.

TOPAMAX Sprinkle Capsules are available in two strengths containing 15 or 25 mg topiramate per capsule. The Sprinkle Capsules contain small white to off-white spheres in white and clear gelatin capsules. The 15 mg capsules are marked with "TOP" and "15 mg" on the side; the 25 mg capsules are marked with "TOP" and "25 mg" on the side. The Sprinkle Capsules are available in bottles of 60 capsules without desiccant.

TOPAMAX is a schedule F drug.

References:

1. TOPAMAX* topiramate Tablets and Sprinkle Capsules Product Monograph April 26, 1999.
2. Biton V, Montouris GD, Ritter F et al. A Randomized placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. *Neurology* 1999:52;1330-1337.
3. Sachdeo R, Glauser TA, Ritter F, Reife R, Lim P, Pledger G et al. A Double-blind, Randomized Trial of Topiramate in Lennox-Gastaut Syndrome. *Neurology* In press 1999.
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6. Walker MC and Sander JWAS. Topiramate: a new antiepileptic drug for refractory epilepsy. *Seizure* 1996: 5: 199-203.
7. Potter D, Edwards KR, Norton J. Sustained weight loss associated with 12-month topiramate therapy. *Epilepsia* 1997; 38(Suppl 8):97.
8. Sander JWAS. Using Topiramate in Patients with Epilepsy: Practical Aspects. *The Canadian Journal of Neurological Sciences* 1998: 25(Suppl.3):S16-18.

Product Monograph available upon request.

Janssen-Ortho Inc.
Toronto, Ontario
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TOPAMAX
topiramate

Date of Issuance: June 1999

PITX991011A

PAAB

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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, April 6, 1998.
2 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.
3 Data on file, PRB#8154-1, Biogen, Inc., November 20, 1997.
4 Data on file, Biogen, Inc.
5 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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PAAB

See pages A-4, A-5

Continued from page A-44

achieve an individualized maintenance dose.
The smallest available strength of LAMICTAL Chewable/Dispersible Tablets is 5 mg, and only whole tablets should be administered (scoreline on the 5 mg tablet is not intended for tablet splitting). Therefore, recommended doses have been determined based on the individual, or combination of, tablet strengths which most closely approximate, but do NOT exceed, the target dose calculated on the basis of patient weight. LAMICTAL should not be administered if the calculated daily dose is less than 2.5 mg (e.g., patients weighing less than 17 kg [37 lbs] and on concomitant VPA, or patients weighing less than 9 kg [20 lbs] and on concomitant EIAEDs without VPA). If the initial calculated daily dose of LAMICTAL is 2.5 to 5 mg, then 5 mg of LAMICTAL should be taken on alternative days for the first 2 weeks.
For patients taking AEDs whose pharmacokinetic interactions with LAMICTAL are currently unknown, follow the titration schedule for concomitant VPA.

Elderly 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.

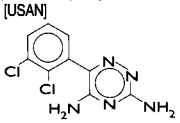
Patients with impaired hepatic function

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.

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 pK_a 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 glycollate, and colouring agents:

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

LAMICTAL Chewable/Dispersible Tablets (5 mg) contain lamotrigine and the following non-medicinal ingredients: aluminum magnesium silicate, blackcurrant flavour, calcium carbonate, hydroxypropylcellulose, magnesium stearate, povidone, saccharin sodium and sodium starch glycollate.

Administration of LAMICTAL Chewable/Dispersible Tablets

LAMICTAL Chewable/Dispersible Tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit juice. The scoreline on the 5 mg tablet is not intended for tablet splitting. If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in swallowing. To disperse the tablets, add the tablets to a small amount of liquid (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the tablets are completely dispersed, swirl the solution and consume the entire quantity immediately. No attempt should be made to administer partial quantities of the dispersed tablets.

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 (scored, shield-shaped, engraved "LAMICTAL") are available in three different strengths in the following pack formats:

- 25 mg tablets (white) in bottles of 100;
- 100 mg tablets (peach) in bottles of 100;
- 150 mg tablets (cream) in bottles of 60.

LAMICTAL Chewable/Dispersible Tablets (white, scored and biconvex, engraved "LAMICTAL") are available in the following pack format:

- 5 mg (initiation dose only) in blisters of 28.

Product Monograph available to healthcare professionals upon request.

References:

1. Motte J, Trevathan E, Arvidsson JFV, et al. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. *N Engl J Med* 1997;337:1807-1812. **2.** Product Monograph of PrLamictal® (lamotrigine), Glaxo Wellcome Inc. May 1999. **3.** Mullens L, Gallagher J, and Manasco P. Improved neurological function accompanies effective control of the Lennox-Gastaut syndrome with Lamictal®: results of a multinational, placebo-controlled trial. *Epilepsia* 1996;37(Suppl. 5):163.

See pages A-6, A-7, A-20, A-21

NEUROPSYCHIATRIC CLINICAL SCIENTIST

The Kunin-Lunenfeld Applied Research Unit and the Department of Psychiatry of Baycrest Centre for Geriatric Care invites applications for a neuropsychiatric scientist position. The successful candidate will engage in an interdisciplinary clinical research program in the Department of Psychiatry. The person will work closely with clinician researchers, basic neuroscientists and the program of neuropsychiatry at the Rotman Research Institute and at the University of Toronto. The position will involve an emphasis on the neurobehavioural underpinnings of late life mental disorders with opportunity for collaboration in multimodality functional neuroimaging. With the recent addition of Dr. Helen Mayberg, Chair of the Neuropsychiatry program and the awarding of the Canadian Foundation for Innovation grant, to purchase modern imaging equipment, new and rewarding opportunities will provide for the further development and growth of the Neuropsychiatry program.

The candidate must have an MD or a Ph.D. (or equivalent) in a related field. The candidate will be eligible for a cross appointment at the University of Toronto at the Assistant or Associate professor level. Clinical investigators (psychiatrists, neurologists, neuropsychologists, etc.) with an interest in the neurology of behaviour are especially encouraged to apply.

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Assistant Vice-President, Research; Director, Kunin-Lunenfeld Applied Research Unit; Baycrest Centre for Geriatric Care
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†In controlled clinical trials, the incidence of adverse events was similar to placebo (31% for AMERGE 2.5 mg vs. 32% for placebo[2]).
‡Headache relief=reduction of moderate or severe pain to mild or no pain. AMERGE 2.5 mg n=586: $p<0.001$ vs. placebo 60 min post-dose to 4 hrs; $p<0.05$ vs. placebo at 4, 8, 12, 24 hrs.
§The median percentage does not represent recurrence rate. Headache recurrence equals a return of moderate or severe pain in 4 to 24 hours post-dose following initial relief.

AMERGE (naratriptan hydrochloride) is a selective 5-HT$_1$ receptor agonist indicated for the acute treatment of migraine attacks with or without aura. AMERGE is not indicated for prophylactic therapy of migraine, or for the management of hemiplegic, basilar & ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache which is present in an older, predominantly male population. AMERGE is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias. In addition, patients with other significant underlying cardiovascular diseases should not receive AMERGE. AMERGE is also contraindicated in patients with uncontrolled or severe hypertension.

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For brief prescribing information see pages A-29, A-30

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