ropinirole

REQUIP

Early Therapy | Adjunct Therapy

ropinirole (as ropinirole hydrochloride)

Tablets

0.25 mg, 1.0 mg, 2.0 mg, 5.0 mg

THERAPEUTIC CLASSIFICATION

AntiParkinsonian Agent / Dopamine Agonist

ACTION AND CLINICAL PHARMACOLOGY

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

In vitro studies have shown that ropinirole binds with high affinity to cloned human D_2, D_3 and D_4 receptors. The antiparkinson activity of ropinirole is believed to be due to its stimulatory effects on central post-synaptic dopamine D_2 receptors within the caudate-putamen.

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

Neither ropinirole nor its metabolites bind with high affinity to dopamine D_1 receptors. Ropinirole also has very low affinity for 5-HT_1, 5-HT_2, benzodiazepine, $GABA_A$, muscarinic, alpha- or beta-adrenoreceptors. Ropinirole binds to opiate receptors with low affinity, however, studies show that this weak opiate activity has no consequences at pharmacological doses *in vivo*.

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

In healthy normotensive subjects, single oral doses of REQUIP, in the range of 0.01 to 2.5 mg, had little or no effect on supine blood pressure and pulse rate. Upon standing, REQUIP caused decreases in systolic and mainly diastolic blood pressure at doses above 0.25 mg. In some subjects, these changes were associated with the emergence of orthostatic symptoms, bradycardia and, in one case, transient sinus arrest in the context of a severe vasovagal syncope. The effect of repeat dosing and slow titration of REQUIP was not studied in healthy volunteers. The mechanism of REQUIP-induced orthostatic symptoms probably relates to its dopamine D_2-mediated blunting of the noradrenergic response to standing and subsequent decrease in peripheral vascular resistance. Orthostatic signs and symptoms were often accompanied by nausea.

REQUIP had no dose-related effect on ECG wave form and rhythm in young healthy male volunteers.

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

Pharmacokinetics

Absorption, Bioavailability, and Distribution

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

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

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

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

*median

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

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

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

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

Ropinirole has a blood to plasma ratio of 1.2.

Metabolism

Ropinirole is extensively metabolized by the liver. The N-despropyl metabolite is the major metabolite circulating in the plasma. Based on AUC data, the plasma levels of the metabolite were consistently higher than those of the parent drug suggesting a nonsaturable conversion of ropinirole to the N-despropyl metabolite. The affinity of the N-despropyl metabolite for human cloned D_2 receptors is lower than the affinity of ropinirole. In addition the metabolite does not cross the blood-brain barrier; thus, it is unlikely to contribute to the therapeutic effects of ropinirole. The plasma concentrations of the hydroxylated metabolite are low and account for about 1-5% of the ropinirole concentrations. Although the hydroxylated metabolite was more active than ropinirole in *in vitro* D_2 receptor binding studies, at therapeutic doses it is not expected to contribute to the activity of ropinirole.

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

Elimination

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

Population Subgroups

Renal and Hepatic Impairment

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

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

Gender

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

Estrogen Replacement Therapy

In women, on long-term treatment with conjugated estrogens (n=16, mean age 63 years), the oral clearance of REQUIP was decreased by an average of 36% compared to the oral clearance in women not receiving supplemental estrogens (n=56, mean age 65 years). The average terminal elimination half-life was 9.0 hours in the estrogen group and 6.5 hours in patients not taking estrogens (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Age

Population pharmacokinetic analysis revealed that the oral clearance of REQUIP, seen in patients under the age of 65 years (n=97), was reduced from 62.1 L/h to 45.5 L/h in patients between the ages of 65 and 75 years (n=63). In patients older than 75 years (n=11), oral clearance was similar to that seen in the 65 to 75 year age group (41.7 L/h). However, since the dose of REQUIP is to be individually titrated to clinical response, dosage adjustment is not necessary in the elderly (above 65 years).

Clinical Trials

Up to May 31, 1996, 1599 patients have been exposed to REQUIP, with 481 patients being exposed for over one year and 241 patients being exposed for over two years.

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

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

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

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

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

Early Therapy

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

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

Adjunct Therapy

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

Therapeutic Effect – Plasma Concentration

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

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

INDICATIONS AND CLINICAL USE

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

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

CONTRAINDICATIONS

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

WARNINGS

Orthostatic Symptoms

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

Hallucinations

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

PRECAUTIONS

Cardiovascular

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

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

Neuroleptic Malignant Syndrome

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

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

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

Retinal Pathology in Rats

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

Pregnancy

The use of REQUIP during pregnancy is not recommended.

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

Nursing Mothers

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

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

Use in Women receiving Estrogen Replacement Therapy

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

Pediatric Use

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

Renal and Hepatic Impairment

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

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

Drug Interactions

Psychotropic Drugs:

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

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

Anti-Parkinson Drugs:

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

Levodopa:

The potential pharmacokinetic interaction of levodopa/carbidopa (100 mg/10 mg b.i.d.) and REQUIP (2 mg t.i.d.) was assessed in levodopa naive (*de novo*) male and female patients with Parkinson's disease (n=30, mean age 64 years). The rate and extent of availability of REQUIP at steady state were essentially the same with or without levodopa. Similarly, the rate and extent of availability of levodopa, as well as its elimination half-life, were essentially the same in the presence and absence of REQUIP.

Inhibitors of CYP1A2: Ciprofloxacin

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

Substrates of CYP1A2: Theophylline

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

Digoxin:

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

Alcohol:

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

Psycho-Motor Performance

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

ADVERSE REACTIONS

Adverse Reactions Associated with Discontinuation of Treatment

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

Most Frequent Adverse Events

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

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

Incidence of Adverse Events in Placebo Controlled Trials

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

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

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

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TABLE 2

Adverse events with incidence ≥1% from all placebo-controlled early and adjunct therapy studies

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

a: Incidence of adverse event <1%.

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

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

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

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

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

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

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

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

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

Collagen: *rare,* rheumatoid arthritis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Other Special Senses: *rare,* parosmia.

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

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

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

Renal and Hepatic Impairment

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

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

Estrogen Replacement Therapy

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

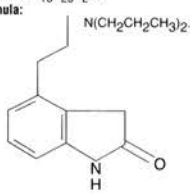
PHARMACEUTICAL INFORMATION

Drug Substance:
Proper Name: Ropinirole Hydrochloride

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

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

Stuctural Formula:



ropinirole hydrochloride

Molecular Weight: 296.84 (260.38 as the free base).

Description: Ropinirole hydrochloride is a white to pale greenish-yellow powder.

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

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

AVAILABILITY OF DOSAGE FORM

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

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

Full Product Monograph available to practitioners upon request.

REFERENCES:

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5. Data on file, SB 1024
6. Flaherty JF, Gidal BE. Parkinson's Disease. Applied Therapeutics: The Clinical Use of Drugs, Applied Therapeutics Inc., Vancouver, WA, 1995; 51.1-51.16.
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SmithKline Beecham Pharma

Oakville, Ontario L6H 5V2

MEMBER PMAC PAAB CCPP

For brief prescribing information see ifc

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.

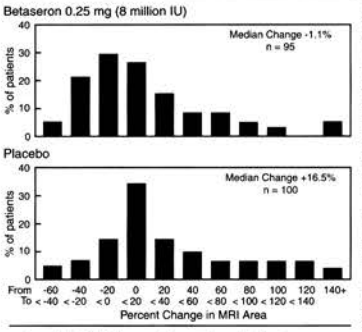
Over the 2-year period, there were 25 MS-related hospitalizations in the 0.25 mg (8 MIU) BETASERON-treated group compared to 48 hospitalizations in the placebo group. In comparison, non-MS hospitalizations were evenly distributed between the groups, with 16 in the 0.25 mg (8 MIU) BETASERON group and 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 Kaplan-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.

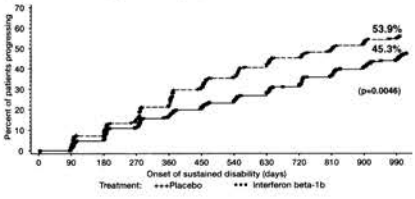
†† Sequelae and Functional Neurologic Status, both required by protocol, were not analyzed individually but are included as a function of the EDSS.

‡ 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 sub-cutaneous 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 corticosteroid or ACTH treatment of relapses for periods of up to 28 days.

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

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 child-bearing 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/mm^3	67%	82%
– ANC < 1500/mm^3*	6%	18%
– WBC < 3000/mm^3*	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%
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 ($p<0.05$)

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%

* 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/mm^3) was observed in 90.9% of BETASERON patients compared to 74.3% of placebo patients and neutropenia (<1400/mm^3) 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/mm^3, 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 ®BETASERON® (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)

NEURONTIN®

(gabapentin capsules)

(Gabapentin)100 mg, 300 mg, 400 mg Capsules
(Antiepileptic Agent)

INDICATIONS AND CLINICAL USE

Neurontin (gabapentin) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

CONTRAINDICATIONS

Neurontin (gabapentin) is contraindicated in patients who have demonstrated hypersensitivity to the drug or to any of the components of the formulation.

PRECAUTIONS

General

Neurontin (gabapentin) is not considered effective in the treatment of absence seizures and should therefore be used with caution in patients who have mixed seizure disorders that include absence seizures.

Tumorigenic Potential

Gabapentin produced an increased incidence of acinar cell adenomas and carcinomas in the pancreas of male rats, but not female rats or in mice, in oncogenic studies with doses of 2000 mg/kg which resulted in plasma concentrations 14 times higher than those occurring in humans at the maximum recommended dose of 2400 mg/day. The relevance of these pancreatic acinar cell tumours in male rats to humans is unknown, particularly since tumours of ductal rather than acinar cell origin are the predominant form of human pancreatic cancer.

Drug Discontinuation

As with other anticonvulsant agents, abrupt withdrawal is not recommended because of the possibility of increased seizure frequency. When in the judgement of the clinician there is a need for dose reduction, discontinuation or substitution with alternative medication, this should be done gradually over a minimum of one week.

Occupational Hazards

Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials, the most common adverse reactions observed were somnolence, ataxia, fatigue and nystagmus. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that Neurontin does not affect them adversely.

Drug Interactions

Antiepileptic Agents:

There is no interaction between Neurontin and phenytoin, valproic acid, carbamazepine, or phenobarbital. Consequently, Neurontin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the plasma concentrations of gabapentin or the other antiepileptic drugs.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving antiepileptic agents.

Oral Contraceptives:

Coadministration of Neurontin with the oral contraceptive Norlestrin does not influence the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Antacids:

Coadministration of Neurontin with an aluminum and magnesium-based antacid reduces gabapentin bioavailability by up to 24%. Although the clinical significance of this decrease is not known, coadministration of similar antacids and gabapentin is not recommended.

Probenecid:

Renal excretion of gabapentin is unaltered by probenecid.

Cimetidine:

A slight decrease in renal excretion of gabapentin observed when it is coadministered with cimetidine is not expected to be of clinical importance.

Use in Pregnancy

No evidence of impaired fertility or harm to the fetus due to gabapentin administration was revealed in reproduction studies in mice at doses up to 62 times, and in rats and rabbits at doses up to 31 times the human dose of 2400 mg/day. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus.

Use in Lactation

It is not known if gabapentin is excreted in human milk, and the effect on the nursing infant is unknown. However, because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from gabapentin, breast-feeding is only recommended if the potential benefit outweighs the potential risks.

Use in Children

Systematic studies to establish safety and efficacy in children have not been performed. Data in 39 patients between the ages of 12 and 18 years included in the double-blind, placebo-controlled trials showed that gabapentin was superior to placebo in reducing seizure frequency. Safety data showed that the incidence of adverse events in this group of patients were similar to those observed in older individuals.

Use in the Elderly

Systematic studies in geriatric patients have not been conducted. Adverse clinical events reported among 59 patients over the age of 65 years treated with Neurontin did not differ from those reported for younger individuals. The small number of individuals evaluated and the limited duration of exposure limits the strength of any conclusions reached about the influence of age, if any, on the kind and incidence of adverse events associated with the use of Neurontin. As Neurontin is eliminated primarily by renal excretion, dosage adjustment may be required in elderly patients because of declining renal function (See Dosage and Administration).

Use in Renal Impairment

Gabapentin clearance is markedly reduced in this patient population and dosage reduction is necessary (See Table 3 in Dosage and Administration).

Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin. Neurontin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or other antiepileptic drugs. For urinary protein determination the sulfosalicylic acid precipitation procedure is recommended, as false positive readings were reported with the Ames N-Multistix SG® dipstick test, when gabapentin or placebo was added to other anticonvulsant drugs.

ADVERSE REACTIONS

Adverse Events in Controlled Trials

The most commonly observed adverse events associated with the use of Neurontin in combination with other antiepileptic drugs, not seen at an equivalent frequency in placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, nystagmus and tremor. Among the treatment-emergent adverse events occurring in Neurontin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship. Patients treated with 1800 mg/day (n=54, from one controlled study) experienced approximately a two-fold increase, as compared to patients on lower doses of 600 to 1200 mg/day (n=489, from several controlled studies), in the incidence of nystagmus (20.4%), tremor (14.8%), rhinitis (13%), peripheral edema (7.4%), abnormal coordination, depression and myalgia (all at 5.6%). Adverse events were usually mild to moderate in intensity, with a median time to resolution of 2 weeks. Since Neurontin was administered most often in combination with other antiepileptic agents, it was not possible to determine which agent(s) was associated with adverse events. Data from long-term, open, uncontrolled studies shows that Neurontin treatment does not result in any new or unusual adverse events.

Withdrawal From Treatment Due to Adverse Events

Approximately 6.4% of the 543 patients who received Neurontin in the placebo-controlled studies withdrew due to adverse events. In comparison, approximately 4.5% of the 378 placebo-controlled participants withdrew due to adverse events during these studies. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue, nausea and/or vomiting and dizziness (all at 0.6%).

Other Adverse Events Observed in All Clinical Trials

Adverse events that occured in at least 1% of the 2074 individuals who participated in all clinical trials are described below, except those already listed in the previous section:

Body As a Whole	: aesthenia, malaise, facial edema
Cardiovascular System	: hypertension
Digestive System	: anorexia, flatulance, gingivitis
Hematologic/Lymphatic System	: purpura, most often described as bruises resulting from physical trauma
Musculoskeletal System	: arthalagia
Nervous System	: vertigo, hyperkinesia, parasthesia, anxiety, hostility, decreased or absent reflexes
Respiratory System	: pneumonia
Special Senses	: abnormal vision

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute, life-threatening toxicity has not been observed with Neurontin (gabapentin) overdoses of up to 49 grams ingested at one time. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, reduce toxicity from overdoses.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

DOSAGE AND ADMINISTRATION

Adults

The usual effective maintenance dose is 900 to 1200 mg/day. Treatment should be initiated with 300 to 400 mg/day. Titration to an effective dose, in increments of 300 mg or 400 mg/day, can progress rapidly and can be accomplished over three days (see Table 1). Neurontin is given orally with or without food.

Table 1. Titration Schedule

DOSE	Day 1	Day 2	Day 3
900 mg/day	300 mg OD	300 mg BID	300 mg TID
1200 mg/day	400 mg OD	400 mg BID	400 mg TID

Data from clinical trials suggest that doses higher than 1200 mg/day may have increased efficacy in some patients; however, higher doses may also increase the incidence of adverse events (See Adverse Reactions).

Daily maintenance doses should be given in three equally divided doses (See Table 2), and the maximum time between doses in a three times daily schedule should not exceed 12 hours. It is not necessary to monitor gabapentin plasma concentrations in order to optimize Neurontin therapy. Further, as there are no drug interactions with commonly used antiepileptic drugs, Neurontin may be used in combination with these drugs without concern for alteration of plasma concentrations of either gabapentin or other antiepileptic drugs.

Table 2. Maintenance Dosage Schedule

Total Daily Dose (mg/day)	Schedule
900	300 mg TID
1200	400 mg TID
1800	2 x 300 mg TID
2400	2 x 400 mg TID

Dosage adjustment in elderly patients due to declining renal function and in patients with renal impairment or undergoing hemodialysis is recommended as follows:

Table 3. Maintenance Dosage of Neurontin in Adults With Reduced Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)	Dose Regimen (mg)
>60	1200	400 Three Times a Day
30-60	600	300 Twice a Day
15-30	300	300 Once a Day
<15	150	300 Once Daily Every Other Day
Hemodialysis[b]	--	200-300[a]

[a] Loading dose of 300 to 400 mg

[b] Maintenance dose of 200 to 300 mg Neurontin following each 4 hours of hemodialysis

Children Over 12 Years of Age

The dosage used in a limited number of patients in this age group was 900-1200 mg/day. Doses above 1200 mg/day have not been investigated.

AVAILABILITY OF DOSAGE FORMS

Neurontin (gabapentin) capsules are supplied as follows:

100-mg capsules;

Hard gelatin capsules with white opaque body and cap printed with "PD" on one side and "Neurontin/100 mg" on the other.
-bottles of 100 capsules

300-mg capsules;

Hard gelatin capsules with yellow opaque body and cap printed with "PD" on one side and "Neurontin/300 mg" on the other.
-bottles of 100 capsules

400-mg capsules;

Hard gelatin capsules with orange opaque body and cap printed with "PD" on one side and "Neurontin/400 mg" on the other.
-bottles of 100 capsules

Full Prescribing Information Available On Request

Parke-Davis Division
Warner-Lambert Canada Inc.
Scarborough, Ontario M1L 2N3

References:

1. The Neurontin STEPS Study Team. Study of Neurontin: Titration to Effect, Profile of Safety. In: Program and Abstracts of the I.L.A.E., Dublin, Ireland July 1997. 2. Data on file: Bruni, J.: "Outcome Evaluation of Gabapentin as Add-on Therapy for Partial Seizures". Canadian Journal of Neurological Science. 1998: vol 25: 134-140. 3. Neurontin Product Monograph

PARKE-DAVIS

For brief prescribing information see pages A-19, A-33, A-35

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Pr **Nimotop®**
I.V. / Capsules

THERAPEUTIC CLASSIFICATION

Adjunct in the Management of Subarachnoid Hemorrhage
Calcium Channel Blocking Agent

ACTIONS AND CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

Hypersensitivity to nimodipine.

WARNINGS

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

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

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

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

Patients with Myocardial Infarction

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

Patients with Unstable Angina

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

Cerebral Edema or Severely Raised Intracranial Pressure -
NIMOTOP® (nimodipine) should be used only with great caution under these conditions.

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

PRECAUTIONS

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

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

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

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

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

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

Drug Interactions:

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

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

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

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

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

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

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

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

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

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

ADVERSE EVENTS

NIMOTOP® (nimodipine capsule)

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

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

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

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

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

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

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

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE
There have been no reports of overdosage from the administration of NIMOTOP® (nimodipine). Symptoms of overdosage would be expected to be related to cardiovascular effects and the patients may experience peripheral vasodilation with flushing, headache, and marked systemic hypotension.

Clinically significant hypotension due to NIMOTOP® overdosage may require active cardiovascular support and should include close monitoring of cardiac and respiratory function. Since nimodipine is 99% bound to serum protein, dialysis is not likely to be of benefit.

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

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

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

Intravenous lines must be changed every 24 hours.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Other common infusion solutions must not be used.

Intravenous lines must be changed every 24 hours.

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

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

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

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

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

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

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

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

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

COMPLETE PRODUCT MONOGRAPH AVAILABLE UPON REQUEST

REFERENCES:

1. Pickard, J.D., et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *Br Med J* 1989; 298: 637-642.
2. Harders A. et al. Traumatic subarachnoid haemorrhage and its treatment with nimodipine. *J Neurosurg* 1996; 85: 82-89.

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Pr (nimodipine)
Nimotop®
I.V. / Capsules
For 21 days. Improving outcomes

NM 95A-1298E

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IMITREX®
SUMATRIPTAN SUCCINATE
SUMATRIPTAN NASAL SPRAY

25mg, 50mg and 100 mg Tablet
6 mg Subcutaneous Injection and Autoinjector
5 mg and 20 mg Nasal Spray

THERAPEUTIC CLASSIFICATION
Migraine Therapy

PHARMACOLOGIC CLASSIFICATION
5-HT_1 Receptor Agonist

INDICATIONS AND CLINICAL USES
IMITREX (sumatriptan succinate/sumatriptan) is indicated for the acute treatment of migraine attacks with or without aura.
IMITREX is 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
IMITREX (sumatriptan succinate/sumatriptan) 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 IMITREX. 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 IMITREX may increase blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension. Concurrent administration of MAO inhibitors or use within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see ACTIONS AND CLINICAL PHARMACOLOGY and PRECAUTIONS: DRUG INTERACTIONS).
Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because IMITREX may also cause coronary vasospasm and these effects may be additive, the use of IMITREX within 24 hours before or after treatment with other 5-HT_1 receptor agonists, or ergotamine-containing drugs or their derivatives (eg. dihydroergotamine, methysergide) is contraindicated.
IMITREX should not be administered to patients with severe hepatic impairment.
IMITREX is contraindicated in patients with hemiplegic, basilar, or ophthalmoplegic migraine.
IMITREX is contraindicated in patients with hypersensitivity to sumatriptan or any of the ingredients of the formulations.
IMITREX Injection should not be given intravenously because of its potential to cause coronary vasospasm.

WARNINGS
IMITREX (sumatriptan succinate/sumatriptan) 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:* IMITREX 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 IMITREX. IMITREX should not be given to patients who have documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that IMITREX not be given to patients in whom unrecognized 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, IMITREX 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 IMITREX 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 IMITREX 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 IMITREX 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 IMITREX, 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 IMITREX.
Cardiac Events and Fatalities Associated with 5-HT_1 Agonists: IMITREX 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. The fact that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to IMITREX use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.

Premarketing Experience With IMITREX: Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral IMITREX, two experienced clinical adverse events shortly after receiving oral IMITREX that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.
Among the more than 1900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous IMITREX, there were eight patients who sustained clinical events during or shortly after receiving IMITREX that may have reflected coronary artery vasospasm. Six of these eight patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these eight patients, four had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.
Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of IMITREX nasal spray, one patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.
Postmarketing Experience With IMITREX: Serious cardiovascular events, some resulting in death, have been reported in association with the use of IMITREX Injection or IMITREX Tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by IMITREX or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of IMITREX and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of IMITREX.
Cardiac events that have been observed to have onset within 1 hour of IMITREX administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.
Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among reports from the USA of serious cardiac events occurring within 1 hour of IMITREX administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).
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 oral or subcutaneous IMITREX, and some have resulted in fatalities. The relationship of IMITREX to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, IMITREX having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. IMITREX should not be administered if the headache being experienced is atypical for the patient. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). If a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given.
Special Cardiovascular Pharmacology Studies: In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT_1 agonist at a subcutaneous dose of 1.5mg 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%), increase in coronary resistance (~20%), and decrease in hyperemic myocardial blood flow (~10%) were noted. The relevance of these finding to the use of the recommended oral doses of this 5-HT_1 agonist is not known.
Similar studies have not been done with IMITREX. 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 IMITREX. 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, IMITREX should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists. There have been reports of patients with known hypersensitivity to sulphonamides exhibiting an allergic reaction following administration of IMITREX. Reactions ranged from cutaneous hypersensitivity to anaphylaxis.
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 IMITREX to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.
Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. IMITREX is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS).

PRECAUTIONS
Cluster Headache: There is insufficient information on the efficacy and safety of IMITREX (sumatriptan succinate/sumatriptan) in the treatment of cluster headache, which is present in an older, predominantly male population. The need for prolonged use and the demand for repeated medication in this condition renders the dosing information inapplicable for cluster headache.
Cardiovascular: Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) has been reported after administration of IMITREX. Because 5-HT_1 agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following IMITREX 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 IMITREX should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS AND WARNINGS).
Neurological Conditions: Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache 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 IMITREX.
Seizures: Caution should be observed if IMITREX is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold.
Psychomotor Impairment: Patients should be cautioned that drowsiness may occur as a result of treatment with IMITREX. They should be advised not to perform skilled tasks (e.g. driving or operating machinery) if drowsiness occurs.
Renal Impairment: The effects of renal impairment on the efficacy and safety of IMITREX have not been evaluated. Therefore IMITREX is not recommended in this patient population.
Hepatic Impairment: The effect of hepatic impairment on the efficacy and safety of IMITREX has not been evaluated, however, the pharmacokinetic profile of sumatriptan in patients with moderate[1] hepatic impairment shows that these patients, following an oral dose of 50 mg, have much higher plasma sumatriptan concentrations than healthy subjects (Table 2). Therefore, an oral dose of 25 mg may be considered in patients with hepatic impairment.

Table 2: Pharmacokinetic Parameters After Oral Administration of IMITREX 50 mg to Healthy Volunteers and Moderately Hepatically Impaired Patients

Parameter	Mean Ratio (hepatic impaired/healthy) n=8	90% CI	p-value
AUC∞	181%	130 to 252%	0.009*
Cmax	176%	129 to 240%	0.007*

* Statistically significant
The pharmacokinetic parameters of 6 mg subcutaneous sumatriptan do not differ statistically between normal volunteers and moderately hepatically impaired subjects. However, sumatriptan should not be administered to patients with severe hepatic impairment (see CONTRAINDICATIONS).
Drug Interactions: Single dose pharmacokinetic drug interaction studies have not shown evidence of interactions with propranolol, flunarizine, pizotifen or alcohol. Multiple dose interaction studies have not been performed. The pharmacokinetics of sumatriptan nasal spray were unaltered when preceded by a single clinical dose of the nasal decongestant xylometazoline (Otrivin®[2]).
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 IMITREX administration (see CONTRAINDICATIONS).
MAO Inhibitors: In studies conducted in a limited number of patients, MAO inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of IMITREX in patients receiving MAO inhibitors is contraindicated (see CONTRAINDICATIONS, and ACTIONS AND CLINICAL PHARMACOLOGY).
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 IMITREX and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline), tricyclic antidepressant, or other drug with serotonergic activity is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised.
Other 5-HT_1 agonists: The administration of IMITREX 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.
Drug/Laboratory Test Interactions: IMITREX are not known to interfere with commonly employed clinical laboratory tests.
Use in Elderly (>65 years): Experience of the use of IMITREX in patients aged over 65 years is limited. Therefore the use of IMITREX in patients over 65 years is not recommended.
Use in Children (<18 years): The safety and efficacy of IMITREX in children has not been established and its use in this age group is not recommended.
Use in Pregnancy: Reproduction studies, performed in rats, have not revealed any evidence of impaired fertility, teratogenicity, or post-natal development due to IMITREX. Reproduction studies, performed in rabbits by the oral route, have shown increased incidence of variations in cervico-thoracic blood vessel configuration in the foetuses. These effects were only seen at the highest dose tested, which affected weight gain in the dams, and at which blood levels were in excess of 50 times those seen in humans after therapeutic doses. A direct association with IMITREX treatment is considered unlikely but cannot be excluded. Therefore, the use of IMITREX is not recommended in pregnancy. In a rat fertility study, oral doses of IMITREX resulting in plasma levels approximately 150 times those seen in humans after a 6 mg subcutaneous dose and approximately 200 times those seen in humans after a 100 mg oral dose were associated with a reduction in the success of insemination. This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 100 times those in humans by the subcutaneous route and approximately 150 times those in humans by the oral route.
To monitor maternal-foetal outcomes of pregnant women exposed to sumatriptan, a Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-722-9292, ext 39441.
Lactation: Sumatriptan is excreted in human breast milk. Therefore, caution is advised when administering IMITREX to nursing women. Infant exposure can be minimized by avoiding breast feeding for 24 hours after treatment.
Binding to Melanin Containing Tissues: In rats treated with a single subcutaneous dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Because there could be an accumulation in melanin rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long term ophthalmologic effects.
Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with IMITREX.

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 IMITREX
Typical 5-HT_1 Agonist Adverse Reactions: As with other 5-HT_1 agonists, IMITREX (sumatriptan succinate/sumatriptan) 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: In placebo-controlled migraine trials, 7,668 patients received at least one dose of IMITREX (3095 oral, 1432 subcutaneous, 3141 intranasal). The following tables (Tables 3-5) list adverse events occurring in these trials at an incidence of 1% or more in any of the IMITREX dose groups and that occurred at a higher incidence than in the placebo groups.

[1]Assessed by aminopyrine breath test (>0.2-0.4 scaling units).
[2]Trademark of Ciba Self Medication

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

	Placebo	IMITREX 25mg	IMITREX 50mg	IMITREX 100mg**
Number of Patients	690	351	723	2021
Number of Migraine Attacks Treated	1187	945	1889	14750
Symptoms of Potentially Cardiac Origin				
• Chest Sensations*	0.6%	2.3%	2.6%	3.2%
• Neck/Throat/Jaw Sensations*	1.4%	2.3%	3.5%	5.2%
• Upper Limb Sensations*	1.2%	1.4%	2.5%	3.6%
• Palpitations	0.6%	0.3%	1.0%	1.1%
Neurological				
• Head/Face Sensations*	1.3%	2.3%	2.5%	4.7%
• Dizziness	2.5%	3.1%	3.3%	6.2%
• Headache	3.3%	4.0%	2.2%	3.3%
• Vertigo	0.6%	1.1%	1.1%	1.0%
• Drowsiness	1.6%	1.1%	1.2%	2.1%
• Tremor	0.4%	0.9%	0.4%	1.1%
Gastrointestinal				
• Nausea	5.8%	2.8%	4.4%	11.0%
• Hyposalivation	1.2%	1.4%	1.1%	1.2%
• Vomiting	2.9%	4.3%	1.1%	4.4%
• Gastrointestinal Discomfort & Pain	1.4%	1.1%	0.8%	2.0%
• Abdominal Discomfort & Pain	0.3%	NR	0.4%	1.2%
• Diarrhea	0.9%	0.3%	0.6%	1.1%
Musculoskeletal				
• Musculoskeletal Pain	0.7%	2.3%	0.4%	1.4%
• Muscle Pain	0.3%	0.9%	0.1%	1.0%
• Muscle Atrophy Weakness & Tiredness	NR	0.6%	0.4%	1.4%
Ear, Nose & Throat				
• Infections	0.6%	0.6%	1.1%	1.4%
• Nasal Signs & Symptoms	0.7%	1.4%	0.8%	1.0%
• Throat & Tonsil Symptoms	0.6%	NR	0.4%	2.3%
Respiratory				
• Viral Infection	0.3%	1.1%	0.1%	1.0%
Non-Site Specific				
• Limb Sensations*	0.4%	1.1%	0.4%	1.5%
• Sensations* (body region unspecified)	*4.5%	5.7%	8.0%	9.0%
• Malaise/Fatigue	5.1%	3.7%	2.6%	9.5%
• Sweating	0.4%	0.6%	0.6%	1.6%

*The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.
**Includes patients receiving up to 3 doses of 100mg
NR = Not Reported

Table 4: Treatment-Emergent Adverse Events in Subcutaneous Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients with Migraine

	Placebo	IMITREX 6mg
Number of Patients	615	1432
Number of Migrane Attacks Treated	742	2540
Symptoms of Potentially Cardiac Origin		
• Chest Sensations*	1.6%	5.7%
• Neck/Throat/Jaw Sensations*	1.3%	12.0%
• Upper Limb Sensations*	2.0%	6.8%
Neurological		
• Head/Face Sensations*	3.7%	16.6%
• Dizziness	3.7%	7.9%
• Headache	0.7%	3.4%
• Drowsiness	1.8%	2.9%
Gastrointestinal		
• Nausea	5.9%	9.4%
• Hyposalivation	2.8%	3.3%
Musculoskeletal		
• Muscle Atrophy Weakness & Tiredness	NR	1.7%
Ear / Nose and Throat		
• Throat & Tonsil Symptoms	0.3%	1.0%
Respiratory		
• Breathing Disorders	0.8%	1.3%
Non-Site Specific		
• Sensations* (body region unspecified)	15.9%	39.0%
• Injection Site Reactions	10.4%	24.7%
• Limb Sensations*	1.5%	6.0%
• Malaise/Fatigue	2.3%	4.7%
• Sweating	1.1%	1.7%
• Trunk Symptoms*	0.5%	1.4%

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

Table 5: Treatment-Emergent Adverse Events in Intranasal Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients with Migraine

	Placebo	IMITREX 5mg	IMITREX 10mg	IMITREX 20mg**
Number of Patients	741	496	1007	1638
Number of Migraine Attacks Treated	1047	933	1434	2070
Symptoms of Potentially Cardiac Origin				
• Chest Sensations*	0.3%	1.0%	0.7%	0.6%
• Neck/Throat/Jaw Sensations*	1.2%	0.6%	1.6%	2.3%
Neurological				
• Head/Face Sensations*	0.8%	1.4%	2.4%	2.4%
• Dizziness	1.2%	1.6%	1.5%	1.2%
• Headache	0.7%	1.4%	0.9%	0.8%
• Migraine	2.6%	3.2%	2.4%	1.8%
Gastrointestinal				
• Nausea	10.4%	14.3%	9.6%	8.3%
• Vomiting	7.6%	11.1%	9.6%	6.8%
Ear, Nose & Throat				
• Sensitivity to Noise	3.1%	4.4%	2.5%	1.5%
• Nasal Signs & Symptoms	1.3%	3.0%	1.6%	1.8%
• Infections	0.9%	1.8%	1.3%	0.5%
• Upper Respiratory Inflammation	0.5%	1.0%	0.6%	0.7%
• Throat & Tonsil Symptoms	0.8%	0.2%	1.0%	0.7%
Non-Site Specific				
• Sensations* (body region unspecified)	1.8%	2.4%	2.7%	2.4%
• Malaise/Fatigue	1.3%	1.8%	1.3%	0.8%
• Descriptions of odor or taste	1.8%	15.3%	20.2%	20.8%

*The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.
**Includes patients receiving up to 3 doses of 20mg
IMITREX is generally well tolerated. Most of the events were transient in nature and resolved within 45 minutes of subcutaneous administration and within 2 hours of oral or intranasal administration.
Of the 3630 patients treated with IMITREX Nasal Spray in clinical trials, there was one report of a coronary vasospasm related to IMITREX administration.
Minor disturbances of liver function tests have occasionally been observed with sumatriptan treatment. There is no evidence that clinically significant abnormalities occurred more frequently with sumatriptan than with placebo.
Patients treated with IMITREX rarely exhibit visual disorders like flickering and diplopia. Additionally cases of nystagmus, scotoma and reduced vision have been observed. Very rarely a transient loss of vision has been reported. However, visual disorders may also occur during a migraine attack itself.

DOSAGE AND ADMINISTRATION

General:
IMITREX (sumatriptan succinate/sumatriptan) is indicated for the acute treatment of migraine headache with or without aura. Sumatriptan should not be used prophylactically. Sumatriptan may be given orally, subcutaneously or as a nasal spray. The safety of treating an average of more than four headaches in a 30 day period has not been established.
In selecting the appropriate formulation for individual patients, consideration should be given to the patient's preference for formulation and the patient's requirement for rapid onset of relief. Significant relief begins about 10-15 minutes following subcutaneous injection, 15 minutes following intranasal administration and 30 minutes following oral administration.
In addition to relieving the pain of migraine, sumatriptan (all formulations) has also been shown to be effective in relieving associated symptoms of migraine (nausea, vomiting, phonophobia, photophobia). Sumatriptan is equally effective when administered at any stage of a migraine attack. Long term (12-24 months) clinical studies with maximum recommended doses of sumatriptan indicate that there is no evidence of the development of tachyphylaxis, or medication-induced (rebound) headache.
Tablets:
The minimal effective single adult dose of IMITREX Tablets is 25mg. The maximum recommended single dose is 100 mg.
The optimal dose is a single 50mg tablet. However, depending on individual patient's needs and response to treatment, some patients may require 100mg.
Clinical trials have shown that approximately 50 - 75% of patients have headache relief within two hours after oral dosing with 100mg, and that a further 15 - 25% have headache relief by 4 hours. Comparator studies have shown similar efficacy rates with the 50mg and 100mg tablets. There is evidence that doses of 50 and 100mg may provide greater effect than 25mg.
If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 2 hours. Not more than 200mg should be taken in any 24 hour period.
If a patient does not respond to the first dose of IMITREX Tablets, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. IMITREX may be taken to treat subsequent migraine attacks.
The tablet should be swallowed whole with water, not crushed, chewed or split.
Hepatic Impairment: In patients with mild or moderate hepatic impairment, plasma sumatriptan concentrations up to two times those seen in healthy subjects have been observed. Therefore, a 25 mg dose (single tablet) may be considered in these patients (see PRECAUTIONS). Sumatriptan should not be administered to patients with severe hepatic impairment (see CONTRAINDICATIONS).
Injection:
IMITREX Injection should be injected subcutaneously (on the outside of the thigh) using an autoinjector.
The recommended adult dose of sumatriptan is a single 6 mg subcutaneous injection.
Clinical trials have shown that approximately 70-72% of patients have headache relief within one hour after a single subcutaneous injection. This number increases to 82% by 2 hours.
If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 1 hour. Not more than 12mg (two 6mg injections) should be taken in any 24 hour period.
If a patient does not respond to the first dose of IMITREX Injection, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. IMITREX may be taken for subsequent attacks.
Administration during migraine aura prior to other symptoms occurring may not prevent the development of a headache.
Patients should be advised to read the patient instruction leaflet regarding the safe disposal of syringes and needles.
Nasal Spray:
The minimal effective single adult dose of sumatriptan nasal spray is 5mg. The maximum recommended single dose is 20mg.
If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 2 hours. Not more than 40mg should be taken in any 24 hour period.
If a patient does not respond to the first dose of IMITREX Nasal Spray, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. IMITREX may be taken for subsequent attacks.
Placebo-controlled clinical trials revealed the following incidence of headache relief, defined as a decrease in migraine severity from severe or moderate to mild or no pain, within 2 hours after treatment with intranasal sumatriptan at doses of 5, 10 or 20mg (see Table 6 below).

TABLE 6. Percentage of patients with headache relief at 2 hours

Study	Placebo (n)	5 mg (n)	10 mg (n)	20 mg (n)
Study 1•	35% (40)	67%√ (42)	67%√ (39)	78%√ (40)
Study 2•	42% (31)	45% (33)	66%√ (35)	74%√ (39)
Study 3	25% (63)	49%√ (122)	46%√ (115)	64%√ † (119)
Study 4	25% (151)	-	44%√ (288)	55%√ † (292)
Study 5	32% (198)	44%√ (297)	54%▲ (293)	60%√ † (288)
Study 6•	35% (100)	-	54%√ (106)	63%√ (202)
Study 7•	29% (112)	-	43% (109)	62%√ (215)

Headache relief was defined as a decrease in headache severity from severe or moderate to mild or none.
n= total number of patients who received treatment
• comparisons between sumatriptan doses not conducted
√ p≤0.05 versus placebo
† p≤0.05 versus lower sumatriptan doses
▲p≤0.05 vs 5mg
- not evaluated
As shown in the table above, optimal rates of headache relief were seen with the 20mg dose. Single doses above 20mg should not be used due to limited safety data and lack of increased efficacy relative to the 20mg single dose.
Within the range of 5-20 mg, an increase in dose was not associated with any significant increase in the incidence or severity of adverse events other than taste disturbance (See ADVERSE REACTIONS).
The nasal spray should be administered into one nostril **only**. The device is a ready to use single dose unit and **must not** be primed before administration.
Patients should be advised to read the patient instruction leaflet regarding the use of the nasal spray device before administration.

AVAILABILITY OF DOSAGE FORMS

IMITREX Tablets 100 mg are pink film-coated tablets available in blister packs containing 6 tablets. Four blister packs are placed in a cardboard carton.
IMITREX Tablets 50 mg are white film-coated tablets available in blister packs containing 6 tablets. Four blister packs are placed in a carton.
IMITREX tablets 25 mg are white film-coated tablets available in blister packs containing 6 tablets. Four blister packs are placed in a carton.
Each tablet contains 100 mg, 50 mg, or 25 mg sumatriptan (base) as the succinate salt.
IMITREX Injection is available in pre-filled syringes containing 6 mg of sumatriptan base, as the succinate salt, in an isotonic solution (total volume = 0.5 mL). Syringes are placed in a tamper-evident carrying/disposal case. Two pre-filled syringes plus an autoinjector are packed in a patient starter kit. A refill pack is available containing 2 X 2 pre-filled syringes in a carton.
IMITREX Injection is also available to physicians or hospitals in a single dose vial (total volume = 0.5 mL) containing 6 mg of sumatriptan base, as the succinate salt. There are 5 vials per carton.
IMITREX Nasal Spray 5 mg and 20 mg are each supplied in boxes of 6 nasal spray devices (3 X 2 devices). Each unit dose spray supplies 5 and 20 mg, respectively, of sumatriptan (base) as the hemisulphate salt.

Product Monograph available to physicians and pharmacists upon request.
Please contact Glaxo Wellcome Inc., 7333 Mississauga Road N, Mississauga, Ontario, L5N 6L4.
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Once-a-day Aricept*

donepezil HCl 5 & 10 mg tablets

PHARMACOLOGIC CLASSIFICATION
Cholinesterase Inhibitor

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

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

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

Clinical Pharmacokinetics and Metabolism

Absorption: Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations (C_{max}) approximately 3 to 4 hours after dose administration. Plasma concentrations and area under the curve (AUC) were found to rise in proportion to the dose administered within the 1 -to- 10 mg dose range studied. The terminal disposition half-life ($t_{1/2}$) is approximately 70 hours and the mean apparent plasma clearance (Cl/F) is 0.13L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold and steady state is reached within 15 days. The minimum, maximum and steady-state plasma concentrations (C) and 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)	$AUC_{0\text{-}24}$ (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
$AUC_{0\text{-}24}$: 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.

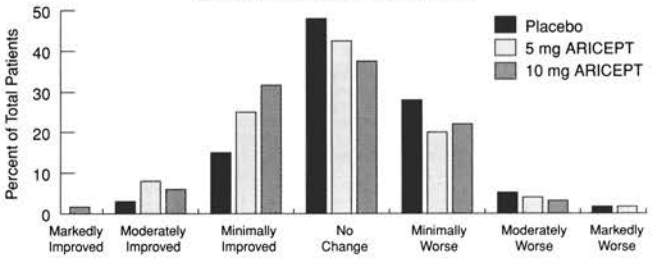
The data shown below for the two primary outcome measures in donepezil clinical trials were obtained from the Intent-To-Treat population (ITT analysis, i.e., all patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete 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 0.29 ± 0.08 and 0.34 ± 0.08 units for the 5 mg/day and 10 mg/day treatment groups, respectively. These differences from placebo were statistically significant. There was no significant difference between the two active treatments. Figure 1 is a histogram of the frequency distribution of CIBIC Plus scores achieved at Week 12 by patients assigned to each of the three treatment groups.

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

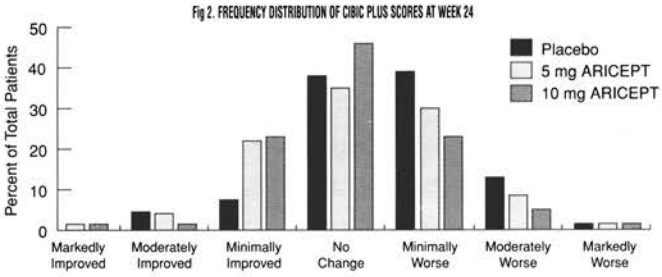


Thirty-Week Study (24 weeks of treatment + 6-week placebo washout): In this study, 473 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of donepezil for 24 weeks of double-blind active treatment followed by a 6-week single-blind placebo washout period. As in the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

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

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

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



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

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

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

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

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

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

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

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

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

Gastrointestinal: Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent 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 650 patients treated for 3 months, 475 patients treated for 6 months and 115 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days.

Treatment-emergent signs and symptoms that occurred during three controlled clinical trials and two open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the studies were integrated and the events were grouped into a smaller number of standardized categories using a modified *COSTART* dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving **ARICEPT**. All adverse events occurring at least twice are included. Adverse events already listed in Tables 2 and 3 are not repeated here (i.e., events occurring at an incidence >2%). Also excluded are *COSTART* terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed as occurring in ≥1% and <2% of patients (i.e., in 1/100 to 2/100 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 ≥ 85 years old and in females. It is recommended that **ARICEPT** be used with caution in elderly women of low body weight and that the dose should not exceed 5 mg/day.

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

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

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

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

AVAILABILITY OF DOSAGE FORMS

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

ARICEPT is available in high density polyethylene (HDPE) bottles of 30 tablets and in blister strips boxed as 28 tablets (combination of 2 strips of 14 tablets).

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Full product monograph available upon request.

For brief prescribing information see page A-38

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Lamictal® Antiepileptic

Lamotrigine

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;
†Parameter not estimated. VPA=Valproic acid

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

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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 anmiocentesis, 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 (Female patients)		(n=365)	(n=207)
	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.

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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 $t_{1/2}$ of lamotrigine. Under these conditions, it may be necessary to reduce the dose of LAMICTAL. In contrast, the withdrawal of enzyme inhibiting AEDs (i.e., valproic acid) will result in a decrease in the $t_{1/2}$ of lamotrigine and may require an increase in the dose of LAMICTAL.

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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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.

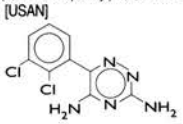
Elderly patients
There is little experience with the use of LAMICTAL in elderly patients. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions.

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.

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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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Experience in Controlled Clinical Trials with AMERGE

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

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

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

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

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

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

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

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

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

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

Endocrine & Metabolic: Infrequent were thirst and polydipsia, dehydration and fluid retention. Rare were 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 % (N)	AMERGE 1 mg % (N)	AMERGE 2.5 mg % (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.

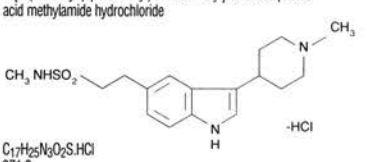
Pharmaceutical Information

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

PERMAX®

(Pergolide Mesylate) Tablets
Dopamine Agonist

INDICATIONS AND CLINICAL USE

As an adjunct to levodopa (usually with a peripheral decarboxylase inhibitor) in the symptomatic management of Parkinson's disease.

Evidence to support the efficacy of PERMAX was obtained in a double-blind, placebo-controlled multicentre study which enrolled patients with mild to moderate Parkinson's disease who were intolerant to l-dopa/carbidopa treatment as manifested by moderate to severe dyskinesia and/or on-off phenomena.

Permax has not been assessed in the treatment of newly diagnosed patients or as the sole medication in Parkinson's disease.

CONTRAINDICATIONS

In patients who are hypersensitive to this drug or other ergot derivatives.

WARNINGS

Hypotension

PERMAX may cause syncope or hypotension (i.e., a fall in systolic blood pressure to less than 100 mmHg). It is therefore important to warn patients of the risk, to begin therapy with low doses, and to increase the dosage in carefully adjusted increments over a period of several weeks (see Dosage and Administration.)

Syncope or excessive hypotension were observed in patients on PERMAX therapy, especially during initiation of treatment. Episodes of moderate hypotension also occurred. With gradual dosage titration, tolerance to hypotension usually develops.

Care should be exercised when administering concomitantly with antihypertensive agents or other medications known to lower blood pressure.

Patients should be cautioned with regard to engaging in activities requiring rapid and precise responses, such as driving an automobile or operating machinery.

Hallucinosis

In controlled trials, PERMAX with levodopa caused hallucinosis in about 14% of patients as opposed to 3% taking placebo with levodopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

Fatalities

In the placebo-controlled trial, 2 of 187 patients treated with placebo died as compared with 1 of 189 patients treated with PERMAX. In the latter group, three additional patients died who continued on PERMAX beyond the controlled phase of the study. Of the 2,299 patients treated with PERMAX in premarketing studies 143 died while on the drug or shortly after discontinuing the drug. The patient population under evaluation was elderly, ill, and at high risk for death. It seems unlikely that PERMAX played any role in these deaths, but the possibility that PERMAX shortens survival of patients cannot be excluded with absolute certainty.

PRECAUTIONS

General

The abrupt discontinuation of PERMAX in patients receiving it chronically as an adjunct to levodopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of PERMAX should be undertaken gradually wherever possible, even if the patient is to remain on levodopa.

A symptom complex resembling the neuroleptic malignant syndrome (NMS), characterized by elevated body temperature, muscular rigidity, altered consciousness, and autonomic instability, has been reported in antiparkinsonian therapy. Therefore, patients should be observed carefully when the dosage of PERMAX is reduced abruptly or discontinued.

The administration of PERMAX to patients receiving levodopa may cause and/or exacerbate pre-existing dyskinesia.

Cardiovascular Effects

PERMAX has not been systematically evaluated in patients with heart disease. In the multicentre clinical trial, patients with heart disease, i.e., recent angina pectoris, decompensated heart failure (New York Scale III or IV), myocardial infarction within the last 12 months, or any arrhythmia requiring antiarrhythmic therapy at the time of the study or within 12 months prior to the study were excluded. Since there is only limited experience with PERMAX in these patients, PERMAX should be administered only if in the judgement of the physician the potential benefits clearly outweigh the potential risks.

In a study comparing perogolide mesylate and placebo, patients taking pergolide mesylate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

Drug Interactions

Dopamine antagonists such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide ordinarly should not be administered concurrently with PERMAX (a dopamine agonist) because these agents may diminish the effectiveness of PERMAX.

Because PERMAX is approximately 90% bound by plasma proteins, caution should be exercised if PERMAX is coadministered with other drugs known to affect protein binding.

Use in Pregnancy

In teratology studies performed in mice and rabbits, there was no evidence of harm to the fetus due to PERMAX. There are however, no adequate and well-controlled studies in pregnant women. In a small number of women who received PERMAX for endocrine disorders, there were 33 pregnancies that resulted in healthy babies and 6 pregnancies that resulted in congenital abnormalities (3 major, 3 minor); a causal relationship has not been established. Because human data are limited and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only, if in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risks to the fetus.

Nursing Mothers

It is not known whether PERMAX is excreted in human milk. The pharmacologic action of PERMAX suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to PERMAX in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Commonly Observed

Nervous system complaints, including dyskinesia, dizziness, hallucinations, somnolence, and insomnia; gastrointestinal complaints, including nausea, constipation, diarrhea and dyspepsia; cardiovascular complaints, including postural hypotension, and respiratory system complaints, including rhinitis.

Adverse Reactions Resulting in Discontinuation of Treatment

Twenty-seven percent of approximately 1,200 patients, receiving PERMAX for treatment of Parkinson's disease in premarketing clinical trials in the U.S. and Canada, discontinued treatment due to adverse reactions. Events most often causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (1.8%).

Incidence of Adverse Reactions in Controlled Clinical Trials

Table 1 enumerates adverse events that occurred at a frequency of 1% or more among PERMAX treated patients who participated in the double-blind controlled clinical trial comparing PERMAX with placebo. The prescriber should be aware that these figures 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 which prevail in clinical trials. 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 side effect incidence rate in the population studied.

Certain adverse experiences (e.g., dyskinesias, hallucinations) are frequently observed in patients receiving levodopa pergolide and/or other dopamine agonists. These are dose related and tend to improve with reduction of the dosage of levodopa or of pergolide. Hallucinations may infrequently persist after discontinuation of pergolide.

Postural hypotension and nausea are most frequently reported during the initial titration phase.

Abnormalities in laboratory tests may include elevations of AST, ALT, alkaline phosphatase and urea nitrogen.

Table 1
Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

Adverse Reaction Events	Percentage of Patients Reporting	
	PERMAX N = 189	Placebo N = 187
Body as a Whole System		
Pain	7.0	2.1
Abdominal Pain	5.8	2.1
Injury, accident	5.8	7.0
Headache	5.3	6.4
Asthenia	4.2	4.8
Chest Pain	3.7	2.1
Flu syndrome	3.2	2.1
Neck Pain	2.7	1.6
Back pain	1.6	2.1
Surgical Procedure	1.6	<1
Chills	1.1	0
Face edema	1.1	0
Infection	1.1	0
Nervous System		
Dyskinesia	62.4	24.6
Dizziness	19.1	13.9
Hallucinations	13.8	3.2
Dystonia	11.6	8.0
Confusion	11.1	9.6
Somnolence	10.1	3.7
Insomnia	7.9	3.2
Anxiety	6.4	4.3
Tremor	4.2	7.5
Depression	3.2	5.4
Abnormal dreams	2.7	4.3
Personality disorders	2.1	<1
Psychosis	2.1	0
Abnormal gait	1.6	1.6
Akathisia	1.6	0
Extrapyramidal syndrome	1.6	1.1
Incoordination	1.6	<1
Paresthesia	1.6	3.2
Akinesia	1.1	1.1
Hypertonia	1.1	0
Neuralgia	1.1	<1
Speech disorder	1.1	1.6
Gastrointestinal		
Nausea	24.3	12.8
Constipation	10.6	5.9
Diarrhea	6.4	2.7
Dyspepsia	6.4	2.1
Anorexia	4.8	2.7
Dry mouth	3.7	<1
Vomiting	2.7	1.6
Cardiovascular system		
Postural hypotension	9.0	7.0
Sinus tachycardia	4.8	1.6
Vasodilation	3.2	<1
Palpitation	2.1	<1
Hypotension	2.1	<1
Syncope	2.1	1.1
Hypertension	1.6	1.1
Arrhythmia	1.1	<1
Myocardial infarction	1.1	<1
Respiratory System		
Rhinitis	12.2	5.4
Dyspnea	4.8	1.1
Epistaxis	1.6	<1
Hiccup	1.1	0
Metabolic & Nutritional System		
Peripheral edema	7.4	4.3
Edema	1.6	0
Weight gain	1.6	0
Special Senses		
Abnormal vision	5.8	5.4
Diplopia	2.1	0
Taste perversion	1.6	0
Eye disorder	1.1	0
Musculoskeletal System		
Arthralgia	1.6	2.1
Bursitis	1.6	<1
Myalgia	1.1	<1
Twitching	1.1	0
Skin and Appendages		
Rash	3.2	2.1
Sweating	2.1	2.7
Urogenital System		
Urinary frequency	2.7	6.4
Urinary tract infection	2.7	3.7
Hematuria	1.1	<1
Hemic & Lymphatic System		
Anemia	1.1	<1

DOSAGE AND ADMINISTRATION

Administration of PERMAX should be initiated with a single daily dose of 0.05 mg for the first 2 days. The dose should then be gradually increased by 0.1 to 0.15 mg/day every third day over the next 12 days of therapy. The dosage may then be increased by 0.25 mg/day every third day until an optimal dosage is achieved.

PERMAX is usually administered in divided doses 3 times/day. During dosage titration, the dosage of levodopa/carbidopa may be cautiously decreased.

Since rapid escalation of PERMAX causes severe adverse reactions, it is recommended that a slow increase of PERMAX be combined with a concomitant, gradual and limited reduction of levodopa dosage.

In clinical studies, the mean therapeutic dose of PERMAX was 3 mg/day. The average concurrent levodopa/carbidopa daily dosage (expressed as levodopa) was approximately 650 mg/day. The safety of PERMAX at doses above 5 mg /day has not been systematically evaluated.

DOSAGE FORM

Availability:

PERMAX (pergolide mesylate) tablets are modified rectangle shaped, scored and engraved with the company logo and Identi-code number.

Available in amber HDPE bottles.

PERMAX tablets 4131, 0.05 mg (pergolide as pergolide mesylate) are ivory coloured in bottles of 30.

PERMAX tablets 4133, 0.25 mg (pergolide as pergolide mesylate) are green coloured in bottles of 100.

PERMAX tablets 4135, 1 mg (pergolide as pergolide mesylate) are pink coloured in bottles of 100.

Storage:

PERMAX should be stored at room temperature.

Product monograph available upon request.

DRAXIS

Draxis Health Inc.
6870 Goreway Drive
Mississauga, Ontario L4V 1P1

PAAB

For brief prescribing information see pages A-13

COPAXONE®
(glatiramer acetate for injection)

20 mg, single use vials for Subcutaneous Injection

Therapeutic Classification: Immunomodulator

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

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

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

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

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

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

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

Considerations Involving the Use of a Product Capable of Modifying Immune Responses: COPAXONE® is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. There is also no information on whether COPAXONE® can alter normal human immune responses, such as the recognition of foreign antigens. It is therefore possible that treatment with COPAXONE® may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done.

Studies in both the rat and monkey have shown that immune complexes are deposited in renal glomeruli. Furthermore, in a controlled trial of 125 patients with relapsing-remitting MS treated for 2 years with 20 mg/day COPAXONE,® serum IgG levels reached approximately 3 times baseline values in 80% of patients within 3 to 6 months of treatment. These values returned to about 50% greater than baseline during the remainder of treatment.

Although COPAXONE® is intended to attenuate the autoimmune response to myelin, whether chronic treatment with COPAXONE,® and in consequence, continued alteration of cellular immunity can result in detrimental effects is unknown. Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats are still in progress.

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

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

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

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

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

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

ADVERSE REACTIONS

Immediate Post-Injection Reaction – Approximately 10% of Multiple Sclerosis patients exposed to COPAXONE® in pre-marketing studies reported a post-injection reaction immediately following subcutaneous injection of COPAXONE.® Symptoms experienced could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria. These symptoms were invariably transient, self-limited, did not require specific treatment and in general arose after several months after initiation of treatment, although they may occur earlier in the course of treatment.

Chest Pain – Approximately 26% of glatiramer acetate patients in the multicenter controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae.

Table 1. Adverse Experiences ≥ 5% Incidence and ≥ 2% Above Placebo*

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

*Table adapted from Table 3 of Product Monograph.

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

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

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

References: 1. COPAXONE Product Monograph. **2.** Johnson, KP et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting Multiple Sclerosis. *Neurology*, **45**: 1268-1276, 1995.

Full Prescribing Information and Product Monograph available upon request.

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For brief prescribing information see pages A-36, A-37

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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 mm Hg 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 mm Hg) 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 (grade1/0) 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 1mg
†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 mm Hg 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 mm Hg 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

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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 perfomance 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 co-administration 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, co-administration 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 1g 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 10mg/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

	Placebo	Zomig 1 mg	Zomig 2.5 mg	Zomig 5 mg
Number of patients	401	163	498	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 5mg Zomig in any 24 hour period (see PRECAUTIONS, Drug Interactions).

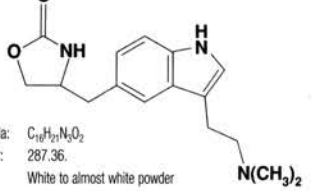
PHARMACEUTICAL INFORMATION

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 (1.3mg/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.

References: 1. Zomig® Product Monograph, AstraZeneca. 2. 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. 3. Solomon GD et al. Clinical efficacy and tolerability of 2.5 mg zolmitriptan for the acute treatment of migraine. *Neurology* 1997;49:1219-1225. 4. Saper J et al. Zomig is consistently effective in the acute treatment of migraine. *Headache* 1998;(38):400. 5. Zagami AS. 311C90: Long-term efficacy and tolerability profile for the acute treatment of migraine. *Neurology* 1997;48 (Suppl 3):S25-S28. 6. Edmeads JG, Millson DS. Tolerability profile of zolmitriptan (Zomig™; 311C90), a novel dual central and peripherally acting 5-$HT_{1B/1D}$ agonist. *Cephalalgia* 1997;17(Suppl 18):41-52.

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For brief prescribing information see pages A-30, A-31

VIAGRA*

Tablets 25 mg, 50 mg and 100 mg
sildenafil as sildenafil citrate

PRESCRIBING INFORMATION

THERAPEUTIC CLASSIFICATION: cGMP-specific phosphodiesterase type 5 inhibitor

Treatment of Erectile Dysfunction

ACTION AND CLINICAL PHARMACOLOGY: VIAGRA (sildenafil citrate) is a cGMP-specific phosphodiesterase type 5 (PDE5) inhibitor, used for the treatment of male erectile dysfunction.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the *corpus cavernosum* in response to sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the *corpus cavernosum* and allowing inflow of blood.

Sildenafil has no direct relaxant effect on isolated human *corpus cavernosum*, but enhances the effect of NO by inhibiting PDE5, which is responsible for the biodegradation of cGMP in the *corpus cavernosum*. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil produces increased levels of cGMP in the *corpus cavernosum*, resulting in smooth muscle relaxation and increased inflow of blood to the *corpus cavernosum*. Sildenafil, at recommended doses, has no effect in the absence of sexual stimulation.

Studies *in vitro* have shown that sildenafil has between 10 and 10,000-fold greater selectivity for PDE5 than for other phosphodiesterase isoforms (PDEs 1, 2, 3, 4, and 6). In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility. Sildenafil is about 10-fold as potent for PDE5 compared to PDE6, an isoenzyme found in the retina; this lower selectivity is thought to be the basis for colour vision abnormalities observed with higher doses or plasma levels of sildenafil (see **PRECAUTIONS**).

PDE5 is also found in lower concentrations in platelets, vascular and visceral smooth muscles, and skeletal muscle. The sildenafil-induced inhibition of PDE5 in these tissues appears to be the basis for the enhanced platelet antiaggregatory activity of nitric oxide observed *in vitro*, and inhibition of platelet thrombus formation *in vivo*, and peripheral arterial-venous dilation *in vivo* (see **PRECAUTIONS**).

Pharmacokinetics and Metabolism

Absorption: Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute bioavailability is 41% (range 25%-63%). The oral pharmacokinetics of **VIAGRA** is proportional over the recommended dose range studied (25 mg to 100 mg).

When **VIAGRA** was administered with a high-fat meal the rate of absorption was significantly decreased, with a 29% reduction in C_{max} and a 60-minute delay in T_{max}. The extent of sildenafil absorption was significantly reduced by 11% in the presence of food. The relative bioavailability fed/fasted was 89% (90% CI; 84-94%) (see **PRECAUTIONS**).

Distribution: The mean steady state volume of distribution (VSS) for sildenafil is 105 litres, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Based upon measurements of sildenafil in the semen of healthy volunteers, less than 0.001% of the ingested dose may appear in the semen of patients 90 minutes after drug intake.

Metabolism: Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil at the N-methyl piperazine moiety. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency against PDE5 approximately 50% that of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolized, with a terminal half-life of approximately 4 hours.

Elimination: The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3-5 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered dose) and to a lesser extent in the urine (approximately 13% of the administered dose).

Pharmacokinetics in Special Populations

Geriatrics: Healthy elderly subjects (65 years or older) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).

Renal insufficiency: In volunteers with mild (CLcr = 50-80 mL/min) and moderate (CLcr = 30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of **VIAGRA** (50 mg) were not altered. In volunteers with severe (CLcr < 30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in increases in AUC (100%) and C_{max} (88%) compared to age-matched volunteers with no renal impairment.

Hepatic insufficiency: In volunteers with hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment.

Since sildenafil clearance is reduced in geriatric patients (65 years or older), patients with renal impairment or patients with hepatic impairment, a starting dose of 25 mg should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg or 100 mg (see **PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

Pharmacodynamics

Effects of VIAGRA on Blood Pressure (BP): Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease of 8.4/5.5 mm Hg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing. The effects are not related to dose or plasma levels. Larger effects were recorded among patients receiving concomitant nitrates (see **CONTRAINDICATIONS**).

Effects of VIAGRA on Cardiac Parameters: Single oral doses of **VIAGRA** up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG.

INDICATIONS AND CLINICAL USE: VIAGRA is indicated for the treatment of erectile dysfunction.

CONTRAINDICATIONS: VIAGRA has been shown to potentiate the hypotensive effects of nitrates in healthy volunteers and in patients, and is therefore contraindicated in patients who are taking any type of nitrate drug therapy, or who utilize short-acting nitrate-containing medications, due to the risk of developing potentially life-threatening hypotension. The use of organic nitrates, either regularly and/or intermittently, in any form (e.g. oral, sublingual, transdermal, by inhalation) is absolutely contraindicated (see ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

After patients have taken **VIAGRA**, it is unknown when nitrates, if necessary, can be safely administered. Plasma levels of sildenafil at 24 hours post-dose are much lower (2 ng/mL) than at peak concentration (440 ng/mL). In the following patients: age > 65, hepatic impairment (e.g. cirrhosis), severe renal impairment (e.g. CLcr < 30 mL/min), and concomitant use of potent cytochrome P-450 3A4 inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post-dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post-dose are much lower than at peak concentration, it is unknown whether nitrates can be safely coadministered at this time point.

Treatments for erectile dysfunction should not be generally used in men for whom sexual activity is inadvisable (see also **WARNINGS**).

VIAGRA is contraindicated in patients with a known hypersensitivity to any component of the tablet (see **PHARMACEUTICAL INFORMATION**).

WARNINGS: As with all treatments for erectile dysfunction, there is a potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for erectile dysfunction, including **VIAGRA**, should not be generally administered in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

There are no controlled clinical data on the safety or efficacy of **VIAGRA** in the following groups, if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months
- Patients with resting hypotension (BP < 90/50 at rest) or hypertension (BP > 170/110 at rest)
- Patients with cardiac failure or coronary artery disease causing unstable angina
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases) (see **ACTION AND CLINICAL PHARMACOLOGY**).

Although **priapism** had not been reported during clinical trials, prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently during the post-marketing surveillance of **VIAGRA**. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result (see **ADVERSE REACTIONS**).

The safety and efficacy of combinations of **VIAGRA** with other agents for the treatment of erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

PRECAUTIONS

General: The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

Agents for the treatment of erectile dysfunction should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease) or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma or leukemia).

In humans, **VIAGRA** has no effect on bleeding time when taken alone or with acetylsalicylic acid. *In vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and **VIAGRA** had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans (see **ACTION AND CLINICAL PHARMACOLOGY**).

There is no safety information on the administration of **VIAGRA** to patients with bleeding disorders or active peptic ulceration. Therefore, **VIAGRA** should be administered with caution to these patients.

Effect of VIAGRA on Vision: A small percentage of patients experience visual effects (e.g. impairment of colour discrimination, increased perception to light, blurred vision) after taking **VIAGRA**. If this happens, then the patient should not operate a motor vehicle or any heavy machinery until the adverse effects disappear (see **ACTION AND CLINICAL PHARMACOLOGY**).

Drug Interactions: Sildenafil metabolism is principally mediated by the cytochrome P-450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route) (see **ACTION AND CLINICAL PHARMACOLOGY**). Therefore inhibitors of these isoenzymes may reduce sildenafil clearance.

Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the active metabolite, N-desmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by nonspecific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

The concomitant use of potent cytochrome P-450 3A4 inhibitors (e.g. erythromycin, ketoconazole, itraconazole) as well as the non-specific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION**).

Sildenafil is a weak inhibitor of the cytochrome P-450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC_{50} > 150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that **VIAGRA** will alter the clearance of the substrates of these isoenzymes.

When a single 100 mg dose of **VIAGRA** was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg b.i.d. for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). Stronger CYP3A4 inhibitors such as ketoconazole, itraconazole would be expected to have still greater effects. It can be expected that concomitant administration of CYP3A4 inducers, such as rifampin, will decrease plasma levels of sildenafil.

Cimetidine (800 mg), a non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with **VIAGRA** (50 mg) to healthy volunteers.

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). However, there was no increased incidence of adverse events in these patients.

No significant interactions were shown with tolbutamide (single 250 mg dose) or warfarin (single 40 mg dose), both of which are metabolized by CYP2C9 when co-administered with 50 mg sildenafil.

VIAGRA (50 mg) did not potentiate the increase in bleeding time, measured using a standard simplate method, caused by acetylsalicylic acid (150 mg). **VIAGRA** (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

When **VIAGRA** (100 mg) was co-administered with amlodipine, 5 mg or 10 mg, in hypertensive patients, the mean additional reduction of supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic (see **ACTION AND CLINICAL PHARMACOLOGY**).

Interaction with Food: When **VIAGRA** is taken with a high-fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%. The patient may find that it takes longer to work if taken with a high-fat meal (see **ACTION AND CLINICAL PHARMACOLOGY**).

Use with Other Concomitant Therapies: Patients on multiple antihypertensive medications were included in the pivotal clinical trials for **VIAGRA**. Analysis of the safety database was carried out after pooling of the following classes of antihypertensive medication: diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers. The analysis showed no differences in the adverse effect profile of patients taking **VIAGRA** with and without antihypertensive medication.

Use in Elderly: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in younger volunteers (18 to 45 years).

Since higher plasma levels may increase both the pharmacological action and incidence of some adverse events, a starting dose of 25 mg should be considered (see **ACTION AND CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**).

Use in Patients with Renal Insufficiency: In volunteers with mild (CLcr = 50-80 mL/min) and moderate (CLcr = 30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of **VIAGRA** (50 mg) was not altered. In volunteers with severe (CLcr < 30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in increases in AUC (100%) and C_{max} (88%) compared to age-matched volunteers with no renal impairment.

A starting dose of 25 mg should be considered in patients with severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**).

Use in Patients with Hepatic Insufficiency: In volunteers with hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment.

A starting dose of 25 mg should be considered (see **ACTION AND CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**).

Use in Children: VIAGRA is not indicated for use in children.

Use in Women, Nursing Mothers, Pregnancy: VIAGRA is not indicated for use in women.

ADVERSE REACTIONS

Pre-Marketing Experience: VIAGRA was administered to over 3700 patients (aged 19-87 years) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

In placebo-controlled clinical studies, the discontinuation rate due to adverse events for **VIAGRA** (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.

In trials of all designs, adverse events reported by patients receiving **VIAGRA** were generally similar. In fixed-dose studies, the incidence of some adverse events increased with dose. The nature of the adverse events in flexible-dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies. When **VIAGRA** was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials, the following adverse events were reported:

Table 1. Adverse Events Reported by ≥ 2% of Patients Treated with VIAGRA or Placebo in PRN Flexible-Dose Phase II/III Studies

Adverse Event	Percentage of Patients Reporting Event	
	VIAGRA (n = 734)	Placebo (n = 725)
Headache	15.8%	3.9%
Flushing	10.5%	0.7%
Dyspepsia	6.5%	1.7%
Nasal Congestion	4.2%	1.5%
Respiratory Tract Infection	4.2%	5.4%
Flu Syndrome	3.3%	2.9%
Urinary Tract Infection	3.1%	1.5%
Abnormal Vision†	2.7%	0.4%
Diarrhea	2.6%	1.0%
Dizziness	2.2%	1.2%
Rash	2.2%	1.4%
Back Pain	2.2%	1.7%
Arthralgia	2.0%	1.5%

† Abnormal Vision: Mild and transient changes, predominantly impairment of colour discrimination (blue/green), but also increased perception to light or blurred vision.

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At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.
The following events occurred in < 2% of patients in controlled clinical trials where a causal relationship is uncertain:

***Autonomic*:** sweating, dry mouth;

***Cardiovascular*:** abnormal electrocardiogram, angina pectoris, arrhythmia, AV block, cardiac arrest, cardiomyopathy, heart failure, hypertension, hypotension, palpitation, postural hypotension, myocardial ischemia, syncope, tachycardia, varicose vein, vascular anomaly;

***Central & Peripheral Nervous System*:** tremor, abnormal dreams, anxiety, agitation, ataxia, depression, insomnia, nervousness, somnolence, paresthesia, vertigo, speech disorder, reflexes decreased, hyperesthesia, neuropathy, migraine, myasthenia, oculogyric crisis, neuralgia, hypertonia;

***Gastrointestinal*:** vomiting, gastritis, gastrointestinal disorder, flatulence, increased appetite, gastroenteritis, stomatitis, eructation, dysphagia, colitis, glossitis, constipation, rectal hemorrhage, mouth ulceration, esophagitis, rectal disorder, gingivitis, tooth disorder;

***Hematopoietic*:** anemia and leukopenia;

***Liver/Biliary*:** liver function tests abnormal, ALT increased;

***Metabolic/Nutritional*:** edema, thirst, gout, hyperuricemia, hypoglycemic reaction, unstable diabetes, hyperglycemia, hyperlipidemia, hypernatremia;

***Musculoskeletal*:** myalgia, bone disorder, arthrosis, arthritis, tendon rupture, tenosynovitis, bone pain, joint disorder, synovitis;

***Respiratory*:** asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, respiratory disorder, carcinoma of lung, sputum increased, cough increased;

***Skin/Appendages*:** skin carcinoma, skin disorder, skin hypertrophy, skin ulcer, contact dermatitis, exfoliative dermatitis, pruritus, urticaria, photosensitivity reaction, nail disorder, acne, herpes simplex, furunculosis;

***Special Senses*:** mydriasis, conjunctivitis, photophobia, eye pain, tinnitus, deafness, ear pain, lacrimation disorder, eye disorder, eye hemorrhage, ear disorder, cataract, dry eyes;

***Urogenital*:** penile erection, other sexual dysfunction, cystitis, nocturia, balanitis, urinary frequency, breast enlargement, prostatic disorder, testis disorder, urinary incontinence, urinary tract disorder, urine abnormality, abnormal ejaculation, genital edema and anorgasmia;

***Vascular Disorders*:** cerebrovascular disorder, cerebral thrombosis;

***General*:** face edema, peripheral edema, chills, allergic reaction, asthenia, pain, infection, shock, hernia, accidental fall, abdominal pain, chest pain, accidental injury, intentional overdose.

Post-Marketing Experience: Reports of adverse events temporally associated with **VIAGRA** during post-marketing surveillance that are not listed above and for which the causal relationship is unknown, include the following:

***Cardiovascular*:** Serious cardiovascular events — including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, and transient ischemic attack — have been reported. Most of these patients had pre-existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of **VIAGRA** without sexual activity. Others were reported to have occurred hours to days after the use of **VIAGRA** with sexual activity. It is not possible to determine whether these events are related directly to **VIAGRA**, to sexual activity, to the patient's underlying cardiovascular disease, to combination of these factors, or to other factors (see **WARNINGS**).

***Central & Peripheral Nervous System*:** seizure;

***Urogenital*:** prolonged erection, priapism (see **WARNINGS**) and hematuria;

***Special Senses*:** diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease of bleeding, vitreous detachment/traction and paramacular edema.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: In studies with healthy volunteers of single doses of up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates were increased.

Treatment: In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

TREATMENT OF PRIAPISM: Patients should be instructed to report any erections persisting for more than 4 hours to a physician. The treatment of priapism/prolonged erection should be according to established medical practice. Physicians may refer to two suggested protocols for detumescence presented below.

Detumescence Protocols

1) Aspirate 40 to 60 mL blood from either left or right *corpora* using vacutainer and holder for drawing blood. Patient will often detumesce while aspirating. Apply ice for 20 minutes post aspiration if erection remains.

If procedure 1) is unsuccessful, then try procedure 2).

2) Put patient in supine position. Dilute 10 mg phenylephrine into 20 mL distilled water for injection (0.05%). With an insulin syringe, inject 0.1 to 0.2 mL (50-100 µg) into the corpora every 2 to 5 minutes, until the detumescence occurs. The occasional patient may experience transient bradycardia and hypertension when given phenylephrine injections, therefore monitor patient's blood pressure and pulse every 10 minutes. Patients at risk include those with cardiac arrhythmias and diabetes. Refer to the prescribing information for phenylephrine before use. **Do not give phenylephrine to patients on MAO inhibitors**. When phenylephrine is used within the first 12 hours of erection, the majority of patients will respond.

3) If the above measures fail to detumesce the patient, a urologist should be consulted as soon as possible, especially if the erection has been present for many hours. If priapism is not treated immediately, penile tissue damage and/or permanent loss of potency may result.

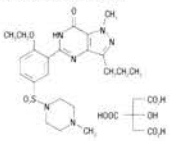
DOSAGE AND ADMINISTRATION: For most patients, the recommended dose of **VIAGRA** is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, **VIAGRA** may be taken anywhere from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.
The following factors are associated with increased plasma levels of sildenafil:

- age 65 years or over (40% increase in AUC)
- hepatic impairment (e.g. cirrhosis) (84% increase in AUC)
- severe renal impairment (e.g. creatinine clearance < 30 mL/min) (100% increase in AUC)
- concomitant use of potent cytochrome P-450 3A4 inhibitors (e.g. erythromycin, ketoconazole, itraconazole) (182% increase in AUC)

A starting dose of 25 mg should be considered in these patients (see **ACTION AND CLINICAL PHARMACOLOGY, PRECAUTIONS**).

VIAGRA has been shown to potentiate the hypotensive effects of nitrates in healthy volunteers and in patients, and is therefore contraindicated in patients who are taking any type of nitrate drug therapy, or who utilize short-acting nitrate-containing medications, due to the risk of developing potentially life-threatening hypotension. The use of organic nitrates, either regularly and/or intermittently, in any form (e.g. oral, sublingual, transdermal, by inhalation) is absolutely contraindicated (see ACTION AND CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

PHARMACEUTICAL INFORMATION
Tradename: VIAGRA*
Drug Substance
Generic Name: sildenafil citrate
Code Name: UK-92,480-10
Chemical Name: Piperazine, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methyl-,2-hydroxy-1,2,3-propanetricarboxylate
Structural Formula:



Molecular Formula: $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$
Molecular Weight: 666.7
Description: Sildenafil citrate is a white to off-white crystalline powder.

pk_a: protonation of tertiary amine	6.53
deprotonation of pyrimidirone moiety	9.17
Partition Coefficient: octanol/water	2.7

Solubility (23°C):	water	3.5 mg/mL
	0.1M HCl	5.8 mg/mL
	0.1M NaOH	42.3 mg/mL

Composition: VIAGRA tablets contain sildenafil citrate equivalent to 25 mg, 50 mg or 100 mg of sildenafil per tablet for oral administration. The tablets also contain the following non-medicinal ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, lactose, triacetin, and FD & C Blue #2 aluminum lake.

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

AVAILABILITY OF DOSAGE FORMS
VIAGRA - 25 mg tablets (sildenafil citrate equivalent to 25 mg of sildenafil per tablet) are supplied as blue, rounded, diamond-shaped tablets marked 'PFIZER' on one side and 'VGR 25' on the other side and supplied as follows:
– Blister pack of 4 tablets
VIAGRA - 50 mg tablets (sildenafil citrate equivalent to 50 mg of sildenafil per tablet) are supplied as blue, rounded, diamond-shaped tablets marked 'PFIZER' on one side and 'VGR 50' on the other side, and supplied as follows:
– Blister pack of 4 and 8 tablets
VIAGRA - 100 mg tablets (sildenafil citrate equivalent to 100 mg of sildenafil per tablet) are supplied as blue, rounded, diamond-shaped tablets marked 'PFIZER' on one side and 'VGR 100' on the other side, and supplied as follows:
– Blister pack of 4 and 8 tablets

References:

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Product monograph available on request. PMAB

For brief prescribing information see page A-27

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ONCE-A-WEEK

AVONEX®

(Interferon beta-1a)

IM Injection

PRESCRIBING INFORMATION

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

Description

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

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

General

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

Biologic Activities

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

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

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

CLINICAL TRIALS: EFFECTS IN MULTIPLE SCLEROSIS

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

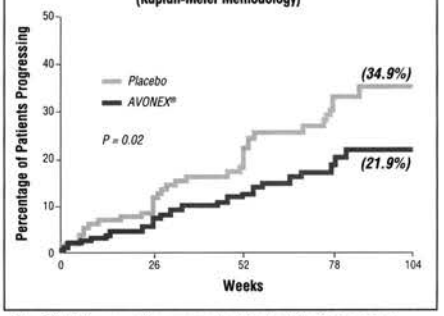
All patients had a definite diagnosis of MS of at least 1 year duration and had at least 2 exacerbations in the 3 years prior to study entry (or 1 per year if the duration of disease was less than 3 years). At entry, study participants were without exacerbation during the prior 2 months and had Kurtzke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

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

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

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

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



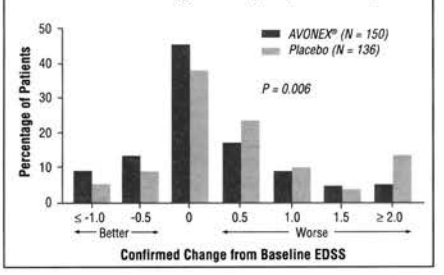
Note: Disability progression represents at least a 1.0 point increase in EDSS score sustained for at least 6 months. The value p=0.02 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given timepoint (e.g., 34.9% vs. 21.9%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

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

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

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

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



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

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

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

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

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

Table 1
MAJOR CLINICAL ENDPOINTS

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

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

[1] Patient data included in this analysis represent variable periods of time on study.

[2] Analyzed by Mantel-Cox (logrank) test.

[3] Analyzed by Mann-Whitney rank-sum test.

[4] Analyzed by Cochran-Mantel-Haenszel test.

[5] Analyzed by likelihood ratio test.

[6] Analyzed by Wilcoxon rank-sum test.

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INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General

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

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

Laboratory Tests

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

Drug Interactions

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

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

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

Use in Pregnancy

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

Nursing Mothers

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

Pediatric Use

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

Information to Patients

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

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

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

ADVERSE EVENTS

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

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

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

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

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

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

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

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

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

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

TOPAMAX®
topiramate

TOPAMAX®
(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**
(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

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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

	TOPAMAX Dosage (mg/day)			
Adverse Event	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.

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Product Monograph available upon request.

Janssen-Ortho Inc.
Toronto, Ontario
M3C 1L9

TOPAMAX
topiramate

Date of Issuance: June 1999

PITX991011A

For brief prescribing information see pages A10, A11, A24, A25

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Canadian League Against Epilepsy-Glaxo Wellcome Epilepsy Fellowship

This fellowship has been created to support research and clinical training in the field of epilepsy in Canada. The fellowship is valued at $45,000 and will be awarded for a one year period. The award will be tenable as of July 1st, 2000.

Candidates must have an MD or PhD degree. Preference will be given to those who have completed a specialty program approved by the Royal College of Physicians and Surgeons of Canada, but others are welcome to apply and will be considered. Applications must contain a research proposal relevant to epilepsy. The proposed research must be done in Canada.

Applications must be received by December 1, 1999.

Further details and instructions for applicants may be obtained from:

CLAE-GW Fellowship
Sally Gregg
Canadian Congress of Neurological Sciences
P.O. Box 4220, Stn. C.
Calgary AB Canada
T2T 5N1

Ligue Canadienne contre l'épilepsie Bourse de recherche clinique en épilepsie

Cette bourse a été cré afin de soutenir la recherche clinique dans le domaine de épilepsie au Canada. D'une valeur de 45 000 $, la bourse sera attribuée pour une période d'un an et prendra effet le 1er juillet 2000.

Les candidats doivent être titulaire d'un diplôme de médecine ou d'un doctorat de 3ième cycle. Une préférence sera donnée à ceux qui sont inscrits à un programme de spécialité approuvé par le Collège royal des médecins et chirurgiens du Canada. Tous les autres canadidats seront les bienvenus et leurs demandes seront considérés. Les demandes doivent contenir un projet de recherche dans le domaine de l'épilepsie. La recherche proposé doit être entreprise au Canada.

La date limite de réception des demandes de bourse : le 1er decembre 1999.

Pour obtenir plus de précisions, écrire à l'adresse suivante:

CLAE-GW Fellowship
Sally Gregg
Canadian Congress of Neurological Sciences
P.O. Box 4220, Stn. C.
Calgary AB Canada
T2T 5N1

Canadian Headache Society-Glaxo Wellcome Headache Fellowship

This fellowship has been created to support research and clinical training in the field of headache in Canada. The fellowship is valued at $45,000 and will be awarded for a one year period. The award will be tenable as of July 1st, 2000.

Candidates must have an MD or PhD degree. Preference will be given to those who have completed a specialty program approved by the Royal College of Physicians and Surgeons of Canada, but others are welcome to apply and will be considered. Applications must contain a research proposal relevant to headache. The proposed research must be done in Canada.

Applications must be received by December 1, 1999.

Further details and instructions for applicants may be obtained from:

Dr. WJ Becker
President, Canadian Headache Society
c/o Neurology
12th Floor, Foothills Hospital
1403 29th St. NW
Calgary AB Canada T2N 2T9

Société canadienne des céphalées Bourse de rechereche clinique en céphalée

Cette bourse a été cré afin de soutenir la recherche clinique dans le domaine de la céphalée au Canada. D'une valeur de 45 000 $, la bourse sera attribuée pour une période d'un an et prendra effet le 1er juillet 2000.

Les candidats doivent être titulaire d'un diplôme de médecine ou d'un doctorat de 3ième cycle. Une préférence sera donnée à ceux qui sont inscrits à un programme de spécialité approuvé par le Collège royal des médecins et chirurgiens du Canada. Tous les autres canadidats seront les bienvenus et leurs demandes seront considérés. Les demandes doivent contenir un projet de recherche dans le domaine de la céphalée. La recherche proposé doit être entreprise au Canada.

La date limite de réception des demandes de bourse : le 1er decembre 1999.

Pour obtenir plus de précisions, écrire à l'adresse suivante:

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Rotman Research Institute, Baycrest Centre for Geriatric Care

(fully affiliated with University of Toronto)

Two-year research fellowships in: neuropsychiatry; cognitive neuroscience; cognitive neuropsychology; behavioural neurology (board certified or board eligible in neurology), and applied clinical research. Techniques used may include structural and functional imaging and experimental, cognitive, and neuropsychiatric procedures. The Rotman is dedicated to neurobehavioural research into cognition and aging. Baycrest Centre for Geriatric Care is a comprehensive campus of care for the elderly, including a geriatric hospital, with a 20-bed behavioural neurology unit, home for the aged, Alzheimer's day care program, supported seniors apartment residence, community centre for older adults and day hospital. Bursaries are in line with the fellowship scales of the MRC Canada, and include an allowance for travel and research expenses. Minimum of 80% of each fellow's time will be devoted to research and related activities (behavioural neurology 50% research, 50% clinical). Applicants should have a Ph.D., M.D. or equivalent degree. Baycrest encourages applications from qualified individuals, members of visible minorities, aboriginal peoples, and persons with disabilities. Submit a C.V. and relevant reprints, together with a covering letter describing current research interests and future research goals, and also arrange to have three letters of reference sent independently by December 31, 1999 to:

Dr. C. Grady, Chair, Education Committee, Rotman Research Institute, Baycrest Centre for Geriatric Care,
Fax: (416) 785-2474; E-mail: cgrady@rotman-baycrest.on.ca

Kunin-Lunenfeld Applied Research Unit (KLARU), Baycrest Centre for Geriatric Care

(fully affiliated with University of Toronto)

Two-year research fellowships in the following areas: psychology, speech and communication, occupational therapy, medicine, and nutrition. KLARU is dedicated to fostering a closer integration of scientific research with clinical care at the bedside. Baycrest Centre for Geriatric Care is a comprehensive campus of care for the elderly which includes a geriatric hospital, with a 20-bed behavioural neurology unit, home for the aged, Alzheimer's day care program, supported seniors apartment residence, community centre for older adults, day hospital, and many ambulatory and community outreach programs. Bursaries are in line with the fellowship scales of the MRC Canada, and include an allowance for travel and research expenses. A minimum of 80% of each fellow's time will be devoted to research and related activities. Applicants should have a Ph.D., M.D. or equivalent degree.

Baycrest encourages applications from qualified individuals, members of visible minorities, aboriginal peoples, and persons with disabilities. Submit a C.V. and relevant reprints, together with a covering letter describing current research interests and future research goals, and also arrange to have three letters of reference sent independently by December 31, 1999, to: Dr. D.L. Streiner, Director, KLARU,
Fax: (416) 785-4230;
E-mail: dstreiner@rotman-baycrest.on.ca

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