# 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



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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 $5\text{-}HT_1$, $5\text{-}HT_2$, benzodiazepine, $GABA_A$, muscarinic, alpha- or beta-adrenoreceptors. Ropinirole binds to opiate receptors with low affinity, however, studies show that this weak opiate activity has no consequences at pharmacological doses *in vivo*.

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

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

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

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

**Pharmacokinetics**

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

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

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

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

*median

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

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

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

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

Ropinirole has a blood to plasma ratio of 1.2.

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

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

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

**Population Subgroups**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**WARNINGS**

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

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

**PRECAUTIONS**

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

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

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

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

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

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

**Pregnancy**
The use of REQUIP during pregnancy is not recommended.

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

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

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

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

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

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

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

**Drug Interactions**

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

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

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

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

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

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

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

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

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

**ADVERSE REACTIONS**

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

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

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

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

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

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

**TABLE 2**

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

| | Early Therapy | | Adjunct Therapy | |
|---|---|---|---|---|
| | REQUIP N = 157 % occurrence | Placebo N = 147 % occurrence | REQUIP N = 206 % 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 | 5.8 | – |
| 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.

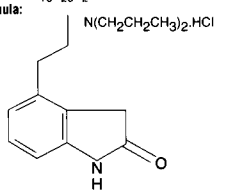
**PHARMACEUTICAL INFORMATION**

**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.

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SmithKline Beecham Pharma



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Pr **Nimotop®**
I.V. / Capsules

**THERAPEUTIC CLASSIFICATION**

Adjunct in the Management of Subarachnoid Hemorrhage
Calcium Channel Blocking Agent

**ACTIONS AND CLINICAL PHARMACOLOGY**

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

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

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

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

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

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

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

**INDICATIONS AND CLINICAL USE**

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

**CONTRAINDICATIONS**

Hypersensitivity to nimodipine.

**WARNINGS**

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

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

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

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

**Patients with Myocardial Infarction**

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

**Patients with Unstable Angina**

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

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

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

**PRECAUTIONS**

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

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

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

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

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

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

**Drug Interactions:**

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

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

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

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

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

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

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

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

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

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

**ADVERSE EVENTS**

NIMOTOP® (nimodipine capsule)

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

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


https://doi.org/10.1017/S0317167100049246 Published online by Cambridge University Press

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

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

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

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

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

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

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

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

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

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

Intravenous lines must be changed every 24 hours.

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

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

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

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

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

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

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

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

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

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

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

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

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

**PARENTERAL PRODUCTS**

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

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

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

**Other common infusion solutions must not be used.**

Intravenous lines must be changed every 24 hours.

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

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

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

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

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

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

**AVAILABILITY OF DOSAGE FORMS**

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

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

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

**COMPLETE PRODUCT MONOGRAPH AVAILABLE UPON REQUEST**

**REFERENCES:**


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



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Healthcare Division

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


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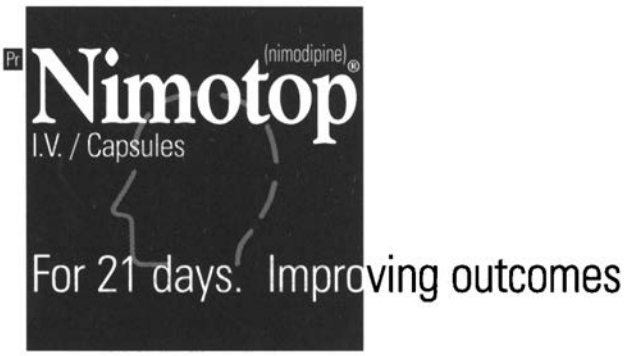


NM 95-0798E



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https://doi.org/10.1017/S0317167100049246 Published online by Cambridge University Press

Lamotrigine

# Lamictal®

**Lamotrigine Tablets (25, 100 and 150 mg)**

**THERAPEUTIC CLASS**

**Antiepileptic**

**ACTION AND CLINICAL PHARMACOLOGY**

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

**Clinical Trials**

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

**Pharmacokinetics: Adults:** LAMICTAL is rapidly and completely absorbed following oral administration, reaching peak plasma concentrations 1.4 to 4.8 hours ($T_{max}$) post-dosing. When administered with food, the rate of absorption is slightly reduced, but the extent remains unchanged. Following single LAMICTAL doses of 50-400 mg, peak plasma concentration ($C_{max}$=0.6-4.6 µg/mL) and the area under the plasma concentration-versus-time curve (AUC=29.9-211 h•µg/mL) increase linearly with dose. The time-to-peak concentration, elimination half-life ($t_{1/2}$) and volume of distribution (Vd/F) are independent of dose. The $t_{1/2}$ averages 33 hours after single doses and Vd/F ranges from 0.9 to 1.4 L/kg. Following repeated dosing in healthy volunteers for 14 days, the $t_{1/2}$ decreased by an average of 26% (mean steady state $t_{1/2}$ of 26.4 hours) and plasma clearance increased by an average of 33%. In a single-dose study where healthy volunteers were administered both oral and intravenous doses of lamotrigine, the absolute bioavailability of oral lamotrigine was 98%. Lamotrigine is approximately 55% bound to human plasma proteins. This binding is unaffected by therapeutic concentrations of phenytoin, phenobarbital or valproic acid. Lamotrigine does not displace other antiepileptic drugs (carbamazepine, phenytoin, phenobarbital) from protein binding sites. Lamotrigine is metabolized predominantly in the liver by glucuronic acid conjugation. The major metabolite is an inactive 2-N-glucuronide conjugate that can be hydrolyzed by ß-glucuronidase. Approximately 70% of an oral LAMICTAL dose is recovered in urine as this metabolite. **Elderly:** The pharmacokinetics of lamotrigine in 12 healthy elderly volunteers (≥ 65 years) who each received a single oral dose of LAMICTAL (150 mg) were not different from those in healthy young volunteers. (However, see PRECAUTIONS, **Use in the Elderly**, and DOSAGE AND ADMINISTRATION.) **Renal Impairment:** The pharmacokinetics of a single oral dose of LAMICTAL (100 mg) were evaluated in 12 individuals with chronic renal failure (with mean creatinine clearance of 13 mL/min) who were not receiving other antiepileptic drugs. In this study, the elimination half-life of unchanged lamotrigine was prolonged (by an average of 63%) relative to individuals with normal renal function (see PRECAUTIONS, **Renal Failure** and DOSAGE AND ADMINISTRATION). **Hemodialysis:** In six hemodialysis patients, the elimination half-life of unchanged lamotrigine was doubled off dialysis, and reduced by 50% on dialysis, relative to individuals with normal renal function. **Hepatic Impairment:** The pharmacokinetics of lamotrigine in patients with impaired liver function have not been evaluated. **Gilbert's Syndrome:** Gilbert's syndrome (idiopathic unconjugated hyperbilirubinemia) does not appear to affect the pharmacokinetic profile of lamotrigine. **Concomitant Antiepileptic Drugs:** In patients with epilepsy, concomitant administration of LAMICTAL with enzyme-inducing AEDs (phenytoin, carbamazepine, primidone or phenobarbital) decreases the mean lamotrigine $t_{1/2}$ to 13 hours. Concomitant administration of LAMICTAL with valproic acid significantly increases $t_{1/2}$ and decreases the clearance of lamotrigine, whereas concomitant administration of LAMICTAL with valproic acid plus enzyme-inducing AEDs can prolong $t_{1/2}$ up to approximately 27 hours. Acetaminophen was shown to slightly decrease the $t_{1/2}$ and increase the clearance of lamotrigine. The key lamotrigine parameters for adult patients and healthy volunteers are summarized in Table 1.

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

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

ND=Not done

1 Range of individual values across studies

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

**INDICATIONS AND CLINICAL USE**

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

**CONTRAINDICATIONS**

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

**WARNINGS**

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

**Hypersensitivity Reactions:** Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema and abnormalities of the blood and liver. The syndrome shows a wide spectrum of clinical severity and may rarely lead to disseminated intravascular coagulation (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and LAMICTAL discontinued if an alternative aetiology cannot be established.

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

**PRECAUTIONS**

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

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

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

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

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

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

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

1 Average daily dose in week 1

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

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

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

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

**ADVERSE REACTIONS**

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

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

**Table 4: Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Studies[1]**

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

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

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

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

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

## DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

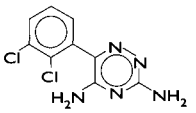
**There have been no controlled studies to establish the effectiveness or optimal dosing regimen of add-on LAMICTAL therapy in patients receiving only non-enzyme-inducing AEDs or valproic acid. However, available data from open clinical trials indicate that the addition of LAMICTAL under these conditions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

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

## PHARMACEUTICAL INFORMATION

***Drug Substance***

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



Molecular Formula: $C_9H_7Cl_2N_5$ Molecular Weight: 256.09
Description: Lamotrigine is a white to pale cream powder. The pKa at 25°C is 5.7. It is practically insoluble in water (0.017% w/v); slightly soluble in ethanol (0.41% w/v), chloroform (0.11% w/v) and octanol (0.28% w/v).

**Composition**

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

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

**Stability and Storage Recommendations**

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

## AVAILABILITY OF DOSAGE FORMS

LAMICTAL Tablets are available in three different strengths:

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

Product Monograph available to healthcare professionals on request.

Date of revision: April 16, 1997

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

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





See pages A-4, A-5, A-18, A-19

# IMITREX®
SUMATRIPTAN SUCCINATE
SUMATRIPTAN NASAL SPRAY

(sumatriptan succinate/sumatriptan)

50 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

**CLINICAL PHARMACOLOGY**

IMITREX (sumatriptan succinate/sumatriptan) has been shown to be effective in relieving migraine headache. It is an agonist for a vascular 5-hydroxytryptamine$_{1D}$ (5-$HT_{1D}$) receptor subtype (a member of the 5-$HT_1$ family), and has only weak affinity for 5-$HT_{1A}$ receptors and no significant activity (as measured using standard radioligand binding assays) or pharmacological activity at 5-$HT_2$, 5-$HT_3$, 5-HT$_4$, 5-$HT_{5A}$, or 5-$HT_7$ receptor subtypes, or at alpha$_1$-, alpha$_2$-, or beta-adrenergic, dopamine$_1$ or dopamine$_2$; muscarinic; or benzodiazepine receptors.

Sumatriptan activates the 5-$HT_{1D}$ receptor subtype which is present on cranial arteries, on the basilar artery and in the vasculature of dura mater. This action correlates with relief of headache. The antimigrainous effect of sumatriptan is believed to be due to vasoconstriction of cranial arteries, which are dilated and edematous during a migraine attack.

Experimental data from animal studies shows that sumatriptan also activates 5-$HT_1$ receptors on peripheral terminals of the trigeminal nerve which innervates cranial blood vessels. This causes the inhibition of neuropeptide release. It is thought that such an action may contribute to the anti-migraine action of sumatriptan in humans. Significant relief begins 10-15 minutes following subcutaneous injection, 15 minutes following intranasal administration and 30 minutes following oral administration.

**Cardiovascular Effects:** *In vitro* studies in human isolated epicardial coronary arteries suggest that the predominant contractile effect of 5-HT is mediated via 5-$HT_2$ receptors. However, 5-$HT_1$ receptors also contribute to some degree to the contractile effect seen. Transient increases in systolic and diastolic blood pressure (up to 20 mmHg) of rapid onset (within minutes), have occurred after intravenous administration of up to 64 µg/kg (3.2 mg for 50 kg subject) to healthy volunteers. These changes were not dose related and returned to normal within 10-15 minutes. Following oral administration of 200 mg or intranasal administration of 40 mg, however, mean peak increases in blood pressure were smaller and of slower onset than after intravenous or subcutaneous administration.

**Pharmacokinetics:** Sumatriptan is rapidly absorbed after oral, subcutaneous and intranasal administration with a mean bioavailability of 96% after subcutaneous dosing and 14% after oral dosing and 16% after intranasal administration. The low oral and intranasal bioavailability is primarily due to metabolism (hepatic and pre-systemic) and partly due to incomplete absorption. The oral absorption of sumatriptan is not significantly affected either during migraine attacks or by food.

Following an oral dose of 100 mg, a mean $C_{max}$ of 54 ng/mL was attained, while the time to peak plasma level was variable (0.5-5 hours). However, 70% to 80% of $C_{max}$ values were attained within 30-45 minutes of oral dosing. The mean plasma half-life was approximately 2 hours (range 1.9-2.2 hours). Following a 6 mg subcutaneous dose (standard injection) in the deltoid region of the arm or thigh or autoinjection into the thigh, a mean $C_{max}$ value of 60 ng/mL was attained at approximately 15 minutes. Mean plasma half-life was approximately 2 hours (range 1.7-2.3 hours). Following a 5 mg, 10 mg and 20 mg intranasal dose, $C_{max}$ values were 4.7 ng/mL, 8.5 ng/mL and 14.4 ng/mL, respectively. The time to peak plasma level was 1 to 1.5 hours. The elimination half life is approximately 2 hours (range 1.3-5.4 hours). Inter-patient and intra-patient variability was noted in most pharmacokinetic parameters assessed. Sumatriptan is extensively metabolised by the liver and cleared to a lesser extent by renal excretion. The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in the urine where it is present as a free acid (35%) and the glucuronide conjugate (11%). It has no known 5-$HT_1$ or 5-$HT_2$ activity. Minor metabolites have not been identified. Plasma protein binding of sumatriptan in humans is low (14%-21%). No differences have been observed between the pharmacokinetic parameters in healthy elderly volunteers compared with younger volunteers (less than 65 years old).

**INDICATIONS AND CLINICAL USES** IMITREX (sumatriptan succinate/sumatriptan) is indicated for the relief of migraine attacks with or without aura. Sumatriptan is not indicated for prophylactic therapy of migraine, or for the management of hemiplegic or basilar migraine.

**CONTRAINDICATIONS** IMITREX (sumatriptan succinate/sumatriptan) is contraindicated in patients with known hypersensitivity to any of the components of the formulation. Sumatriptan is contraindicated in patients with ischemic heart disease, angina pectoris including Prinzmetal angina (coronary vasospasm), previous myocardial infarction and uncontrolled hypertension. Sumatriptan is also contraindicated in patients taking ergotamine containing preparations or ergot derivatives (such as dihydroergotamine), and in patients receiving treatment with monoamine oxidase inhibitors or use within two weeks of discontinuation of MAOI therapy. Until further data are available the use of sumatriptan is contraindicated in patients with hemiplegic migraine, basilar migraine and in patients receiving treatment with selective 5-HT reuptake inhibitors and lithium.

**WARNINGS**

**There is no experience in patients with recent cerebrovascular accidents or cardiac arrhythmias (especially tachycardias). Therefore the use of IMITREX (sumatriptan succinate) in these patients is not recommended.**

Sumatriptan should only be used where there is a clear diagnosis of migraine headache. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. There have been rare reports where patients received sumatriptan for severe headaches which subsequently were shown to have been secondary to an evolving neurological lesion (cerebrovascular accident, subarachnoid haemorrhage). In this regard, it should be noted that migraineurs may be at risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient ischemic attack). However, 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.

Sumatriptan has been associated with transient chest pain and tightness which may mimic angina pectoris and may be intense. Only in rare cases have the symptoms been identified as the result of coronary vasospasm. The vasospasm may result in arrhythmia, ischemia or myocardial infarction. Serious coronary events following sumatriptan have occurred but are extremely rare. Although it is not clear how many of these can be attributed to sumatriptan, because of its potential to cause coronary vasospasm, sumatriptan should not be given to patients in whom unrecognized coronary artery disease (CAD) is likely without a prior evaluation for underlying cardiovascular disease. Such patients include postmenopausal women, males over 40, patients with risk factors for CAD (hypertension, hypercholesterolaemia, obesity, diabetes, smoking, or strong family history of CAD). Consideration should be given to administering the first dose of IMITREX injection in the physician's office to patients in whom unrecognised coronary artery disease is comparatively likely. If the patient experiences symptoms which are severe or persistent and are consistent with angina, appropriate investigations should be carried out to check for the possibility of ischemic changes. A careful medical history should be taken before sumatriptan is prescribed to exclude pre-existing cardiovascular disease. Sumatriptan should be used with caution in patients in whom there is a concern of ischemic heart disease, as well as in patients with arteriosclerotic diseases such as peripheral and/or cerebral vascular disease. There have been rare reports of serious and/or life-threatening arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia and myocardial infarction, as well as transient ischemic ST wave elevations associated with IMITREX injection. Sumatriptan injection should never be given intravenously. The recommended dose of sumatriptan should not be exceeded.

**PRECAUTIONS Cluster Headache:** There is insufficient information on the efficacy and safety of 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.

**General:** Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 hours should elapse before sumatriptan can be taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations should not be taken until 6 hours have elapsed following sumatriptan administration. Sumatriptan should be used with caution in patients with a history of epilepsy or structural brain lesions which lower their convulsion threshold. Chest, jaw or neck tightness is relatively common (3-5% in controlled clinical trials) after IMITREX injection, but has only been rarely associated with ischemic ECG changes. Sumatriptan may cause a short-lived elevation of blood pressure (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS). Patients should be cautioned that drowsiness may occur as a result of treatment with sumatriptan. They should be advised not to perform skilled tasks e.g. driving or operating machinery if drowsiness occurs.

**Concomitant Disease:** Since there have been rare reports of seizures occurring, sumatriptan should be used with caution in patients with a history of epilepsy or structural brain lesions which lower their convulsive threshold.

**Concomitant Medications:** There have been reports of patients with known hypersensitivity to sulphonamides exhibiting an allergic reaction following administration of sumatriptan. Reactions ranged from cutaneous hypersensitivity to anaphylaxis.

**Renal Impairment:** The effects of renal impairment on the efficacy and safety of sumatriptan have not been evaluated. Therefore sumatriptan is not recommended in this patient population.

**Hepatic Impairment:** The effect of hepatic impairment on the efficacy and safety of sumatriptan 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. Therefore, an oral dose of 50 mg may be considered in patients with hepatic impairment.

**Pharmacokinetic Parameters After Oral Administration of Sumatriptan 50 mg to Healthy Volunteers and Moderately Hepatically Impaired Patients**

| Parameter | Mean Ratio (hepatic impaired/healthy) n=8 | 90% CI | p-value |
|---|---|---|---|
| $AUC_\infty$ | 181% | 130 to 252% | 0.009* |
| $C_{max}$ | 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.

**Use in Elderly (>65 years):** Experience of the use of sumatriptan in patients aged over 65 years is limited. Therefore the use of sumatriptan in patients over 65 years is not recommended.

**Use in Children (<18 years):** The safety and efficacy of sumatriptan 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 sumatriptan. Reproduction studies, performed in rabbits by the oral route, have shown increased incidence of variations in cervicothoracic 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 sumatriptan treatment is considered unlikely but cannot be excluded. Therefore, the use of sumatriptan is not recommended in pregnancy.

In a rat fertility study, oral doses of sumatriptan 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.

**Lactation:** Sumatriptan is excreted in breast milk in animals. No data exists in humans, therefore, caution is advised when administering sumatriptan to nursing women.

**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.

**ADVERSE REACTIONS** The most common adverse reaction associated with IMITREX (sumatriptan succinate/sumatriptan) administered subcutaneously is transient pain (local erythema and burning sensation) at the site of injection. Other side effects which have been reported for both the oral and subcutaneous routes, but were more common for the subcutaneous route, include sensations of tingling, heat, heaviness, pressure or tightness in any part of the body, chest symptoms, flushing, dizziness and feelings of weakness. Transient increases in blood pressure arising soon after treatment have been recorded. Hypotension, bradycardia, tachycardia and palpitations have been reported rarely. Sumatriptan may cause coronary vasospasm in patients with a history of coronary artery disease, known to be susceptible to coronary artery vasospasm, and, very rarely, without prior history suggestive of coronary artery disease. There have been rare reports of serious and/or life-threatening arrhythmias, including atrial fibrillation, ventricular fibrillation, ventricular tachycardia, myocardial infarction, and transient ischemic ST elevation associated with IMITREX injection (see WARNINGS). Fatigue and drowsiness have been reported at slightly higher rates for the oral route, as were nausea and vomiting; the relationship of the latter adverse reactions to sumatriptan is not clear. Hypersensitivity reactions to sumatriptan have been reported including anaphylactic shock, anaphylactoid reactions, rash, urticaria, pruritis and erythema. There have been rare reports of seizures, the majority of these patients have a previous history of epilepsy or structural lesions predisposing to epilepsy (see PRECAUTIONS).

The following tables list the incidence of adverse reactions reported in clinical trials undertaken with the oral formulation and the subcutaneous injection (Table 1), and with the intranasal formulation (Table 2).

Most of the events were transient in nature and resolved within 45 minutes of subcutaneous administration and 2 hours of oral *or intranasal* administration.

**Table 1: Incidence of Treatment-Emergent* Adverse Events in Controlled Clinical Trials**

| Event | Tablets n=1456 | S.C. Placebo n=296 | Injection n=2665 | Placebo n=868 |
|---|---|---|---|---|
| **Gastrointestinal:** | | | | |
| nausea / vomiting | 12% | 4% | 8% | 4% |
| gastric symptoms, abdominal discomfort | 1% | ≤1% | 1% | <1% |
| dysphagia | 1% | 0% | 1% | 0% |
| gastro-oesophageal reflux, diarrhea and abnormal stools | <1% | ≤1% | <1% | 0% |
| **Neurological:** | | | | |
| tingling | 1% | <1% | 9% | 2% |
| malaise/ fatigue | 8% | 2% | 2% | <1% |
| dizziness/ vertigo | 5% | 2% | 8% | 3% |
| warm/ hot sensation | 1% | <1% | 8% | 3% |
| burning sensation | <1% | 0% | 5% | <1% |
| numbness | 1% | <1% | 3% | 1% |
| drowsiness/ sedation | 3% | <1% | 2% | <1% |
| paresthesia | 1% | 0% | 1% | <1% |
| **Cardiovascular:** | | | | |
| flushing | <1% | 1% | 5% | 2% |
| hypertension, tachycardia | <1% | 0% | <1% | <1% |
| bradycardia | <1% | 0% | <1% | 0% |
| palpitations | <1% | <1% | <1% | <1% |
| hypotension | <1% | 0% | <1% | <1% |
| pallor | <1% | 0% | <1% | 0% |
| pulsating sensation | <1% | 0% | <1% | <1% |
| **Symptoms of Potentially Cardiac Origin:** | | | | |
| neck pain/ stiffness | 2% | 0% | 3% | <1% |
| feeling of heaviness | 3% | <1% | 8% | 1% |
| pressure sensation | 1% | <1% | 6% | 1% |
| chest symptoms (including chest pain) | 3% | <1% | 4% | <1% |
| throat symptoms (including sore or swollen throat or throat spasms) | 2% | 0% | 2% | <1% |
| **Musculoskeletal:** | | | | |
| weakness | 3% | <1% | 3% | <1% |
| myalgia | 2% | 0% | 1% | <1% |
| feeling of tightness | <1% | 0% | 3% | <1% |
| joint symptoms, backache, muscle stiffness or cramp | <1% | 0% | 0% | 0% |
| **Miscellaneous:** | | | | |
| sweating | 2% | <1% | 2% | <1% |
| disorder of mouth and tongue | 2% | <1% | 4% | 2% |
| disturbance of hearing | <1% | 0% | <1% | 0% |
| visual disturbance | <1% | 0% | <1% | <1% |

**Table 2: Incidence of Treatment-Emergent* Adverse Events Reported by at least 1% of patients in Controlled Clinical Trials with IMITREX Nasal Spray**

| Event | Placebo n=741 | 5 mg n=496 | 10 mg n=1007 | 20 mg n=1249 |
|---|---|---|---|---|
| **Atypical:** | | | | |
| warm / hot sensation | <1% | 1% | <1% | <1% |
| burning sensation | <1% | <1% | <1% | 1% |
| **Gastrointestinal:** | | | | |
| nausea / vomiting | 15% | 17% | 15% | 16% |
| **Neurological:** | | | | |
| dizziness/ vertigo | <1% | 1% | 2% | 1% |
| malaise/ fatigue | <1% | 2% | 1% | <1% |
| headache | <1% | 1% | <1% | <1% |
| **Cardiovascular*:** | | | | |
| flushing | <1% | <1% | <1% | <1% |
| hypertension, tachycardia | <1% | <1% | <1% | <1% |
| palpitations | <1% | <1% | <1% | <1% |
| pulsating sensation | 0% | 0% | <1% | <0% |
| changes in ECG | <1% | <1% | <1% | <1% |
| **Symptoms of Potentially Cardiac Origin*:** | | | | |
| neck pain / stiffness | <1% | 0% | <1% | <1% |
| feeling of heaviness | <1% | <1% | <1% | <1% |
| feeling of tightness | <1% | 0% | <1% | <1% |
| tight feeling in head | 0% | 0% | <1% | <1% |
| pressure sensation | <1% | <1% | <1% | <1% |
| chest symptoms (including chest pain) | <1% | <1% | <1% | <1% |
| throat symptoms (including sore or swollen throat or throat spasms) | 1% | <1% | 2% | 3% |
| **Ear, Nose and Throat:** | | | | |
| disturbance of nasal cavity / sinuses | 3% | 5% | 3% | 4% |
| throat symptoms | 1% | <1% | 2% | 3% |
| **Miscellaneous:** | | | | |
| disorder of mouth and tongue | 0% | 1% | <1% | <1% |
| disturbance of taste | 2% | 15% | 20% | 25% |

*Includes all events regardless of causality that occurred at a frequency of ≥1% in any IMITREX treatment group and were more frequent in this group than in the placebo group. *These events are included in the table regardless of the incidence in the IMITREX group.

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. There is no evidence that clinically significant abnormalities occurred more frequently with sumatriptan than with placebo.

**SYMPTOMS AND TREATMENT OF OVERDOSE** There have been no reports of overdosage with IMITREX (sumatriptan succinate/sumatriptan). Experience with doses outside of the recommended labelling are as follows: One patient received two 6 mg subcutaneous doses within 30 minutes and 1 patient received four 100 mg tablets within 24 hours, with no adverse events. The highest dose of IMITREX Nasal Spray administered without significant adverse effects was 20 mg given three times daily for 4 days. If overdosage with sumatriptan occurs, the patient should be monitored and standard supportive treatment applied as required. Toxicokinetics are not available. The effect of haemodialysis or peritoneal dialysis on the serum concentration of sumatriptan is unknown.

**DOSAGE AND ADMINISTRATION General:**

**IMITREX (sumatriptan succinate/sumatriptan) is indicated only for the intermittent treatment of migraine headache with or without aura. Sumatriptan should not be used prophylactically. Sumatriptan may be given orally or subcutaneously or as a nasal spray.** 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 tachyphylaxis or medication-induced (rebound) headache.

Twenty-four hours should elapse before sumatriptan is taken following any ergotamine-containing preparation or ergot derivative (such as dihydroergotamine). Conversely, ergotamine-containing preparations or ergot derivatives should not be taken until 6 hours have elapsed following sumatriptan administration.

**Tablets:** The recommended adult dose of IMITREX Tablets is a single 100 mg tablet. Clinical trials have shown that approximately 50-75% of patients have headache relief within two hours after oral dosing, and that a further 15-25% have headache relief by 4 hours.

However, based on the physician's clinical judgement, a 50 mg dose may be considered adequate. The appropriateness should be based on the patient's needs and response to treatment.

If adequate relief has not been attained within 4 hours, additional doses should **not** be used as they are unlikely to be of clinical benefit. Sumatriptan may be taken to treat subsequent migraine attacks. Not more than 300 mg should be taken in any 24 hour period.

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 50 mg dose (single tablet) may be considered in these patients (see Precautions).

**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 adequate relief has not been attained within 2 hours, additional doses should **not** be used as they are unlikely to be of clinical benefit. Sumatriptan may be taken for subsequent attacks provided a minimum of 1 hour has elapsed since the last dose. Not more than 12 mg (two 6 mg injections) should be taken in any 24 hour period.

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 5 mg, the maximum recommended single dose is 20 mg.

If adequate relief has not been attained within 2 hours of initial treatment, additional doses should **not** be administered for the same attack as they are unlikely to be of clinical benefit. Sumatriptan may be taken for subsequent attacks provided a minimum of 2 hours has elapsed since the last dose. Not more than a total of 40 mg should be taken in any 24 hour period.

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 20 mg. (see Table 3 below).

**Table 3: 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) |
| Total | | 208/695 | | 232/494 | | 482/985 | | 722/1195 |
| **Weighted Average** | **30%** | | **47%** | | **49%** | | **60%** | |
| **Range** | | **25-42%** | | **44-67%** | | **43-67%** | | **55-78%** |

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 √ $p \leq 0.05$ versus placebo † $p \leq 0.05$ versus lower sumatriptan doses ▲ $p \leq 0.05$ vs 5 mg – not evaluated

As shown in the table above, optimal rates of headache relief were seen with the 20 mg dose. Single doses above 20 mg should not be used due to limited safety data and lack of increased efficacy relative to the 20 mg 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.

**STABILITY AND STORAGE RECOMMENDATIONS** IMITREX Tablets should be stored at 2°C to 30°C. IMITREX Injection and Nasal Spray should be stored between 2°C to 30°C and protected from light.

**COMPOSITION** *IMITREX TABLETS* contain 100 mg or 50 mg sumatriptan (base) as the succinate salt. IMITREX Tablets also contain lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

IMITREX INJECTION contains 6 mg sumatriptan (base) as the succinate salt in an isotonic sodium chloride solution.

IMITREX Nasal Spray contains 5 mg, 10 mg or 20 mg of sumatriptan base (as the hemisulphate salt formed *in situ*) in an aqueous buffered solution containing monobasic potassium phosphate, anhydrous dibasic sodium phosphate, sulphuric acid, sodium hydroxide, and purified water.

**AVAILABILITY OF DOSAGE FORMS** IMITREX TABLETS 100 mg are pink film-coated tablets available in blister packs containing 6 tablets, packed in a cardboard carton.

*IMITREX TABLETS 50 mg are white film-coated tablets available in blister packs* containing 6 tablets.

Each tablet contains 100 mg or 50 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.

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.

IMITREX® (sumatriptan succinate/sumatriptan nasal spray) is a registered trademark of Glaxo Group Limited, Glaxo Wellcome Inc. licenced use. The appearance, namely colour, shape and size of the IMITREX® Nasal Spray device is a trademark of Glaxo Group Limited, Glaxo Wellcome Inc., licensed use. Product monograph available to physicians and pharmacists upon request.

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https://doi.org/10.1017/S0317167100049246 Published online by Cambridge University Press

# BETASERON®

Interferon beta-1b

## THERAPEUTIC CLASSIFICATION

Immunomodulator

## ACTION AND CLINICAL PHARMACOLOGY

**Description:** BETASERON® (interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques and formulated for use by injection. Interferon beta-1b is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human interferon beta$_{ser17}$. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17. Interferon beta-1b is a highly purified protein that has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural material.

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

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

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

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

**Clinical Trials:** The effectiveness of BETASERON in relapsing-remitting MS was evaluated in a double-blind, multiclinic (11 sites: 4 in Canada and 7 in the U.S.), randomized, parallel, placebo-controlled clinical investigation of 2 years duration. The study included MS patients, aged 18 to 50, who were ambulatory (Kurtzke expanded disability status scale [EDSS] of ≤ 5.5), exhibited a relapsing-remitting clinical course, met Poser's criteria for clinically definite and/or laboratory supported definite MS and had experienced at least two exacerbations over 2 years preceding the trial without exacerbation in the preceding month. Patients who had received prior immunosuppressant therapy were excluded.

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

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

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

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

In addition to clinical measures, annual magnetic resonance imaging (MRI) was performed and quantitated for extent of disease as determined by changes in total area of lesions. In a substudy of patients (n=52) at one site, MRIs were performed every 6 weeks and quantitated for disease activity as determined by changes in size and number of lesions.

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

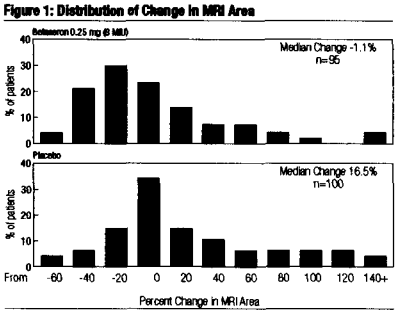
Of the first 372 patients randomized, 72 (19%) failed to complete 2 full years on their assigned treatments. The reasons given for withdrawal varied with treatment assignment. Excessive use of steroids accounted for 11 of the 26 placebo withdrawals. In contrast, among the 25 withdrawals from the 0.25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

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

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

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

**Figure 1: Distribution of Change in MRI Area**




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

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

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

**Table 1: 2-Year Study Results**

**Primary and Secondary Endpoints**

| Efficacy Parameters | | Treatment Groups | | | Statistical Comparisons p-value | | |
|---|---|---|---|---|---|---|---|
| **Primary Clinical Endpoints** | | **Placebo (n=123)** | **0.05 mg (1.6 MIU) (n =125)** | **0.25 mg (8 MIU) (n=124)** | **Placebo vs 0.05 mg (1.6 MIU)** | **0.05 mg (1.6 MIU) vs 0.25 mg (8 MIU)** | **Placebo vs 0.25 mg (8 MIU)** |
| Annual exacerbation rate | | 1.31 | 1.14 | 0.90 | 0.005 | 0.113 | 0.0001 |
| Proportion of exacerbation-free patients† | | 16% | 18% | 25% | 0.609 | 0.288 | 0.094 |
| Exacerbation frequency per patient | 0† | 20 | 22 | 29 | 0.151 | 0.077 | 0.001 |
| | 1 | 32 | 31 | 39 | | | |
| | 2 | 20 | 28 | 17 | | | |
| | 3 | 15 | 15 | 14 | | | |
| | 4 | 15 | 7 | 9 | | | |
| | ≥5 | 21 | 16 | 8 | | | |
| **Secondary Endpoints††** | | | | | | | |
| Median number of months to first on-study exacerbation | | 5 | 6 | 9 | 0.299 | 0.097 | 0.010 |
| Rate of moderate or severe exacerbations per year | | 0.47 | 0.29 | 0.23 | 0.020 | 0.257 | 0.001 |
| Mean number of moderate or severe exacerbation days per patient | | 44.1 | 33.2 | 19.5 | 0.229 | 0.064 | 0.001 |
| Mean change in EDSS score‡ at endpoint | | 0.21 | 0.21 | -0.07 | 0.995 | 0.108 | 0.144 |
| Mean change in Scripps score‡‡ at endpoint | | -0.53 | -0.50 | 0.66 | 0.641 | 0.051 | 0.126 |
| Median duration per exacerbation (days) | | 36 | 33 | 35.5 | ND | ND | ND |
| % change in mean MRI lesion area at endpoint | | 21.4% | 9.8% | -0.9% | 0.015 | 0.019 | 0.0001 |

ND Not done.

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

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

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

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

## INDICATIONS AND CLINICAL USE

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

## CONTRAINDICATIONS

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

## WARNINGS

One suicide and four attempted suicides were observed among 372 study patients during a 3-year period. All five patients received BETASERON (interferon beta-1b) (three in the 0.05 mg [1.6 MIU] group and two in the 0.25 mg [8.0 MIU] group). There were no attempted suicides in patients on study who did not receive BETASERON. Depression and suicide have been reported to occur in patients receiving interferon alpha, a related compound. Patients treated with BETASERON should be informed that depression and suicidal ideation may be a side effect of the treatment and should report these symptoms immediately to the prescribing physician. Patients exhibiting depression should be monitored closely and cessation of therapy should be considered.

## PRECAUTIONS

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

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

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

Eighty-five percent of patients in the controlled MS trial reported injection site reactions at one or more times during therapy. Post-marketing experience has been consistent with this finding, with infrequent reports of injection site necrosis. The onset of injection site necrosis usually appears early in therapy with most cases reported to have occurred in the first two to three months of therapy. The number of sites where necrosis has been observed was variable.

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

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

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

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

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

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

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

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

**Laboratory Tests:** The following laboratory tests are recommended prior to initiating BETASERON therapy and at periodic intervals thereafter: thyroid function test, hemoglobin, complete and differential white blood cell counts, platelet counts and blood chemistries including liver function tests. A pregnancy test, chest roentgenogram and ECG should also be performed prior to initiating BETASERON therapy. In the controlled MS trial, patients were monitored every 3 months. The study protocol stipulated that BETASERON therapy be discontinued in the event the absolute neutrophil count fell below 750/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 fully evaluated. Although studies designed to examine drug interactions have not been done, it was noted that BETASERON patients (n=180) have received corticosteroid or ACTH treatment of relapses for periods of up to 28 days.

BETASERON administered in three cancer patients over a dose range of 0.025 mg (0.8 MIU) to 2.2 mg (71 MIU) led

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to a dose-dependent inhibition of antipyrine elimination. The effect of alternate-day administration of 0.25 mg (8 MIU) BETASERON on drug metabolism in MS patients is unknown.

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

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

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

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

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

## ADVERSE REACTIONS

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

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

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

Laboratory abnormalities included:

- lymphocyte count < 1500/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 child-bearing age treated with placebo reported menstrual disorders. All reports were of mild to moderate severity and included: intermenstrual bleeding and spotting, early or delayed menses, decreased days of menstrual flow, and clotting and spotting during menstruation.

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

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

- injection site reaction (85%),
- lymphocyte count < 1500/mm$^3$ (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 2. In the following table, terms so general as to be uninformative, and those events where a drug cause was remote have been excluded.

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

| Adverse Reaction | Placebo n=123 | 0.25 mg (8 MIU) n=124 |
|---|---|---|
| **Body as a Whole** | | |
| - Injection site reaction* | 37% | 85% |
| - Headache | 77% | 84% |
| - Fever* | 41% | 59% |
| - Flu-like symptom complex* | 56% | 76% |
| - Pain | 48% | 52% |
| - Asthenia* | 35% | 49% |
| - Chills* | 19% | 46% |
| - Abdominal pain | 24% | 32% |
| - Malaise* | 3% | 15% |
| - Generalized edema | 6% | 8% |
| - Pelvic pain | 3% | 6% |
| - Injection site necrosis* | 0% | 5% |
| - Cyst | 2% | 4% |
| - Necrosis | 0% | 2% |
| - Suicide attempt | 0% | 2% |
| **Cardiovascular System** | | |
| - Migraine | 7% | 12% |
| - Palpitation* | 2% | 8% |
| - Hypertension | 2% | 7% |
| - Tachycardia | 3% | 6% |
| - Peripheral vascular disorder | 2% | 5% |
| - Hemorrhage | 1% | 3% |
| **Digestive System** | | |
| - Diarrhea | 29% | 35% |
| - Constipation | 18% | 24% |
| - Vomiting | 19% | 21% |
| - Gastrointestinal disorder | 3% | 6% |
| **Endocrine System** | | |
| - Goiter | 0% | 2% |

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

| Adverse Reaction | Placebo n=123 | 0.25 mg (8 MIU) n=124 |
|---|---|---|
| **Hemic and Lymphatic System** | | |
| - Lymphocytes < 1500/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% |

* Significantly associated with BETASERON treatment

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

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

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

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

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

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

**Hemic and Lymphatic System:** chronic lymphocytic leukemia, hemoglobin less than 9.4 g/100 mL, petechia, platelets less than 75,000/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, hypoda, 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, dysfonia, encephalopathy, euphoria, facial paralysis, foot drop, hallucinations, hemiplegia, hypalgesia, hyperesthesia, incoordination, intracranial hypertension, libido decreased, manic reaction, meningitis, neuralgia, neuropathy, neurosis, nystagmus, oculogyric crisis, ophthalmoplegia, papilledema, paralysis, paranoid reaction, psychosis, reflexes decreased, stupor, subdural hematoma, torticollis, tremor and urinary retention;

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

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

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

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

## DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS USE ONLY

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

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

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

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

## PHARMACEUTICAL INFORMATION

| | |
|---|---|
| Common Name: | interferon beta-1b (USAN) |
| Molecular Weight: | approximately 18,500 daltons |
| Physical Form: | sterile, lyophilized powder |
| *Composition* (each vial contains): | 0.3 mg (9.6 MIU) interferon beta-1b, 15 mg Albumin Human, USP 15 mg Dextrose, USP |
| Stability (before reconstitution): | Store under refrigeration at 2° to 8°C (36° to 46°F). Avoid freezing. If refrigeration is not possible, vials of BETASERON and diluent should be kept as cool as possible, below 30°C (86°F), away from heat and light, and used within 7 days. |
| Stability (after reconstitution): | The reconstituted product contains no preservative. If not used immediately, store under refrigeration at 2° to 8°C (36° to 46°F) and use within 3 hours of reconstitution. Avoid freezing. |

## AVAILABILITY OF DOSAGE FORMS

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

**References:**

**1.** The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. **Neurology** 1995;45:1277-1285. **2.** The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993;43:655-661. **3.** Paty DW, *et al.* Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993;43:662-667. **4.** ®Betaseron® Product Monograph, Berlex Canada Inc. 1996. **5.** Data on file, Haeck confirmations, March 1998.

Product Monograph available to healthcare professionals upon request.



PAAB PMAC



See pages A-6, A-7

Amerge
naratriptan hydrochloride

1 & 2.5 mg Tablets

**Therapeutic Classification:** Migraine Therapy

**Pharmacological Classification:** 5-$HT_1$ Receptor Agonist

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

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

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

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

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

* values quoted are arithmetic mean (standard deviation)

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

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

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

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

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

***Special Populations:***

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

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

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

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

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

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

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

**Table 2: Results at 240 Minutes Post First Dose**

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

[1] Pain relief is defined as a reduction in headache severity from grade 3 or 2 (severe or moderate) to grade 1 or 0 (mild or no pain)

[2] Pain free is defined as a headache severity score of 0 (no pain)

[3] Clinical disability is measured on a 4-point scale (0=able to function normally, 1=ability mildly impaired, 2=ability severely impaired, 3=bed rest required)

^ photophobia and phonophobia collected as one measure

* $p<0.01$ versus placebo

M $p<0.01$ versus AMERGE 1 mg. Note: comparisons were not performed for any parameter other than pain relief and pain free in study 1 and for pain relief in study 2:

! Statistical comparisons not performed

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

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

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

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

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

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

**Warnings:**

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

***Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: AMERGE has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. In rare cases, the symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of another 5-HT1 agonist. AMERGE should not be given to patients who have documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS).*** **It is strongly recommended that AMERGE not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female who is surgically or physiologically postmenopausal, or male who is over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, AMERGE should not be administered (see CONTRAINDICATIONS).**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

theoretical basis for these effects being additive, ergot-containing or ergot-type medications (like dihydroergotamine or methysergide) are contraindicated within 24 hours of AMERGE administration (see CONTRAINDICATIONS).
*Other 5-HT$_1$ Agonists:* The administration of AMERGE with other 5-HT$_1$ agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with co-administration of 5-HT$_1$ agonists, use of these drugs within 24 hours of each other is contraindicated.
*Other Serotonergic Drugs:* Rare postmarketing reports describe patients with weakness, hyperreflexia, and incoordination following the combined use of a selective serotonin reuptake inhibitor (SSRI) and 5-HT$_1$ agonists. If concomitant treatment with AMERGE and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline), tricyclic antidepressant, monoamine oxidase inhibitor, or other drug with serotonergic activity is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised.
*Hormonal contraceptives:* In a population pharmacokinetic study in migraine patients, hormonal contraceptive use was associated with a 32% decrease in naratriptan clearance.
*Tobacco:* In a population pharmacokinetic study in migraine patients, tobacco use was associated with a 29% increase in naratriptan clearance.
*Alcohol and Food:* Clinical studies did not reveal any pharmacokinetic interaction when naratriptan was administered together with alcohol or food.
**Use in Pregnancy:** The safety of AMERGE for use during human pregnancy has not been established. AMERGE Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To monitor fetal outcomes of pregnant women exposed to AMERGE, Glaxo Wellcome Inc. maintains a Naratriptan Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 722-9292, ext. 39441.
**Use in Nursing Mothers:** AMERGE and/or its metabolites are distributed into the milk of lactating rats (at 2 hours post oral gavage dosing, levels in milk were 3.5 times higher than maternal plasma levels). Therefore, caution should be exercised when considering the administration of AMERGE Tablets to nursing women.
**Use in Pediatrics:** Safety and effectiveness of AMERGE Tablets have not been studied in children under 12 years of age. Use of the drug in this age group is, therefore, not recommended.
**Adolescents:** The efficacy of AMERGE Tablets at single doses of 0.25, 1.0 and 2.5 mg was not demonstrated to be greater than placebo in adolescents (12-17 years). Therefore, the use of the drug in adolescents is not recommended.
**Use in the Elderly:** The safety and effectiveness of AMERGE has not been adequately studied in individuals over 65 years of age. AMERGE Tablets are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in elderly patients who have reduced renal function. In addition, elderly patients are more likely to have decreased hepatic function; they are at higher risk for CAD; and blood pressure increases may be more pronounced in the elderly. Clinical studies of AMERGE Tablets did not include patients over 65 years of age. Its use in this age group is, therefore, not recommended.
**Drug/Laboratory Test Interactions:** AMERGE Tablets are not known to interfere with commonly employed clinical laboratory tests.
**Dependence Liability:** In one clinical study enrolling 12 subjects, all of whom had experience using oral opiates and other psychoactive drugs, subjective responses typically associated with many drugs of abuse were produced with less intensity during treatment with AMERGE (1-5 mg) than with codeine (30 to 90 mg). Long term studies (12 months) in migraine patients using AMERGE Tablets revealed no evidence of increased drug utilization.
**Melanin Binding:** In pigmented rats treated with a single oral dose (10 mg/kg) of radiolabelled naratriptan, radioactivity was detected in the eyes at 3 months post-administration, a finding which suggests that the drug or its metabolites may bind to the melanin of the eye. The possible clinical significance of this finding is unknown. No systematic monitoring of ophthalmologic function was undertaken in clinical trials. Prescribers should consider the possibility of long-term ophthalmologic effects due to accumulation of naratriptan in melanin-rich tissues.
**Adverse Reactions: Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT$_1$ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).**
**Experience in Controlled Clinical Trials with AMERGE**
***Typical 5-HT$_1$ Agonist Adverse Reactions:*** As with other 5-HT$_1$ agonists, AMERGE (naratriptan hydrochloride) has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb.
***Acute Safety:*** The safety and efficacy of the 1 and 2.5 mg doses of AMERGE were investigated in four placebo-controlled clinical trials in adult migraine patients. Two of these trials were of parallel group design and involved the treatment of a single migraine attack. A third study was of crossover design and involved the treatment of one migraine attack per dose group. The fourth study was a parallel group trial in which patients treated up to 3 migraine attacks. In all studies, patients who achieved headache relief at 240 minutes post-dose, but experienced a worsening of severity between 4 and 24 hours post-dosing, were permitted to take a second dose of double-blind medication identical to the first.
The overall incidence of adverse events following doses of 1 mg or 2.5 mg AMERGE (one or two doses) were similar to placebo (28.5% and 30.2% versus 28.9% with placebo). AMERGE Tablets were generally well tolerated and most adverse reactions were mild, transient and self-limiting. The most common adverse events to occur at a higher rate than in the corresponding placebo group were malaise/fatigue (2.4% versus 0.8% with placebo) and neck/throat/jaw sensations (2.1% versus 0.3% with placebo). Table 3 lists the most common adverse events that occurred in the four large placebo-controlled clinical trials. Only events that occurred at a frequency of 1% or more in the AMERGE Tablets 2.5 mg or 1 mg group and were more frequent in that group than in the placebo group are included in Table 3. From this table, it appears that many of these adverse events are dose related.

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

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

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

***Long-Term Safety:*** In a long-term open study, 417 patients treated 15,301 migraine attacks with AMERGE over a period of up to 1 year. The most common adverse events in descending order of frequency were as follows: nausea (16%); malaise/fatigue (11%); drowsiness (10%); chest sensations* (8%); neck/throat/jaw sensations* (8%); paresthesia (7%); head/face sensations* (6%); vomiting (6%); and dizziness (5%). Due to the lack of a placebo arm in this study, the role of AMERGE in causation cannot be reliably determined. (*See footnote for Table 3)
***Other Adverse Events Observed in Association with AMERGE:*** In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because some events were observed in open and uncontrolled studies, the role of AMERGE Tablets in their causation cannot be reliably determined. All reported events are included except those already listed in Table 3, those too general to be informative, and those not reasonably associated with the use of the drug. Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (N=2790) exposed to AMERGE Tablets. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare adverse events are those occurring in fewer than 1/1,000 patients.
***Cardiovascular:*** Infrequent were palpitations, increased blood pressure, tachyarrhythmias and abnormal ECGs. Rare were bradycardia, hypotension, varicosities and heart murmur.
***Ear, Nose & Throat:*** Frequent were ear, nose & throat infections. Infrequent were phonophobia, sinusitis, and upper respiratory inflammation. Rare were allergic rhinitis, labyrinthitis, tinnitus, ear, nose & throat haemorrhage and hearing difficulty.
***Endocrine & Metabolic:*** Infrequent were thirst and polydipsia, dehydration and fluid retention. Rare were 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 lightheadedness, 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).

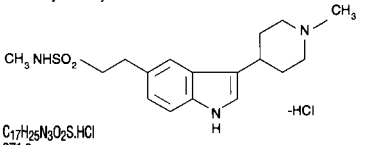
**Table 4: Percentage of Patients with Headache Relief at 4 Hours Post-Dosing?**

| | 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 246EC
**Solubility:** In water (25EC) = 35 mg/mL
**pH and pKa:** pKa = 9.7 (piperidinyl nitrogen)
pH (1% aqueous solution) = 6.3

**Composition:** AMERGE 2.5 mg Tablets contain 2.5 mg of naratriptan (base) as the hydrochloride salt and the following non-medicinal ingredients: croscarmellose sodium; hydroxypropyl methylcellulose; indigo carmine aluminium lake (FD&C Blue No. 2); iron oxide yellow; lactose; magnesium stearate; microcrystalline cellulose; titanium dioxide; and triacetin.
AMERGE 1 mg Tablets contain 1 mg of naratriptan (base) as the hydrochloride salt and the following non-medicinal ingredients: croscarmellose sodium; hydroxypropyl methylcellulose; lactose; magnesium stearate; microcrystalline cellulose; titanium dioxide; and triacetin.
**Stability and Storage Recommendations:** AMERGE Tablets should be stored below 30°C.
**Availability of Dosage Forms:** AMERGE Tablets 2.5 mg are green film-coated, D-shaped tablets embossed GXCE5 on one side, available in blister packs of 2 or 6 tablets (4 blister packs inserted into a carton), or bottles of 60 tablets.
AMERGE Tablets 1 mg are white film-coated, D-shaped tablets embossed GXCE3 on one side, available in blister packs of 2 tablets (4 blister packs inserted into a carton), or bottles of 60 tablets.

**References:**
1. Product Monograph of PrAMERGE®; Glaxo Wellcome Inc. 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



See page A-3

# Once-a-day Aricept*

*donepezil HCl 5 & 10 mg tablets*

**PHARMACOLOGIC CLASSIFICATION**
Cholinesterase inhibitor

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

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

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

**Clinical Pharmacokinetics and Metabolism**

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

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

| Dose (mg/day) | $C_{min}$ (ng/mL) | $C_{max}$ (ng/mL) | $C_{ss}$[1] (ng/mL) | $E_{min}$ % | $E_{max}$% | $E_{ss}$[2]% |
|---|---|---|---|---|---|---|
| 5 | 21.4 ± 3.8 | 34.1 ± 7.3 | 26.5 ± 3.9 | 62.2 ± 5.8 | 71.8 ± 4.3 | 65.3 ± 5.2 |
| 10 | 38.5 ± 8.6 | 60.5 ± 10.0 | 47.0 ± 8.2 | 74.7 ± 4.4 | 83.6 ± 1.9 | 77.8 ± 3.0 |

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

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

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

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

| Dose (mg/day) | $t_{max}$ (hr) | $AUC_{0-24}$ (ng•hr/mL) | $Cl_T/F$ (L/hr/kg) | $V_T/F$ (L/kg) | $t_{1/2}$ (hr) |
|---|---|---|---|---|---|
| 5 | 3.0 ± 1.4 | 634.8 ± 92.2 | 0.110 ± 0.02 | 11.8 ± 1.7 | 72.7 ± 10.6 |
| 10 | 3.9 ± 1.0 | 1127.8 ± 195.9 | 0.110 ± 0.02 | 11.6 ± 1.9 | 73.5 ± 11.8 |

$t_{max}$: Time to maximal plasma concentration
$AUC_{0-24}$: Area under the plasma concentration versus time curve from 0 -to- 24 hours
$Cl_T/F$: Mean apparent plasma clearance
$V_T/F$: Apparent volume of distribution
$t_{1/2}$: Elimination half-life

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

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

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

***Metabolism/Excretion:*** Donepezil hydrochloride is extensively metabolized and is also excreted in the urine as parent drug. The rate of metabolism of donepezil hydrochloride is slow and does not appear to be saturable. There are four major metabolites - two of which are known to be active - and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of a single 5 mg dose of $^{14}$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.

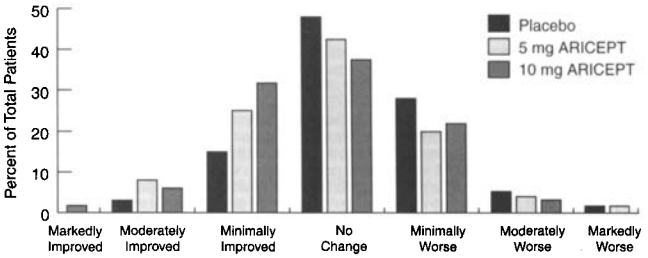
The data shown below for the two primary outcome measures in donepezil clinical trials were obtained from the Intent-To-Treat population (ITT analysis, i.e., All patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete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

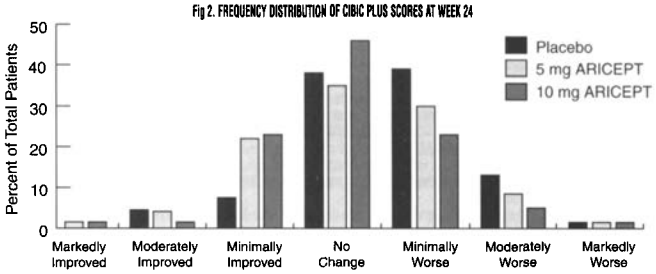



**Thirty-Week Study (24 weeks of treatment + 6-week placebo washout):** In this study, 473 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of donepezil for 24 weeks of double-blind active treatment followed by a 6-week single-blind placebo washout period. As in 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 ≥65 Years Old:*** In controlled clinical studies with 5 and 10 mg of ARICEPT, 536 patients were between the ages of 65 to 84, and 37 patients were aged 85 years or older. In Alzheimer's Disease patients, nausea, diarrhea, vomiting, insomnia, fatigue and anorexia increased with dose and age and the incidence appeared to be greater in female patients. Since cholinesterase inhibitors as well as Alzheimer's Disease can be associated with significant weight loss, caution is advised regarding the use of ARICEPT in low body-weight elderly patients, especially in those ≥ 85 years old.

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

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

**Drug-Drug Interactions:**

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

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

***Effect of ARICEPT on the Metabolism of other Drugs:*** No *in vivo* clinical trials have been conducted to investigate the effect of ARICEPT on the clearance of drugs metabolized by CYP 3A4 (e.g., cisapride, terfenadine) or by CYP 2D6 (e.g., imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean $K_i$ 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 precicted 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, polydypsia, duodenal ulcer, stomach ulcer.*

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

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

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

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

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

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

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

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

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

***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 may have no causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, *hemolytic anemia (rare event), 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.

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Full product monograph available upon request.



PAAB
79035



See page A-28

# 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 [Vasoactive 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 other 5-$HT_1$ agonists, and may therefore also occur with 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 unrecognised 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

symptoms suggestive of angina following ZOMIG should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, *such as ischemic bowel syndrome or Raynaud's syndrome following ZOMIG administration* should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS).

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

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

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

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

Drug Interactions:

*Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged* vasospastic reactions. Because there is a theoretical basis for these effects being additive, ergot-containing or ergot-type medications (like dihydroergotamine or methysergide) are contraindicated within 24 hours of ZOMIG administration (see CONTRAINDICATIONS).

*Other 5-$HT_1$ Agonists:* The administration of ZOMIG with other 5-$HT_1$ agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with 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).

*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.

**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 heavi*ness 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 pro*phylactic 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 fre*quency 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).

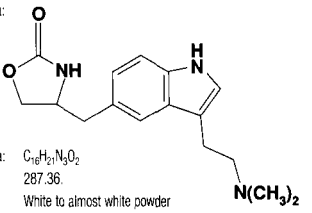
## PHARMACEUTICAL INFORMATION

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 intaglio-ated 'Z' on one side. Available in blister packs of 3 and 6 tablets.

Product Monograph available on request.

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See pages A-24, A-25

# TOPAMAX
topiramate

**TOPAMAX*** Tablets
(Topiramate)
25, 100 and 200 mg tablets
Antiepileptic

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

TOPAMAX (topiramate) is a novel antiepileptic agent classified as a sulphamate substituted monosaccharide. Three pharmacological properties of topiramate are believed to contribute to its anticonvulsant activity. First, topiramate reduces the frequency at which action potentials are generated when neurons are subjected to a sustained depolarization indicative of a state-dependent blockade of voltage-sensitive sodium channels. Second, topiramate markedly enhances the activity of GABA at some types of GABA receptors. Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of $GABA_A$ receptor. Third, topiramate antagonizes the ability of kainate to activate the kainate/AMPA subtype of excitatory amino acid (glutamate) receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.

In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This pharmacologic effect is much weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major component of topiramate's antiepileptic activity.

### Pharmacokinetics

Absorption and Distribution

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

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

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

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

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

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

Metabolism and Excretion

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

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

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

Special Populations

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

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

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

*Age and Gender:* Age (18-67) and gender appear to have no effect on the plasma clearance of topiramate.

In well-controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations and its clinical efficacy.

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

Pediatric Pharmacokinetics

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

### Clinical Experience

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

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

Table 1
Median Percent Seizure Rate Reduction and Percent Responders
in Six Double-Blind, Placebo-Controlled, Add-On Trials

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

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

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

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

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

## INDICATIONS AND CLINICAL USE

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

## CONTRAINDICATIONS

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

## WARNINGS

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

### Central Nervous System Effects

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

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

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

## PRECAUTIONS

### Effects Related to Carbonic Anhydrase Inhibition

Kidney Stones

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

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

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

Paresthesia

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

### Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with impaired renal function ($CL_{cr}$ ≤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**).

https://doi.org/10.1017/S0317167100049246 Published online by Cambridge University Press

**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 2:

Table 2
Drug Interactions with TOPAMAX Therapy

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

* Is not administered but is an active metabolite of carbamazepine
↔ No effect on plasma concentration
** Plasma concentrations increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin
↓ Plasma concentrations decrease in individual patients
NS Not studied
AED Antiepileptic drug

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## ADVERSE REACTIONS

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

The most common dose-related adverse events at dosages of 200 to 1,000 mg/day were: nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, and mood problems (see Table 4).

Table 3
Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials [a,b]
(Events that occurred in ≥ 2% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

| | TOPAMAX® Dosage (mg/day) | | |
|---|---|---|---|
| **Body System/** Adverse Event | Placebo (n=216) | 200-400 (n=113) | 600-1,000 (n=414) |
| **Body as a Whole** | | | |
| Asthenia | 1.4 | 8.0 | 3.1 |
| Back Pain | 4.2 | 6.2 | 2.9 |
| Chest Pain | 2.8 | 4.4 | 2.4 |
| Influenza-Like Symptoms | 3.2 | 3.5 | 3.6 |
| Leg Pain | 2.3 | 3.5 | 3.6 |
| Hot Flushes | 1.9 | 2.7 | 0.7 |
| **Nervous System** | | | |
| Dizziness | 15.3 | 28.3 | 32.1 |
| Ataxia | 6.9 | 21.2 | 14.5 |
| Speech Disorders/Related Speech Problems | 2.3 | 16.8 | 11.4 |
| Nystagmus | 9.3 | 15.0 | 11.1 |
| Paresthesia | 4.6 | 15.0 | 19.1 |
| Tremor | 6.0 | 10.6 | 8.9 |
| Language Problems | 0.5 | 6.2 | 10.4 |
| Coordination Abnormal | 1.9 | 5.3 | 3.6 |
| Hypoaesthesia | 0.9 | 2.7 | 1.2 |
| Abnormal Gait | 1.4 | 1.8 | 2.2 |
| **Gastrointestinal System** | | | |
| Nausea | 7.4 | 11.5 | 12.1 |
| Dyspepsia | 6.5 | 8.0 | 6.3 |
| Abdominal Pain | 3.7 | 5.3 | 7.0 |
| Constipation | 2.3 | 5.3 | 3.4 |
| Dry Mouth | 0.9 | 2.7 | 3.9 |
| **Metabolic and Nutritional** | | | |
| Weight Decrease | 2.8 | 7.1 | 12.8 |
| **Neuropsychiatric** | | | |
| Somnolence | 9.7 | 30.1 | 27.8 |
| Psychomotor Slowing | 2.3 | 16.8 | 20.8 |
| Nervousness | 7.4 | 15.9 | 19.3 |
| Difficulty with Memory | 3.2 | 12.4 | 14.5 |
| Confusion | 4.2 | 9.7 | 13.8 |
| Depression | 5.6 | 8.0 | 13.0 |
| Difficulty with Concentration/Attention | 1.4 | 8.0 | 14.5 |
| Anorexia | 3.7 | 5.3 | 12.3 |
| Agitation | 1.4 | 4.4 | 3.4 |
| Mood Problems | 1.9 | 3.5 | 9.2 |
| Aggressive Reaction | 0.5 | 2.7 | 2.9 |
| Apathy | 0 | 1.8 | 3.1 |
| Depersonalization | 0.9 | 1.8 | 2.2 |
| Emotional Lability | 0.9 | 1.8 | 2.7 |
| **Reproductive, Female** | (n=59) | (n=24) | (n=128) |
| Breast Pain, Female | 1.7 | 8.3 | 0 |
| Dysmenorrhea | 6.8 | 8.3 | 3.1 |
| Menstrual Disorder | 0 | 4.2 | 0.8 |
| **Reproductive, Male** | (n=157) | (n=89) | (n=286) |
| Prostatic Disorder | 0.6 | 2.2 | 0 |
| **Respiratory System** | | | |
| Pharyngitis | 2.3 | 7.1 | 3.1 |
| Rhinitis | 6.9 | 7.1 | 6.3 |
| Sinusitis | 4.2 | 4.4 | 5.6 |
| Dyspnea | 0.9 | 1.8 | 2.4 |
| **Skin and Appendages** | | | |
| Pruritus | 1.4 | 1.8 | 3.1 |
| **Vision** | | | |
| Diplopia | 5.6 | 14.2 | 10.4 |
| Vision Abnormal | 2.8 | 14.2 | 10.1 |
| **White Cell and RES** | | | |
| Leukopenia | 0.5 | 2.7 | 1.2 |

a Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX or placebo.
b Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Table 4
Dose-Related Adverse Events From
Six Placebo-Controlled, Add-On Trials

| | 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 |


https://doi.org/10.1017/S0317167100049246 Published online by Cambridge University Press

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

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

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

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

In acute TOPAMAX (topiramate) overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdosage is not recommended. Treatment should be appropriately supportive.

Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, including doses of over 20 g in one individual, hemodialysis has not been necessary.

## DOSAGE AND ADMINISTRATION

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

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

The recommended titration rate is:

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

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

**Geriatrics**
See **PRECAUTIONS** section.

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

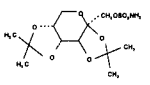
**Patients with Renal Impairment**
In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m$^2$), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady state at each dose.

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

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

## PHARMACEUTICAL INFORMATION

**I) Drug Substance**
Proper Name: topiramate
Chemical Name: 2,3:4,5-bis-*O*-(1-methylethylidene)-ß-D-fructopyranose sulfamate
Chemical Structure



Molecular Formula: $C_{12}H_{21}NO_8S$
Molecular Weight: 339.36
Description: Topiramate is a white crystalline powder having a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate with a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3.

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

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

## AVAILABILITY OF DOSAGE FORMS

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

| | |
|---|---|
| 25 mg: | white, round, coated tablets containing 25 mg topiramate. |
| 100 mg: | yellow, round, coated tablets containing 100 mg topiramate. |
| 200 mg: | salmon-coloured, round, coated tablets containing 200 mg topiramate. |
| Supplied: | Bottles of 60 tablets with desiccant. |

## INFORMATION FOR THE CONSUMER

**"TOPAMAX" Tablets**
**(Topiramate)**

**Please read this carefully before you start to take TOPAMAX* (topiramate), even if you have taken this drug before. Please do not discard this leaflet; you may need to read it again. If you have any questions about this medicine ask your doctor or pharmacist.**

**What is TOPAMAX?**
TOPAMAX, the brand name for topiramate, has been prescribed to you to control your epilepsy. Please follow your doctor's recommendations carefully.

**Before taking TOPAMAX**
Tell your doctor about any medical problems and about any allergies you have or have had in the past.

You should not use TOPAMAX if you are allergic to any of the ingredients in the product. (See last paragraph in this Leaflet.)

Tell your doctor if you have or have had kidney stones or kidney disease. Your doctor may want you to increase the amount of fluids you drink while you are taking this medicine.

Tell your doctor if you are pregnant, or if you are planning to become pregnant.

Tell your doctor if you are breast-feeding (nursing).

TOPAMAX may cause some people to be less alert than normal. Make sure you know how you are affected by this medicine before you drive, use machines or do anything else that could be dangerous if you are not alert.

Tell your doctor about all medications (prescription and non-prescription) and dietary supplements you are using. It is especially important that your doctor know if you are taking digoxin, oral contraceptives or any other antiepileptic drugs, such as phenytoin or carbamazepine. Inform your doctor of your usual alcohol consumption or if taking medicines that slow down the nervous system (CNS depressants).

**How should I use TOPAMAX?**
Follow your doctor's instructions about when and how to take this medicine.

The usual dose is 200 to 400 mg per day. TOPAMAX is usually taken twice a day; however, your doctor may tell you to use it once a day or at a higher or lower dose.

Your doctor will start with a low dose and slowly increase the dose to the lowest amount needed to control your epilepsy.

Always swallow the tablets with plenty of water. You can take the tablets with or without food.

If you miss a dose, take it as soon as you remember. But, if it is almost time for the next dose, do not take the missed dose. Instead, take the next scheduled dose.

Do not suddenly stop taking this medicine without first checking with your doctor.

Always check that you have enough tablets and do not run out.

**What undesirable effects may TOPAMAX have?**
Any medicine may have unwanted effects. Tell your doctor or pharmacist about any unusual sign or symptom whether listed or not.

Those reported most often were: *coordination problems, changes in thinking, including difficulty concentrating, slow thinking, confusion and forgetfulness, dizziness, tiredness, tingling and drowsiness.* Less frequently reported side effects are: *agitation, decrease in appetite, speech disorders, depression, vision disorders, mood swings, nausea, taste changes, weight loss, kidney stones that may be present as blood in the urine or pain in the lower back or genital area.*

**What to do in case of an overdose**
If you accidentally take an overdose of TOPAMAX, contact your doctor or the nearest hospital Emergency, even though you may not feel sick.

**How should I store TOPAMAX?**
Do not use this product after the expiry date written on the package.

Store in a cool, dry place.

Keep this and all medicines in a safe place away from children.

**What does TOPAMAX contain?**
TOPAMAX contains topiramate as the active ingredient and the following inactive ingredients: lactose monohydrate, pregelatinized starch, pregelatinized starch (modified), purified water, carnauba wax, microcrystalline cellulose, sodium starch glycolate and magnesium stearate. Depending upon the color, TOPAMAX may also contain: hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide and polysorbate 80.

Product Monograph available on request

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

Janssen-Ortho Inc.
North York, Ontario
M3C 1L9

TOPAMAX*
topiramate

*Trademark


BPITMX981001A



See pages A-10, A-11, A-26, A-27

https://doi.org/10.1017/S0317167100049246 Published online by Cambridge University Press

# 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, $\beta_2$-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.

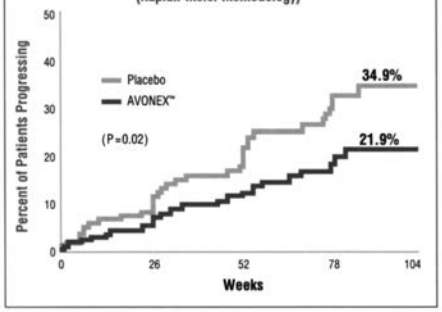
All patients had a definite diagnosis of MS of at least 1 year duration and had at least 2 exacerbations in the 3 years prior to study entry (or 1 per year if the duration of disease was less than 3 years). At entry, study participants were without exacerbation during the prior 2 months and had Kurtzke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



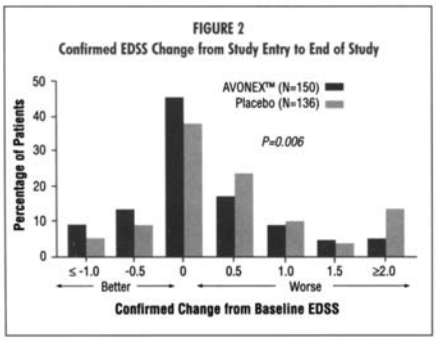

*Note: Disability progression represents at least a 1.0 point increase in EDSS score sustained for at least 6 months. The value p=0.02 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given timepoint (e.g., 34.9% vs. 21.9%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

See pages A-20, A-21



continued on page A-50

https://doi.org/10.1017/S0317167100049246 Published online by Cambridge University Press

## 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, pharyngeal edema, pneumonia; **Skin and Appendages:** basal cell carcinoma, blisters, cold clammy skin, contact dermatitis, erythema, furunculosis, genital pruritus, nevus, rash, seborrhea, skin ulcer, skin discolouration; **Special Senses:** abnormal vision, conjunctivitis, earache, eye pain, labyrinthitis, vitreous floaters; **Urogenital:** breast fibroadenosis, breast mass, dysuria, epididymitis, fibrocystic change of the breast, fibroids, gynecomastia, hematuria, kidney calculus, kidney pain, leukorrhea, menopause, nocturia, pelvic inflammatory disease, penis disorder, Peyronies Disease, polyuria, post menopausal hemorrhage, prostatic disorder, pyelonephritis, testis disorder, urethral pain, urinary urgency, urinary retention, urinary incontinence, vaginal hemorrhage.

**Serum Neutralizing Antibodies**

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

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**

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

**DOSAGE AND ADMINISTRATION**

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

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

**PHARMACEUTICAL INFORMATION**

**Composition:**

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

**Reconstitution:**

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

**Stability and Storage:**

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

**AVAILABILITY OF DOSAGE FORMS**

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

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


REFERENCES:

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

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**Multiple Sclerosis Society of Canada**

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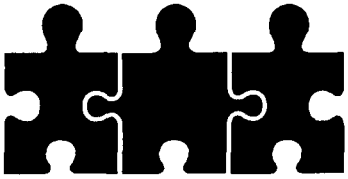
# What if having a steel rod in your spine was something to look forward to.

Life with muscular dystrophy often means a very weak back and life in a wheelchair. So, having a metal rod placed in your spine provides relief, but only temporarily. Because there isn't a cure, there's us. We're making the lives of people with neuromuscular disorders better. For information, please call

1-800-567-2873

**Muscular Dystrophy Association of Canada**





https://doi.org/10.1017/S0317167100049246 Published online by Cambridge University Press

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

# CANADIAN CONGRESS OF NEUROLOGICAL SCIENCES PARTNERS PROGRAM

The Partners are comprised of the CCNS societies and affiliate groups, for-profit and non-profit organizations with an interest in the neurosciences.

The Partners Program will generate greater awareness of neurological disorders in the general public and through to government bodies. Current and future challenges include an ageing population, an increased incidence of neurological disorders, increasing demands on health-care services, and increasing health costs.

The Partners are working together to raise awareness of neurological disorders, to promote and support research education relevant to neurological health and disease, and to promote cost-effective health services to patients and their caregivers.

Benefits to Partners:

- ☞ Joint Program Initiatives
- ☞ Access to a Neurosciences Communication Network
- ☞ Web links
- ☞ Canadian Journal of Neurological Sciences
- ☞ Preferred CCNS conference registration fees
- ☞ Newsletters

## FOR MORE INFORMATION REGARDING THE CCNS PARTNERSHIP PROGRAM


Mail: Suite 810, 906 12th Avenue SW,
Calgary, AB T2R 1K7
Phone: 403-229-9544
Fax: 403-229-1661
Email: brains@ccns.org





https://doi.org/10.1017/S0317167100049246 Published online by Cambridge University Press

## POSITION AVAILABLE

**Montreal Neurological Institute and Hospital**
**Department of Neurology/Neurosurgery**
**McGill University**

### Neurologist and/or PhD with Expertise in Epileptology

Applications are invited, by the Montreal Neurological Institute and the Department of Neurology/Neurosurgery at McGill University, for neurologists (MD or MD/PhD) with expertise in epileptology. The successful candidate will be expected to spend the majority of his/her time in research and obtain peer reviewed funding for an independent research programme related to epilepsy. The individual selected will start at the Assistant Professor level. The research programme should preferably be in the fields of neuroimaging, human molecular genetics or neurophysiology. At the Montreal Neurological Institute and in the Department of Neurology/Neurosurgery at McGill University, a multidisciplinary epilepsy group has the support of a strong research programme in imaging including magnetic resonance spectroscopy, fMRI and PET, as well as in molecular neurobiology, neurosurgery, clinical neurogenetics, neuropsychology and neurophysiology.

In accordance with Canadian Immigration requirements, preference will be given to Canadian citizens and permanent residents of Canada.

McGill University is committed to equity in employment.

Prospective candidates should send their CV to: **Dr. F. Dubeau, Chair, Epilepsy Search Committee, Montreal Neurological Institute and Hospital, 3801 University, Room 111, Montreal, Quebec, Canada H3A 2B4.**

**Deadline for applications is May 1, 1999.**

## Academic Appointment
## University of Saskatchewan, Neurosurgeon

The Department of Surgery invites applications for a full-time tenure faculty appointment in the Division of Neurosurgery. The successful candidate will be appointed to the active staff of the Department of Surgery at Royal University Hospital, one of the hospitals of the Saskatoon District Health Board, and hold a full-time faculty appointment with the College of Medicine. The candidate must be certified in Neurosurgery by the Royal College of Physicians and Surgeons of Canada. Applicants should have senior experience in general neurosurgery with special expertise in Neurovascular Surgery, Academic experience in a North American centre would be an advantage. The successful candidate will participate in the clinical, educational and research activities of the Division. The University of Saskatchewan is committed to Employment Equity. Members of Designated Groups (women, aboriginal people, people with disabilities and visible minorities) are encouraged to self-identify on their applications. This position has been cleared for advertising at the two tier level. Interested candidates should submit a letter of application, current curriculum vitae and names of three references to: Dr. R.G. Keith, Chairman, Department of Surgery, University of Saskatchewan, Royal University Hospital, Saskatoon, SK S7N 0W8

**Deadline: March 1, 1999**

**University of Toronto**
**Sunnybrook & Women's College Health Sciences Centre**

### STROKE NEUROLOGIST

A neurologist with interest and expertise in stroke is sought for the Sunnybrook & Women's College Health Sciences Centre Division of Neurology at the University of Toronto. The applicant must hold certification from the Royal College of Physicians and Surgeons of Canada in Neurology, or be eligible for certification. The successful candidate will be expected to be an excellent clinician teacher and to help develop a high quality stroke care and training program, as well as to participate in research. Neurodoppler training would be an asset. Academic appointment in the Division of Neurology, University of Toronto and salary will be commensurate with training and experience.

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

Please send curriculum vitae and letter of application with references to:

**Dr. Sandra E. Black**
Head, Division of Neurology
Sunnybrook & Women's College Health Sciences Centre
Room A421, 2075 Bayview Avenue
Toronto, Ontario, M4N 3M5
Tel: (416) 480-4551

Fax: (416) 480-4552
Email: Black@srcl.sunnybrook.utoronto.ca

**University of Toronto**
**Sunnybrook & Women's College Health Sciences Centre**

### NEUROLOGIST

Two neurologists are needed for the Sunnybrook & Women's College Health Sciences Centre Division of Neurology, Department of Medicine at the University of Toronto. The applicants must hold certification from the Royal College of Physicians and Surgeons of Canada in Neurology, or be eligible for certification. The successful candidates will be expected to be excellent teachers who can help maintain our high quality resident training program and develop outpatient services at both the Sunnybrook and Women's College sites. Academic appointment in the Division of Neurology, University of Toronto and salary will be commensurate with training and experience.

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

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