PERMAX®
Shire BioChem
Pergolide Mesylate
Antiparkinsonian Agent-Dopamine Agonist

ACTION and CLINICAL PHARMACOLOGY

PERMAX, (pergolide mesylate), a synthetic ergot derivative, is a dopamine receptor agonist at both D_1 and D_2 receptor sites.

In Parkinson's disease, pergolide is believed to exert its therapeutic effect by directly stimulating postsynaptic dopamine receptors in the corpus striatum. In addition, pergolide suppresses the secretion of prolactin, causes a transient increase in serum concentration of growth hormone and a decrease in serum concentration of luteinizing hormone.

To date, only very limited pharmacokinetic data are available. Following oral administration of ^{14}C-pergolide, radioactivity in plasma appeared after 15 to 30 minutes, peaked at one or two hours, and was barely detectable after 96 hours. Radioactivity was eliminated as pergolide metabolites in urine (55%), in feces (40%) and in breath (5%). No unchanged pergolide was detected in excreta.
At least 10 radioactive metabolites have been isolated, including N-despropylpergolide, pergolide sulfoxide and pergolide sulfone. The latter two metabolites are dopamine agonists in animals. The other detected metabolites have not been identified and it is not known whether they are pharmacologically active.

Pergolide is approximately 90% bound to plasma proteins. This extent of protein binding may be important to consider when pergolide is coadministered with other drugs known to affect protein binding.

INDICATIONS AND CLINICAL USE

PERMAX (pergolide mesylate) is indicated in the treatment of the signs and symptoms of idiopathic Parkinson's disease.

PERMAX may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa (usually with a peripheral decarboxylase inhibitor).

CONTRAINDICATIONS

PERMAX (pergolide mesylate) is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.

WARNINGS

Hypotension - PERMAX (pergolide mesylate) 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 PERMAX concomitantly with antihypertensive agents or other medications known to lower blood pressure.

Effect on the ability to drive and use of machines – Physicians should caution patients that pergolide may cause somnolence or episodes of sudden onset of sleep (see Adverse Reactions, Post-marketing Reports). Patients should be cautioned about operating hazardous machinery, including motor vehicles, while taking pergolide.

Hallucinations: In controlled clinical trials in patients with early PD, hallucinations were observed in 2.4% of patients taking pergolide, as compared to 1% in those taking placebo. Treatment was discontinued due to hallucinations in about 0.8% of those enrolled. In these trials, this effect occurred primarily some weeks into the maintenance period. In controlled trials in patients with advanced PD, hallucinations were observed in about 14% of those taking PERMAX with levodopa, compared to 3% of those taking placebo with levodopa. Treatment was discontinued due to hallucinations in about 3% of PERMAX patients; tolerance to this untoward effect was not observed.

Serous Inflammation and Fibrosis – There have been rare reports of pleuritis, pleural effusion, pleural fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves or retroperitoneal fibrosis in patients taking pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide. Pergolide should be used with caution in patients with a history of these conditions, particularly those patients who experienced the events while taking other ergot derivatives. Patients with a history of such events should be carefully monitored clinically and with appropriate radiographic
and laboratory studies while taking pergolide.

PRECAUTIONS

General – The abrupt discontinuation of PERMAX (pergolide mesylate) 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 whenever 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, have been reported in association with rapid dose reduction, withdrawal of, or change 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 multicenter 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 pergolide 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 ordinarily 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 in Controlled Trials.

The most commonly observed adverse events
(≥ 5%) associated with the use of pergolide are as follows:

For Early Therapy: gastrointestinal complaints, including nausea, anorexia, constipation, dyspepsia; nervous system complaints, including dizziness, insomnia, somnolence and depression; and whole body complaints, including asthenia, abdominal pain, pain, and headache.

For Adjunctive Therapy: nervous system complaints, including dyskinesia, dizziness, hallucinations, dystonia, confusion, somnolence, insomnia and anxiety; gastrointestinal complaints, including nausea, constipation, diarrhea, and dyspepsia; cardiovascular complaints, including postural hypotension; whole body complaints, including pain, abdominal pain, accidental injury and headache; peripheral edema; rhinitis; and abnormal vision.

In clinical trials for pergolide early therapy, the overall reported incidence of nausea was higher than that reported in trials for adjunctive therapy (38.0% vs 24.3%, respectively); this nausea rate occurred despite a mandatory regimen of the anti-emetic domperidone during the initial 3 or 8 week up-titration period, for all patients in early therapy clinical trials.

Certain adverse experiences (eg. dyskinesia, 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 AST, ALT, alkaline phosphatase, creatine phosphokinase, and urea nitrogen.

Adverse Reactions resulting in Discontinuation in Controlled Trials

Early Therapy: Gastrointestinal (6%) and CNS (2%).

Adjunctive Therapy: CNS (15.5%), primarily hallucinations (7.8) and confusion (1.8%).

Incidence of Adverse Reactions in Controlled Clinical Trials: The table that follows enumerates adverse events occurring at a frequency of 1% or more among all pergolide-treated patients who participated in controlled trials. 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.

TABLE 1: Incidence of Treatment-Emergent Adverse Experiences in Controlled Clinical Trials in Patients with Early or Advanced Parkinson's Disease

	Adjunctive Therapy (Advanced PD)		Early Therapy (Early PD)	
	PERMAX n=189% Patients reporting events	PERMAX n=187% Patients reporting events	PERMAX n=250% Patients reporting events	PERMAX n=104% Patients reporting events
Body as a Whole				
Asthenia	4.2	4.8	7.2	3.8
Pain	7.0	2.1	5.2	1.9
Abdominal Pain	5.8	2.1	6.4	4.8
Injury, accident	5.8	7.0	1.2	1.9
Headache	5.3	6.4	5.2	4.8
Chest Pain	3.7	2.1	2.4	2.9
Back pain	1.6	2.1	3.2	3.8
Surgical Procedure	1.6	<1	3.2	1.0
Flu syndrome	3.2	2.1	2.8	2.9
Neck Pain	2.7	1.6	1.6	1.9
Infection	1.1	0	2.4	0
Malaise	< 1	< 1	2	0
Hernia	< 1	< 1	2	0
Chills	1.1	0	< 1	< 1
Face edema	1.1	0	< 1	< 1
Nervous System				
Dyskinesia	62.4	24.6	0	0
Dizziness	19.1	13.9	12.4	3.8
Hallucinations	13.8	3.2	2.4	1.0
Dystonia	11.6	8.0	<1	<1
Confusion	11.1	9.6	<1	<1
Somnolence	10.1	3.7	8	5.8
Insomnia	7.9	3.2	8.8	1.9
Anxiety	6.4	4.3	4.4	1.9
Depression	3.2	5.4	5.6	3.8
Tremor	4.2	7.5	1.2	1.0
Vertigo	<1	<1	3.2	0
Abnormal dreams	2.7	4.3	1.2	1.0
Nervousness	<1	<1	2.4	0
Sleep Disorder	<1	<1	2.4	1.0
Personality disorder	2.1	<1	<1	<1
Psychosis	2.1	0	<1	<1
Abnormal Thinking	<1	<1	2	0
Abnormal gait	1.6	1.6	<1	<1
Akathisia	1.6	0	<1	<1
Extrapyramidal syndrome	1.6	1.1	<1	<1
Incoordination	1.6	<1	<1	<1
Paresthesia	1.6	3.2	1.6	1.0
Neuralgia	1.1	<1	1.2	1.9
Apathy	<1	<1	1.2	0
Akinesia	1.1	1.1	<1	<1
Hypertonia	1.1	0	<1	<1
Speech disorder	1.1	1.6	<1	<1
Gastrointestinal				
Nausea	24.3	12.8	38.0*	4.8
Constipation	10.6	5.9	5.6	1.9
Anorexia	4.8	2.7	6.8	1.0
Diarrhea	6.4	2.7	2.8	3.8
Dyspepsia	6.4	2.1	5.2	1.9
Vomiting	2.7	1.6	6.0	1.0
Dry mouth	3.7	<1	1.6	0
Gastrointestinal Disorder	<1	<1	1.6	1.9
Cardiovascular system				
Postural Hypotension	9.0	7.0	4.8	1.9
Sinus Tachycardia	4.8	1.6	<1	<1
Vasodilation	3.2	<1	<1	<1
Hypertension	1.6	1.1	2.8	2.9
Palpitation	2.1	<1	<1	<1
Hypotension	2.1	<1	<1	<1
Syncope	2.1	1.1	1.2	0

Vascular Disorder	<1	<1	1.2	0
Peripheral Vascular Disorder	<1	<1	1.2	0
Arrhythmia	1.1	<1	<1	<1
Myocardial infarction	1.1	<1	<1	<1
Respiratory System				
Rhinitis	12.2	5.4	2.4	0
Dyspnea	4.8	1.1	3.2	0
Cough Increased	<1	<1	2.8	1.9
Bronchitis	<1	<1	2.4	2.9
Epistaxis	1.6	<1	<1	<1
Pharyngitis	<1	<1	1.2	0
Hiccup	1.1	0	<1	<1
Metabolic & Nutritional System				
Peripheral edema	7.4	4.3	2.4	1.0
Edema	1.6	0	2	1
Weight gain	1.6	0	0	0
Special Senses				
Abnormal vision	5.8	5.4	<1	<1
Diplopia	2.1	0	<1	<1
Amblyopia	<1	<1	2	0
Taste perversion	1.6	0	<1	<1
Eye disorder	1.1	0	<1	<1
Musculoskeletal System				
Arthralgia	1.6	2.1	<1	<1
Bursitis	1.6	<1	<1	<1
Joint Disorder	<1	<1	1.2	0
Myalgia	1.1	<1	2	1.9
Twitching	1.1	0	<1	<1
Skin & Appendages				
Rash	3.2	2.1	1.2	1.0
Sweating	2.1	2.7	1.2	1.0
Urogential System				
Urinary frequency	2.7	6.4	1.6	1
Urinary tract infection	2.7	3.7	<1	0
Hematuria	1.1	<1	<1	<1
Hemic & Lymphatic System				
Anemia	1.1	<1	<1	<1

*Patients in the controlled clinical trials for early PD were on a mandatory regimen of the anti-emetic domperidone for the duration of the up-titration period.

Other Events Observed During the Pre-marketing Evaluation of PERMAX

This section reports event frequencies of adverse reactions that occurred in approximately 1,700 patients who took multiple doses of PERMAX in premarketing studies worldwide. The conditions and duration of exposure to PERMAX varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a causal relationship to PERMAX treatment cannot be determined.

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.

Other Events By Body System - The following definitions of frequency are used: 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 events are those occurring in less than 1/1,000 patients.

Body as a Whole System:

Frequent: Headache, asthenia, injury accident, abdominal pain, chest pain, back pain, fever, flu syndrome, neck pain.

Infrequent: Enlarged abdomen, malaise, neoplasm, hernia, pelvic pain, facial edema, chills, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia.

Rare: Acute abdominal syndrome, LE syndrome, erythromelalgia.

Nervous System:

Frequent: Hallucinations, psychosis, paranoid reaction, personality disorder, akinesia, dyskinesia, choreoathetosis, dystonia, tremor, abnormal gait, incoordination, speech disorders, dizziness, confusion, depression, anxiety, somnolence, insomnia, abnormal dreams, amnesia.

Infrequent: Neuropathy, hypertonia, delusions, convulsion, libido increased, euphoria, emotional lability, libido decrease, akathisia, vertigo, neuralgia, myoclonus, coma, apathy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis, meningitis, manic reaction, hypokinesia, hostility, agitation.

Rare: Stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis.

Gastrointestinal System

Frequent: Nausea, vomiting, constipation, dyspepsia, anorexia, diarrhea, dry mouth, dysphagia.

Infrequent: Flatulence, abnormal liver function tests, increased appetite, salivary gland enlargement, thirst, gastroenteritis, gastritis, rectal disorder, peridontal abscess, intestinal obstruction, nausea and vomiting, gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulcer, melena, hepatomegaly, hematemesis, eructation.

Rare: Sialadenitis, peptic ulcer, pancreatitis, colitis, cholecystitis, aphthous stomatitis.

Cardiovascular System

Frequent: Postural hypotension, hypotension, syncope, hypertension, palpitations, arrhythmia, vasodilatation, congestive heart failure.

Infrequent: Myocardial infarct, tachycardia, cardiac arrest, abnormal electrocardiogram, angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystoles, cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atrial fibrillation, varicose vein, pulmonary embolus, AV block, shock.

Rare: Vasculitis, pulmonary hypertension, pericarditis, migraine, heart block, cerebral hemorrhage.

Respiratory System

Frequent: Rhinitis, dyspnea, pneumonia, pharyngitis, cough increased.

Infrequent: Sinusitis, bronchitis, epistaxis, voice alteration, hemoptysis, asthma, lung edema, hiccup, pleural effusion, laryngitis, emphysema, apnea.

Rare: Pneumothorax, lung fibrosis, larynx edema, hypoxia, hypoventilation, hyperventilation, hemothorax, carcinoma of lung.

Metabolic and Nutritional Findings

Frequent: Peripheral edema, weight loss, weight gain.

Infrequent: Dehydration, hypokalemia, hypoglycemia, gout, hyperglycemia, iron deficiency anemia, hypercholesteremia.

Rare: Electrolyte imbalance, cachexia, acidosis, hyperuricemia.

Special Senses System

Frequent: Diplopia.

Infrequent: Otitis media, conjunctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma, eye hemorrhage.

Rare: Blindness, cataract, retinal detachment, retinal vascular disorder.

Musculoskeletal System

Frequent: Twitching, myalgia, arthralgia.

Infrequent: Bursitis, bone pain, tenosynovitis, myositis, bone sarcoma.

Rare: Osteoporosis, muscle atrophy.

Skin and Appendages System

Frequent: Sweating, rash.

Infrequent: Skin discolouration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma, seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis.

Rare: Vesiculobullous rash, subcutaneous nodule, skin nodule, skin benign neoplasm, lichenoid dermatitis, herpes zoster.

Urogenital System

Frequent: Urinary tract infection, urinary frequency, urinary incontinence, prostatic disorder, dysmenorrhea, hematuria.

Infrequent: Dysuria, breast pain, menorrhagia, impotence, cystitis, urinary retention, menstrual disorder, abortion, vaginal hemorrhage, vaginitis, abnormal ejaculation, priapism, kidney calculus, fibrocystic breast, lactation, uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause, kidney failure, breast neoplasm.

Rare: Amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea, nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding.

Hemic and Lymphatic System

Frequent: Anemia.

Infrequent: Leukopenia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis.

Rare: Purpura, lymphocytosis, eosinophilia, acute lymphoblastic leukemia.

Post-marketing Reports

Voluntary reports of adverse events temporally associated with PERMAX that have been received since market introduction and which may have no causal relationship with the drug, include the following: Pericarditis; Pericardial effusion; Pleuritis; Pleural effusion; Pleural fibrosis; Retroperitoneal fibrosis; Neuroleptic malignant syndrome (with rapid de-titration of pergolide); Sudden onset of sleep; Cardiac valvulopathy

In post-marketing experience, less than 0.01% of patients were reported for sudden onset of sleep. (see Warnings).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no clinical experience with massive overdosage. Symptoms and signs may include vomiting, hypotension, agitation, severe hallucinations, severe involuntary movements, tingling sensations, palpitations, and ventricular extrasystoles.

Management of overdosage may require supportive measures to maintain arterial blood pressure. Cardiac function should be monitored; an antiarrhythmic agent may be necessary. If signs of CNS stimulation are present, a phenothiazine or butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs has not been assessed in reversing the effects of overdose. Activated charcoal may be considered instead of or in addition to gastric emptying. There is no experience with dialysis or hemoperfusion; these procedures are unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

General

The following dosage escalation recommendations apply to the use of pergolide for both early therapy (without levodopa) and late therapy (with levodopa).

These dosage escalation recommendations are derived from both clinical trial data and clinical experience, and are provided as a guide only, as individual tolerance to dose increases will vary. A slower schedule may reduce the incidence of adverse events, particularly hypotension, and GI and CNS symptoms (see WARNINGS, Hypotension; and ADVERSE EVENTS).

Early and Late Stage Parkinson's Disease

Administration of PERMAX (pergolide mesylate) 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 3 - 4 days over the next 2 - 3 weeks of therapy.

Once a patient reaches approximately 0.75 mg/day, the dosage may then be increased by 0.25 mg/day every 3 - 4 days until an optimal maintenance dosage is achieved.

PERMAX is usually administered in divided doses 3 times/day.

The safety of PERMAX, for early Parkinson's disease, has not been systematically evaluated at doses above 3 mg/day. In clinical studies of PERMAX for treatment of early Parkinson's disease, the average dose after one year of treatment was approximately 2.25 mg/day

The safety of PERMAX, for advanced Parkinson's disease, has not been systematically evaluated at doses above 5 mg/day. In clinical studies, the average therapeutic dose of PERMAX was approximately 3 mg/day. The average concurrent levodopa/carbidopa daily dosage (expressed as levodopa) was approximately 650 mg/day. Since rapid escalation of PERMAX can cause severe adverse reactions, it is recommended that a slow increase of PERMAX be combined with a concomitant gradual, cautious and limited reduction of levodopa dosage.

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.

Date of revision : October 15, 2003

References: 1. Barone P, et al. Pergolide monotherapy in the treatment of early PD. A randomized , controlled study. *Neurology* 1999;53(3):S73-S79. **2.** Olanow CW, Fahn S. Muenter M. et al. A multicentered double-blind placebo controlled trial of pergolide as an adjunct to Sinemet in Parkinson's Disease. *Mov Disor.* 1994; 9(1); 40-47.

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Zanaflex (tizanidine hydrochloride)

Relieves Spasticity. Restores Possibilities.

Zanaflex®
(tizanidine hydrochloride) tablets
2 & 4 mg tizanidine
Antispastic Agent

CLINICAL PHARMACOLOGY

Mechanism of Action

Tizanidine is an agonist at α_2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons.

Pharmacokinetics

Following oral administration, tizanidine is essentially completely absorbed and has a half-life of approximately 2.5 hours (coefficient of variation [CV] = 33%). Following administration of tizanidine peak plasma concentrations occurred at 1.5 hours (CV = 40%) after dosing.

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

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

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

Special Populations

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

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

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

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

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

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

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

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

WARNINGS

Hypotension

Tizanidine HCl is an α_2-adrenergic agonist (like clonidine) and can produce hypotension. In a single dose study where blood pressure was monitored closely after dosing, two thirds of patients treated with 8 mg of Zanaflex had a 20% reduction in either the diastolic or systolic BP. The reduction was seen within 1 hour after dosing, peaked 2 to 3 hours after dosing and was associated, at times, with bradycardia, orthostatic hypotension, lightheadedness/dizziness and rarely syncope. The hypotensive effect is dose related and has been measured following single doses of ≥2 mg. The chance of significant hypotension may possibly be minimized by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to a fixed upright position may be at increased risk for hypotensive and orthostatic effects.

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

Risk of Liver Injury

Zanaflex use occasionally causes drug induced liver injury, most often hepatocellular in type. In controlled clinical studies, approximately 5% of patients treated with Zanaflex had elevations of liver function tests (ALT/SGPT, AST/SGOT) to greater than 3 times the upper limit of normal (or 2 times if baseline levels were elevated). The patients usually remain asymptomatic despite increased aminotransferases. In occasional symptomatic cases, nausea, vomiting, anorexia and jaundice have been reported. The onset of the elevated liver enzymes typically occurred within the first 6 months of treatment with Zanaflex and most resolved rapidly upon drug withdrawal with no reported residual problems. In postmarketing experience, three deaths associated with liver failure have been reported in patients treated with tizanidine, including one case of fatal fulminant hepatitis. Monitoring of aminotransferase levels is recommended during the first 6 months of treatment (e.g., baseline, 1, 3 and 6 months) and periodically thereafter, based on clinical status. Because of the potential toxic hepatic effect of tizanidine, the drug should be used only with extreme caution in patients with impaired hepatic function.

Sedation

In the multiple dose, controlled clinical studies, 48% of patients receiving any dose of Zanaflex reported sedation as an adverse event. In 10% of these cases, the sedation was rated as severe compared to <1% in the placebo treated patients. Sedation may interfere with every day activity. The effect appears to be dose related. In a single dose study, 92% of the patients receiving 16 mg, when asked, reported that they were drowsy during the 6 hour study. This compares to 76% of the patients on 8 mg and 35% of the patients on placebo. Patients began noting this effect 30 minutes following dosing. The effect peaked 1.5 hours following dosing. Of the patients who received a single dose of 16 mg, 51% continued to report drowsiness 6 hours following dosing compared to 13% in the patients receiving placebo or 8 mg of Zanaflex.

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

Hallucinations

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

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

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

PRECAUTIONS

General

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

Cardiovascular

Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses equal to the maximum human dose on a mg/m² basis. ECG evaluation was not performed in the controlled clinical studies. Reduction in pulse rate has been noted in association with decreases in blood pressure in the single dose controlled study (see WARNINGS).

Ophthalmic

Dose-related retinal degeneration and corneal opacities have been found in animal studies at doses equivalent to approximately the maximum recommended dose on a mg/m² basis. There have been no reports of corneal opacities or retinal degeneration in the clinical studies.

Use in Elderly

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

Use in Children

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

Use in Obstetrics

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

Reproduction studies performed in rats at a dose of 3 mg/kg, equal to the maximum recommended human dose on a mg/m² basis and in rabbits at 30 mg/kg, 16 times the maximum recommended human dose on a mg/m² basis did not show evidence of teratogenicity. Tizanidine at doses that are equal to and up to 8 times the maximum recommended human dose on a mg/m² basis increased gestation duration in rats. Prenatal and postnatal pup loss was increased and developmental retardation occurred. Postimplantation loss was increased in rabbits at doses of 1 mg/kg or greater, equal to or greater than 0.5 times the maximum recommended human dose on a mg/m² basis. Zanaflex has not been studied in pregnant women. Zanaflex should be given to pregnant women only if clearly needed.

Nursing Mothers

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

PATIENTS WITH SPECIAL DISEASES AND CONDITIONS

Use in Renally Impaired Patients

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

Use in Women Taking Oral Contraceptives

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

Dependence Liability

Monkeys were shown to self-administer tizanidine in a dose-dependent manner, and abrupt cessation of tizanidine produced transient signs of withdrawal at doses > 35 times the maximum recommended human dose on a mg/m² basis. These transient withdrawal signs (increased locomotion, body twitching, and aversive behavior toward the observer) were not reversed by naloxone administration.

Drug Interactions

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

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

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

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

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

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

ADVERSE REACTIONS

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

Common Adverse Events Leading to Discontinuation

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

Most Frequent Adverse Clinical Events Seen in Association With the Use of Tizanidine

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

Adverse Events Reported in Controlled studies

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

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

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

* weakness, fatigue and/or tiredness

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

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

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

* weakness, fatigue and/or tiredness

Other Adverse Events Observed During the Evaluation of Tizanidine

Zanaflex was administered to 1187 patients in additional clinical studies where adverse event information was available. The conditions and duration of exposure varied greatly, and included (in overlapping categories) double-blind and open-label studies, uncontrolled and controlled studies, inpatient and outpatient studies, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

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

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients.

Body as a Whole: *Frequent:* fever; *Infrequent:* allergic reaction, moniliasis, malaise, abscess, neck pain, sepsis, cellulitis, death, overdose; *Rare:* carcinoma, congenital anomaly, suicide attempt.

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

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

Hemic and Lymphatic System: *Infrequent:* ecchymosis, hypercholesteremia, anemia, hyperlipemia, leukopenia, leukocytosis, sepsis; *Rare:* petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional System: *Infrequent:* edema, hypothyroidism, weight loss; *Rare:* adrenal cortex insufficiency, hyperglycemia, hypokalemia, hyponatremia, hypoproteinemia, respiratory acidosis.

Musculoskeletal System: *Frequent:* myasthenia, back pain; *Infrequent:* pathological fracture, arthralgia, arthritis, bursitis.

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

Respiratory System: *Infrequent:* sinusitis, pneumonia, bronchitis; *Rare:* asthma.

Skin and Appendages: *Frequent:* rash, sweating, skin ulcer; *Infrequent:* pruritus, dry skin, acne, alopecia, urticaria; *Rare:* exfoliative dermatitis, herpes simplex, herpes zoster, skin carcinoma.

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

PHARMACEUTICAL INFORMATION

Composition

Zanaflex (tizanidine hydrochloride) tablets are composed of the active ingredient, tizanidine hydrochloride (2.29 mg equivalent to 2 mg tizanidine base) or (4.576 mg equivalent to 4 mg tizanidine base), and the inactive ingredients, silicon dioxide colloidal, stearic acid, microcrystalline cellulose and anhydrous lactose.

Stability and Storage Recommendations

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

AVAILABILITY OF DOSAGE FORMS

Zanaflex contains 2 or 4 mg tizanidine as tizanidine hydrochloride for oral administration. The 2 mg Zanaflex has a bisecting score on one side and embossed with "A592" on the other. These white tablets are available in bottles of 150.The 4 mg Zanaflex is embossed with "A594" on one side and cross-scored on the other. The white tablets are available in bottles of 150.

FULL PRODUCT MONOGRAPH AVAILABLE UPON REQUEST.

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See page A-3

Interferon beta-1a

Rebif®

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

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTIONS AND CLINICAL PHARMACOLOGY

Description: Rebif® (Interferon beta-1a) is a purified, sterile glycoprotein product produced by recombinant DNA techniques and formulated for use by injection. The active ingredient of Rebif® is produced by genetically engineered Chinese Hamster Ovary (CHO) cells. Interferon beta-1a is a highly purified glycoprotein that has 166 amino acids and an approximate molecular weight of 22,500 daltons. It contains a single N-linked carbohydrate moiety attached to Asn-80 similar to that of natural human Interferon beta. The specific activity of Rebif® is approximately 0.27 million international units (MIU)/mcg Interferon beta-1a. The unit measurement is derived by comparing the antiviral activity of the product to an in-house natural hIFN-beta NIH standard that is obtained from human fibroblasts (BILS 11), which has been calibrated against the NIH natural hIFN-beta standard (GB 23-902-531). General: Interferons are a family of naturally occurring proteins, which have molecular weights ranging from 15,000 to 21,000 daltons. Three major classes of interferons have been identified: alpha, beta, gamma. Interferon beta, Interferon alpha and Interferon gamma have overlapping yet distinct biologic activities.

Interferon beta-1a acts through various mechanisms:

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

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

Relapsing-Remitting Multiple Sclerosis

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

PRISMS STUDY

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

The main criteria for inclusion were:

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

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

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

Effect on exacerbation

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

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

The results after one year of treatment were also significant.

Effect on time to first progression in disability

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

Effect on multiple sclerosis pathology as detected by MRI scans

Efficacy parameters	Treatment Groups			p-value	
	Placebo	Rebif® 66 mcg/wk	Rebif® 132 mcg/wk	Rebif® 66 mcg/wk vs placebo	Rebif® 132 mcg/wk vs placebo
Burden of disease (BOD) Median % change	+10.9	-1.2	-3.8	<0.0001	<0.0001
MRI activity					
All patients					
Number of active lesions (per 6 months)	2.25	0.75	0.5	<0.0001	<0.0001
% active scans	75%	50%	25%	<0.0001	<0.0001
Patients with monthly MRIs (9 months)					
Number active lesions (per month)	0.88	0.17	0.11	<0.0001	<0.0001
% active scans	44%	12.5%	11%	<0.0001	<0.0001
Patients with monthly MRIs throughout the study (2 years)					
Number active lesions	0.9	0.1	0.02	0.0905	0.0105
% active scans	52%	10%	2%	0.0920	0.0117

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

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

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

Additional analyses were conducted in order to study the efficacy of Rebif® in populations of patients with adverse predictive outcome factors, who were likely to be at higher risk for progression in disability. The primary predictive factor examined was baseline EDSS >3.5. Patients in this cohort have a more severe degree of disability and are at higher risk for progression than those with lower EDSS: natural history studies have shown that patients at EDSS levels of 4.0 to 5.0 spend less time at these EDSS levels than at lower levels of disability. Treatment with Rebif® at both doses significantly reduced the mean exacerbation count per patient compared to placebo treatment. Progression in this group of patients is of particular concern, as it involves development of difficulty in ambulation. The 132 mcg weekly dose significantly prolonged time to confirmed progression whereas the 66 mcg weekly dose did not. Both doses of Rebif® significantly affected percent change from baseline in MRI burden of disease in the high-EDSS cohort, and the 132 mcg weekly dose significantly reduced the number of T_2 active lesions in this population. The efficacy results in this cohort of patients with established disability confirms that the 132 mcg weekly dose has a marked effect on progression in disability and the underlying pathology of the disease.

Effect on exacerbation (High-EDSS cohort)

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

*Log-linear model.

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

Treatment Group	% of progressors*	Time to Progression		
		# patients	Median (days)	Q1 (days)
Placebo	56%	28	638	218
Rebif® 66 mcg weekly	41%	35	not reached	226
Rebif® 132 mcg weekly	27%	31	not reached	638

*Excludes patients lost to follow-up without progression.

Progression in disability: statistical comparisons

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

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

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

*ANOVA on the ranks.

Number of T2 Active Lesions (High-EDSS cohort)

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

*ANOVA on the ranks.

CROSS-OVER STUDY

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

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

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

Six-months observation vs six-months treatment:

Treatment with Rebif® at both doses used in this study, achieved a statistically significant reduction in both the MRI evidence of MS activity in the brain and the clinical relapse rate versus the corresponding observation periods. This pattern of improvement was also reflected in additional MRI measures. In the biannual T_2-weighted scans, a reduction in the mean number of new lesions and in the mean number of enlarging lesions was demonstrated.

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

Two-year results: At the end of this study, 62 patients continued treatment for a further 18 months. Each of these patients continued to receive the dose to which they were randomized. Validation of the results of the 2 year treatment period is ongoing, however, the results from the continuation of treatment at both doses demonstrate that Rebif® maintained its dose-dependent effect in reducing the relapse rate and the brain lesion volume detected by T_2 weight MRI scans compared to the observation period, which corroborates the findings of the longer, placebo-controlled study.

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

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

INDICATIONS AND CLINICAL USE

Multiple Sclerosis: Rebif® (Interferon beta-1a) is indicated for the treatment of relapsing-remitting multiple sclerosis in patients with an EDSS between 0 and 5.0, to reduce the number and severity of clinical exacerbations, slow the progression of physical disability, reduce the requirement for steroids, and reduce the number of hospitalizations for treatment of multiple sclerosis. The efficacy has been confirmed by T_1-Gd enhanced and T_2 (burden of disease) MRI evaluations. Evidence of efficacy beyond 2 years is not known since the primary evidence of efficacy derives from 2-year trials.

Condyloma acuminatum: Rebif® is best suited for the patient who has less than nine lesions, and who has failed several prior treatments. In the case of patients with nine or more lesions, if the first Rebif® treatment is successful, the remaining lesions could be treated with a second course of Rebif® therapy. Rebif® should also be considered for the treatment of condyloma acuminatum in patients for whom the side-effects from other treatments, e.g., scarring, are of concern. While not all patients who were treated with Rebif® attained a complete response, patients whose lesions decreased in size and had at least a partial response may have also benefitted from treatment because lesion shrinkage may facilitate subsequent management with other therapies, as has been reported with IFN-alpha.

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

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

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

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

PRECAUTIONS

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

Based on the results of clinical trials of Rebif® in MS, in which more than 500 patients were randomized to drug treatment, there is no indication of an increased risk of seizure disorder with Rebif® therapy. However, since seizures have been reported with other interferon therapies, caution should be exercised when administering interferon-beta-1a to patients with pre-existing seizures disorder. For patients without a pre-existing seizure disorder who develop seizures during therapy, an etiologic basis should be established and appropriate anti-convulsant therapy instituted prior to considering resuming treatment with Rebif®. The effect of Rebif® administration on the medical management of patients with seizure disorder is unknown.

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

Hypersensitivity reactions, both local and systemic, have developed during therapy with Rebif®.

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

Pregnancy and Lactation: Rebif® should not be administered in case of pregnancy and lactation. There are no studies of interferon beta-1a in pregnant women. At high

doses in monkeys, abortifacient effects were observed with other interferons. Fertile women receiving Rebif® should take appropriate contraceptive measures. Patients planning for pregnancy and those becoming pregnant should be informed of the potential hazards of interferons to the foetus and Rebif® should be discontinued. It is not known whether Rebif® is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made either to discontinue nursing or to discontinue Rebif® therapy.

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

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

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

Laboratory Tests

Relapsing-Remitting Multiple Sclerosis: Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete and differential white blood cell counts, platelet counts and blood chemistries, including liver and thyroid function tests are recommended during Rebif® therapy. These tests should be performed at months 1, 3 and 6, and every 6 months thereafter.

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

Information to be provided to the patient: Flu-like symptoms (fever, headache, chills, muscle aches) are not uncommon following initiation of therapy with Rebif®. Acetaminophen may be used for relief of flu-like symptoms. Patients should contact their physician or pharmacist if they experience any undesirable effects. Depression may occur in patients with relapsing-remitting multiple sclerosis and may occur while patients are taking Rebif®. Patients should be asked to contact their physician should they feel depressed. Patients should be advised not to stop or modify their treatment unless instructed by their physician. Instruction on self-injection technique and procedures: patients treated for relapsing-remitting multiple sclerosis should be instructed in the use of aseptic technique when administering Rebif®. Appropriate instruction for reconstitution of Rebif® and self-injection should be given including careful review of the Rebif® patient leaflet. The first injection should be performed under the supervision of an appropriately qualified healthcare professional. Injection sites should be rotated at each injection. Injections may be given prior to bedtime as this may lessen the perception of side effects. Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture resistant container for disposal of used needles and syringes should be supplied to the patient along with instructions for safe disposal of full containers. In the controlled MS trial reported injection site reactions were commonly reported by patients at one or more times during therapy. In general, they did not require discontinuation of therapy, but the nature and severity of all reported reactions should be carefully assessed. Patient understanding and use of aseptic self-injection technique and procedures should be periodically re-evaluated.

ADVERSE REACTIONS

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

Less frequent adverse reactions include cold sores, stuffy nose, light headedness, mucosal irritation, haematological disorders (leukopenia, lymphopenia, granulocytopenia), and alterations in liver function tests such as elevated SGOT and SGPT. These effects are usually mild and reversible. Tachyphylaxis with respect to most side-effects is well recognized. Fever and flu-like symptoms can be treated with acetaminophen. Depending on the severity and persistence of the side-effects, the dose may be lowered or temporarily interrupted, at the discretion of the physician. Most injection site reactions are mild to moderate. Rare cases of skin ulceration/necrosis at the site of injection have been reported with long term treatment. The most frequently reported adverse events and the most common laboratory abnormalities observed during the placebo-controlled study in relapsing-remitting multiple sclerosis (560 patients, 2 years treatment) are presented in the table below for patients on placebo and Rebif® (Interferon beta-1a). The frequencies are patients who reported this event at least once during the study, as a *percentage of the total number of patients, by study-arm.*

	Placebo	Rebif® 66 mcg weekly	Rebif® 132 mcg weekly
Adverse Events			
Injection site disorders (all)	**38.5**	**89.9**	**92.4**
Upper respiratory tract infections	**85.6**	**75.1**	**74.5**
Headache	62.6	64.6	70.1
Flu-like symptoms	51.3	56.1	58.7
Fatigue	35.6	32.8	41.3
Depression	27.8	20.6	23.9
Fever	**15.5**	**24.9**	**27.7**
Back pain	21.4	19.6	23.4
Myalgia	19.8	24.9	25.0
Nausea	23.0	24.9	24.5
Insomnia	21.4	19.6	23.4
Diarrhoea	18.7	17.5	19.0
Laboratory Test Abnormalities			
Lymphopenia	11.2	20.1	28.8
Leukopenia	3.7	12.7	22.3
Granulocytopenia	3.7	11.6	15.2
AST increase	3.7	10.1	17.4
ALT increase	4.3	19.6	27.2

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

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

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

Body System	Preferred term	Placebo (n=187)	Rebif® 66 mcg weekly (n=189)	Rebif® 132 mcg weekly (n=184)
Application Site Disorders	Injection site inflammation (a)(b)	15.0%	65.6%	65.8%
	Injection site reaction (a)(b)	13.4%	31.2%	34.8%
	Injection site pain (b)	14.4%	20.1%	22.8%
Body as a Whole - General Disorders	Influenza-like symptoms	51.3%	56.1%	58.7%
	Fatigue	35.8%	32.8%	41.3%
	Fever (a)(b)	15.5%	24.9%	27.7%
	Leg pain	14.4%	10.1%	13.0%
	Rigors(b)(c)	5.3%	6.3%	13.0%
Centr & Periph Nervous System Disorders	Headache	62.6%	64.6%	70.1%
	Dizziness	17.6%	14.3%	16.3%
	Paraesthesia	18.7%	19.6%	16.3%
	Hypoaesthesia	12.8%	12.2%	7.6%
Respiratory System Disorders	Rhinitis	59.9%	52.4%	50.5%
	Upper Resp Tract Infection	32.6%	36.0%	29.3%
	Pharyngitis (b)	38.5%	34.9%	28.3%
	Coughing	21.4%	14.8%	19.0%
	Bronchitis	9.6%	10.6%	9.2%
Gastro-Intestinal System Disorders	Nausea	23.0%	24.9%	24.5%
	Abdominal pain	17.1%	22.2%	19.6%
	Diarrhoea	18.7%	17.5%	19.0%
	Vomiting	12.3%	12.7%	12.0%
Musculo-Skeletal System Disorders	Back pain	19.8%	23.3%	24.5%
	Myalgia	19.8%	24.9%	25.0%
	Arthralgia	17.1%	15.3%	19.0%
	Skeletal pain	10.2%	14.8%	9.8%
Psychiatric Disorders	Depression	27.8%	20.6%	23.9%
	Insomnia	21.4%	19.6%	23.4%
White Cell & Res Disorders	Lymphopenia (a)(b)	11.2%	20.1%	28.8%
	Leucopenia (a)(b)(c)	3.7%	12.7%	22.3%
	Granulocytopenia (a)(b)	3.7%	11.6%	15.2%
	Lymphadenopathy	8.0%	11.1%	12.0%
Skin & Appendages Disorders	Pruritus	11.8%	9.0%	12.5%
Liver & Biliary System Disorders	SGPT increased (a)(b)	4.3%	19.6%	27.2%
	SGOT increased (a)(b)(c)	3.7%	10.1%	17.4%
Urinary System Disorders	Urinary tract infection	18.7%	18.0%	16.8%
Vision Disorders	Vision abnormal	7.0%	7.4%	13.0%
Secondary Terms	Fall	16.0%	16.9%	15.8%

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

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

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

Percentage of patients positive for neutralizing antibodies

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

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

Condyloma acuminata

Most common adverse events for patients treated for Condyloma acuminatum

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

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

DOSAGE AND ADMINISTRATION:

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

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

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

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

Reconstitution Table

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

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

CONDYLOMA ACUMINATUM: The recommended posology is 3.67 mcg (1MIU) per lesion three times per week for 3 weeks. The recommended route of administration is intra- or peri-lesional. The pre-filled syringes are not to be used for this indication.

Preparation of Solution: Lyophilized formulation (Condyloma acuminatum) Reconstitute the contents of a vial of Rebif® in sterile diluent in order to obtain a final concentration of 3.7 mcg per 0.1 mL solution. The reconstituted solution should be used immediately.

Reconstitution Table

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

COMPOSITION

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

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

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

Liquid formulation

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

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

STABILITY AND STORAGE RECOMMENDATIONS

Lyophilized formulation: Refer to the date indicated on the labels for the expiry date. Rebif® (Interferon beta-1a) lyophilized product should be stored at 2–8°C.

Liquid formulation: Refer to the date indicated on the labels for the expiry date. Rebif® liquid in a pre-filled syringe should be stored at 2–8°C. Rebif® syringes may be stored for a limited period at room temperature (up to 25°C), but not more than 1 month. Do not freeze.

RECONSTITUTED SOLUTIONS

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

Liquid formulation: The liquid in the prefilled syringe is ready for use.

PARENTERAL PRODUCTS

See "Preparation of Solution" for table of reconstitution.

AVAILABILITY OF DOSAGE FORM

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

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

The route of administration for Relapsing-Remitting Multiple Sclerosis is subcutaneous . The route of administration for condyloma acuminatum is intra- and peri-lesional.

References: 1. The PRISMS (Prevention of Relapses and Disability by Interferon Beta-1a in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon ß-1a in relapsing/remitting multiple sclerosis. *Lancet*, 1998;352: 1498–504. 2. Rebif® Product Monograph, June 8, 2001. Serono Canada Inc. 3. IMS Canada: Canadian Compuscript March 2002, Canadian Drugstore and Hospital Audit February 2002.

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IMITREX®
SUMATRIPTAN SUCCINATE
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25 mg, 50 mg and 100 mg Tablet
6 mg Subcutaneous Injection and Autoinjector
5 mg and 20 mg Nasal Spray

THERAPEUTIC CLASSIFICATION
Migraine Therapy

PHARMACOLOGIC CLASSIFICATION
5-HT_1 Receptor Agonist

INDICATIONS AND CLINICAL USES
IMITREX® (sumatriptan succinate/sumatriptan) is indicated for the acute treatment of migraine attacks with or without aura.
IMITREX® is not for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine (see CONTRAINDICATIONS). Safety and efficacy have not been established for cluster headache which is present in an older, predominantly male population.

CONTRAINDICATIONS
IMITREX® (sumatriptan succinate/sumatriptan) is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease) should not receive IMITREX®. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS).
Because IMITREX® may increase blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension. Concurrent administration of MAO inhibitors or use within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see PRECAUTIONS: Drug Interactions).
Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because IMITREX® may also cause coronary vasospasm and these effects may be additive, the use of IMITREX® within 24 hours before or after treatment with other 5-HT_1 receptor agonists, or ergotamine-containing drugs or their derivatives (eg. dihydroergotamine, methysergide) is contraindicated.
IMITREX® should not be administered to patients with severe hepatic impairment.
IMITREX® is contraindicated in patients with hemiplegic, basilar, or ophthalmoplegic migraine.
IMITREX® is contraindicated in patients with hypersensitivity to sumatriptan or any of the ingredients of the formulations.
IMITREX® Injection should not be given intravenously because of its potential to cause coronary vasospasm.

WARNINGS
IMITREX® (sumatriptan succinate/sumatriptan) should only be used where a clear diagnosis of migraine has been established.
Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: IMITREX® has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. In rare cases, the symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of IMITREX®. IMITREX® should not be given to patients who have documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). **It is strongly recommended that IMITREX® not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female who is surgically or physiologically postmenopausal, or male who is over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, IMITREX® should not be administered (see CONTRAINDICATIONS).**
For patients with risk factors predictive of CAD, who are considered to have a satisfactory cardiovascular evaluation, the first dose of IMITREX® should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining electrocardiograms in patients with risk factors during the interval immediately following IMITREX® administration on the first occasion of use. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.
Intermittent long term users of IMITREX® who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluations over the course of treatment.
If symptoms consistent with angina occur after the use of IMITREX®, ECG evaluation should be carried out to look for ischemic changes. ***The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to IMITREX®.***
Cardiac Events and Fatalities Associated with 5-HT_1 Agonists: IMITREX® can cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low. The fact that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to IMITREX® use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.
Premarketing Experience With IMITREX®: Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral IMITREX®, two experienced clinical adverse events shortly after receiving oral IMITREX® that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.
Among the more than 1900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous IMITREX®, there were eight patients who sustained clinical events during or shortly after receiving IMITREX® that may have reflected coronary artery vasospasm. Six of these eight patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these eight patients, four had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.
Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of IMITREX® nasal spray, one patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.
Postmarketing Experience With IMITREX®: Serious cardiovascular events, some resulting in death, have been reported in association with the use of IMITREX® Injection or IMITREX® Tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by IMITREX® or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of IMITREX® and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of IMITREX®.
Cardiac events that have been observed to have onset within 1 hour of IMITREX® administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.
Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among reports from the USA of serious cardiac events occurring within 1 hour of IMITREX® administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).
Cerebrovascular Events and Fatalities with 5-HT_1 Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous IMITREX®, and some have resulted in fatalities. The relationship of IMITREX® to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, IMITREX® having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. IMITREX® should not be administered if the headache being experienced is atypical for the patient. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). If a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given.
Special Cardiovascular Pharmacology Studies: In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT_1 agonist at a subcutaneous dose of 1.5 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%), increase in coronary resistance (~20%), and decrease in hyperemic myocardial blood flow (~10%) were noted. The relevance of these findings to the use of the recommended oral doses of this 5-HT_1 agonist is not known.
Similar studies have not been done with IMITREX®. However, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.
Hypersensitivity: Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as IMITREX®. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS). Owing to the possibility of cross-reactive hypersensitivity reactions, IMITREX® should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists. There have been reports of patients with known hypersensitivity to sulphonamides exhibiting an allergic reaction following administration of IMITREX®. Reactions ranged from cutaneous hypersensitivity to anaphylaxis.
Other Vasospasm Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of IMITREX® to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.
Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. IMITREX® is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS). In patients with controlled hypertension, IMITREX® should be administered with caution as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

PRECAUTIONS
Cluster Headache: There is insufficient information on the efficacy and safety of IMITREX® (sumatriptan succinate/sumatriptan) in the treatment of cluster headache, which is present in an older, predominantly male population. The need for prolonged use and the demand for repeated medication in this condition renders the dosing information inapplicable for cluster headache.
Cardiovascular: Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) has been reported after administration of IMITREX®. Because 5-HT_1 agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following IMITREX® should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following IMITREX® should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS AND WARNINGS).
Neurological Conditions: Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of IMITREX®.
Seizures: Caution should be observed if IMITREX® is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold.
Psychomotor Impairment: Patients should be cautioned that drowsiness may occur as a result of treatment with IMITREX®. They should be advised not to perform skilled tasks (e.g. driving or operating machinery) if drowsiness occurs.
Renal Impairment: The effects of renal impairment on the efficacy and safety of IMITREX® have not been evaluated. Therefore IMITREX® is not recommended in this patient population.
Hepatic Impairment: The effect of hepatic impairment on the efficacy and safety of IMITREX® has not been evaluated, however, the pharmacokinetic profile of sumatriptan in patients with moderate[1] hepatic impairment shows that these patients, following an oral dose of 50 mg, have much higher plasma sumatriptan concentrations than healthy subjects (Table 2). Therefore, an oral dose of 25 mg may be considered in patients with hepatic impairment.

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

Parameter	Mean Ratio (hepatic impaired/healthy) n=8	90% CI	p-value
AUC^{∞}	181%	130 to 252%	0.009*
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. However, sumatriptan should not be administered to patients with severe hepatic impairment (see CONTRAINDICATIONS).
Drug Interactions: Single dose pharmacokinetic drug interaction studies have not shown evidence of interactions with propranolol, flunarizine, pizotifen or alcohol. Multiple dose interaction studies have not been performed. The pharmacokinetics of sumatriptan nasal spray were unaltered when preceded by a single clinical dose of the nasal decongestant xylometazoline (Otrivin®[2]).
Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis for these effects being additive, ergot-containing or ergot-type medications (like dihydroergotamine or methysergide) are contraindicated within 24 hours of IMITREX® administration (see CONTRAINDICATIONS).
MAO Inhibitors: In studies conducted in a limited number of patients, MAO inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of IMITREX® in patients receiving MAO inhibitors is contraindicated (see CONTRAINDICATIONS).
Other Serotonergic Drugs: Rare postmarketing reports describe patients with weakness, hyperreflexia, and incoordination following the combined use of a selective serotonin reuptake inhibitor (SSRI) and 5-HT_1 agonists. If concomitant treatment with IMITREX® and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline), tricyclic antidepressant, or other drug with serotonergic activity is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised.
Other 5-HT_1 agonists: The administration of IMITREX® with other 5-HT_1 agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with co-administration of 5-HT_1 agonists, use of these drugs within 24 hours of each other is contraindicated.
Drug/Laboratory Test Interactions: IMITREX® is not known to interfere with commonly employed clinical laboratory tests.
Use in Elderly (>65 years): Experience with the use of IMITREX® in patients aged over 65 years is limited. Therefore the use of IMITREX® in patients over 65 years is not recommended.
Use in Children (<18 years): The safety and efficacy of IMITREX® in children has not been established and its use in this age group is not recommended.
Use in Pregnancy: Reproduction studies, performed in rats, have not revealed any evidence of impaired fertility, teratogenicity, or post-natal development due to IMITREX®. Reproduction studies, performed in rabbits by the oral route, have shown increased incidence of variations in cervico-thoracic blood vessel configuration in the foetuses. These effects were only seen at the highest dose tested, which affected weight gain in the dams, and at which blood levels were in excess of 50 times those seen in humans after therapeutic doses. A direct association with IMITREX® treatment is considered unlikely but cannot be excluded. Therefore, the use of IMITREX® is not recommended in pregnancy.
In a rat fertility study, oral doses of IMITREX® resulting in plasma levels approximately 150 times those seen in humans after a 6 mg subcutaneous dose and approximately 200 times those seen in humans after a 100 mg oral dose were associated with a reduction in the success of insemination. This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 100 times those in humans by the subcutaneous route and approximately 150 times those in humans by the oral route.
To monitor maternal-foetal outcomes of pregnant women exposed to sumatriptan, a Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-336-2176.
Lactation: Sumatriptan is excreted in human breast milk. Therefore, caution is advised when administering IMITREX® to nursing women. Infant exposure can be minimized by avoiding breast feeding for 24 hours after treatment.
Binding to Melanin Containing Tissues: In rats treated with a single subcutaneous dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Because there could be an accumulation in melanin rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long term ophthalmologic effects.
Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with IMITREX®.

ADVERSE REACTIONS
Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).
Experience in Controlled Clinical Trials with IMITREX®
Typical 5-HT_1 Agonist Adverse Reactions: As with other 5-HT_1 agonists, IMITREX® (sumatriptan succinate/sumatriptan) has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb.
Acute Safety: In placebo-controlled migraine trials, 7,668 patients received at least one dose of IMITREX® (3095 oral, 1432 subcutaneous, 3141 intranasal). The following tables (Tables 3-5) list adverse events occurring in these trials at an incidence of 1% or more in any of the IMITREX® dose groups and that occurred at a higher incidence than in the placebo groups.

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

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

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

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

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

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

*The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.
NR = Not Reported

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

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

*The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.
**Includes patients receiving up to 3 doses of 20 mg

IMITREX® is generally well tolerated. Most of the events were transient in nature and resolved within 45 minutes of subcutaneous administration and within 2 hours of oral or intranasal administration.
Of the 3630 patients treated with IMITREX® Nasal Spray in clinical trials, there was one report of a coronary vasospasm related to IMITREX® administration. Minor disturbances of liver function tests have occasionally been observed with sumatriptan treatment. There is no evidence that clinically significant abnormalities occurred more frequently with sumatriptan than with placebo. Patients treated with IMITREX® rarely exhibit visual disorders like flickering and diplopia. Additionally cases of nystagmus, scotoma and reduced vision have been observed. Very rarely a transient loss of vision has been reported. However, visual disorders may also occur during a migraine attack itself.

DOSAGE AND ADMINISTRATION

General:

IMITREX® (sumatriptan succinate/sumatriptan) is indicated for the acute treatment of migraine headache with or without aura. Sumatriptan should not be used prophylactically. Sumatriptan may be given orally, subcutaneously or as a nasal spray. The safety of treating an average of more than four headaches in a 30 day period has not been established.

In selecting the appropriate formulation for individual patients, consideration should be given to the patient's preference for formulation and the patient's requirement for rapid onset of relief. Significant relief begins about 10-15 minutes following subcutaneous injection, 15 minutes following intranasal administration and 30 minutes following oral administration.
In addition to relieving the pain of migraine, sumatriptan (all formulations) has also been shown to be effective in relieving associated symptoms of migraine (*nausea, vomiting, phonophobia, photophobia*). *Sumatriptan is equally* effective when administered at any stage of a migraine attack. Long term (12-24 months) clinical studies with maximum recommended doses of sumatriptan indicate that there is no evidence of the development of tachyphylaxis, or medication-induced (rebound) headache.

Tablets:

The minimal effective single adult dose of IMITREX® Tablets is 25 mg. The maximum recommended single dose is 100 mg.
The optimal dose is a single 50 mg tablet. However, depending on individual patient's needs and response to treatment, some patients may require 100 mg. Clinical trials have shown that approximately 50 - 75% of patients have headache relief within two hours after oral dosing with 100 mg, and that a further 15 - 25% have headache relief by 4 hours. Comparator studies have shown similar efficacy rates with the 50 mg and 100 mg tablets. There is evidence that doses of 50 and 100 mg may provide greater effect than 25 mg.
If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 2 hours. Not more than 200 mg should be taken in any 24 hour period.
If a patient does not respond to the first dose of IMITREX® Tablets, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. IMITREX® may be taken to treat subsequent migraine attacks.
The tablet should be swallowed whole with water, not crushed, chewed or split.

Hepatic Impairment: In patients with mild or moderate hepatic impairment, plasma sumatriptan concentrations up to two times those seen in healthy subjects have been observed. Therefore, a 25 mg dose (single tablet) may be considered in these patients (see PRECAUTIONS). Sumatriptan should not be administered to patients with severe hepatic impairment (see CONTRAINDICATIONS).

Injection:

IMITREX® Injection should be injected subcutaneously (on the outside of the thigh or in the upper arm) using an autoinjector.
The recommended adult dose of sumatriptan is a single 6 mg subcutaneous injection. Clinical trials have shown that approximately 70-72% of patients have headache relief within one hour after a single subcutaneous injection. This number increases to 82% by 2 hours.
If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 1 hour. Not more than 12 mg (two 6mg injections) should be taken in any 24 hour period.
If a patient does not respond to the first dose of IMITREX® Injection, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. IMITREX® may be taken for subsequent attacks.
Administration during migraine aura prior to other symptoms occurring may not prevent the development of a headache.
Patients should be advised to read the patient instruction leaflet regarding the safe disposal of syringes and needles.

Nasal Spray:

The minimal effective single adult dose of sumatriptan nasal spray is 5 mg. The maximum recommended single dose is 20 mg.
If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 2 hours. Not more than 40 mg should be taken in any 24 hour period.
If a patient does not respond to the first dose of IMITREX® Nasal Spray, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. IMITREX® may be taken for subsequent attacks.
Placebo-controlled clinical trials revealed the following incidence of headache relief, defined as a decrease in migraine severity from severe or moderate to mild or no pain, within 2 hours after treatment with intranasal sumatriptan at doses of 5, 10 or 20 mg (see Table 6 below).

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

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

Headache relief was defined as a decrease in headache severity from severe or moderate to mild or none.
n= total number of patients who received treatment
• comparisons between sumatriptan doses not conducted
√ p≤0.05 versus placebo † p≤0.05 versus lower sumatriptan doses
▲p≤0.05 vs 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.

AVAILABILITY OF DOSAGE FORMS

IMITREX® Tablets are available as pink 100 mg, white 50 mg, or white 25 mg film-coated tablets in blister packs containing 6 tablets. Four blister packs are placed in a carton.
IMITREX® Injection (6 mg; total volume = 0.5 mL) is available in pre-filled syringes placed in a tamper-evident carrying case/disposal case. Two pre-filled syringes plus the IMITREX STATdose Pen™ autoinjector are packed in an IMITREX STATdose System™ autoinjector kit. A refill pack is available containing 2 pre-filled syringes in a carton.
IMITREX® Injection is also available to physicians or hospitals in a single dose vial (6 mg; total volume = 0.5mL). There are 5 vials per carton.
IMITREX® Nasal Spray 5 mg and 20 mg are each supplied in boxes of 6 nasal spray devices (3 x 2 devices). Each unit dose spray supplies 5 and 20 mg respectively.

Product Monograph available to physicians and pharmacists upon request.

Please contact GlaxoSmithKline Inc., 7333 Mississauga Road N., Mississauga, Ontario L5N 6L4.
IMITREX® is a registered trademark, used under license by GlaxoSmithKline Inc. ™The appearance, namely the colour, shape, and size of the IMITREX Nasal Spray device and IMITREX STATdose System are trademarks, used under license by GlaxoSmithKline Inc.

Date of preparation: January 17, 1992
Date of revision: February 14, 2003

References: **1.** Product Monograph of ®IMITREX® (sumatriptan succinate/sumatriptan); GlaxoSmithKline Inc. February 2003. **2.** *Cady R, McNeal S, O'Quinn S, Putman G.* Effect of early intervention with sumatriptan on migraine pain: Retrospective analyses of data from three clinical trials. *Clinical Therapeutics* 2000;22(9):1035-1048.

GlaxoSmithKline
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BRIEF PRESCRIBING INFORMATION

CONSULT FULL PRODUCT MONOGRAPH FOR COMPLETE PRESCRIBING INFORMATION

PrTOPAMAX*
topiramate

25, 100 and 200 mg Tablets and 15 and 25 mg Sprinkle Capsules

Antiepileptic

INDICATIONS AND CLINICAL USE

TOPAMAX (topiramate) is indicated as adjunctive therapy for the management of patients (adults and children two years and older) with epilepsy who are not satisfactorily controlled with conventional therapy.

There is limited information on the use of TOPAMAX in monotherapy at this time.

Geriatrics (> 65 years of age):

There is limited information in patients over 65 years of age. (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

General

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

Endocrine and Metabolism

Oligohidrosis and Hyperthermia

Oligohidrosis (decreased sweating) and hyperthermia, infrequently resulting in hospitalization, have been reported in patients treated with topiramate. Oligohidrosis and hyperthermia may have potentially serious sequelae and may be preventable by prompt recognition of symptoms and appropriate treatment. Decreased sweating and elevation of body temperature above normal characterized the cases reported in patients treated with topiramate. Some of the cases were reported after exposure to elevated environmental temperatures.

These reports have primarily involved children. Patients treated with TOPAMAX, especially pediatric patients, should be monitored closely for evidence of decreased sweating and increased body temperature, particularly in hot weather. Proper hydration before and during activities such as exercise or exposure to warm temperatures is recommended.

Caution should be used when TOPAMAX is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity. (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**)

Nutritional Supplementation

A dietary supplement or increased food intake may be considered if the patient is losing weight while on this medication.

Hepatic/Biliary/Pancreatic

Decreased Hepatic Function

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

Neurologic

Central Nervous System Effects

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

Additional nonspecific CNS effects occasionally observed with TOPAMAX 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, Post-Market Adverse Drug Reactions**).

Paresthesia

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

Ophthalmologic

Acute Myopia and Secondary Angle Closure Glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within a few days to 1 month of initiating TOPAMAX therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with TOPAMAX has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TOPAMAX as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of TOPAMAX, may be helpful (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

In all cases of acute visual blurring and/or painful/red eye(s), immediate consultation with an ophthalmologist/emergency room is recommended.

Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequalae including permanent vision loss.

Renal

Kidney Stones

A total of 32/1,715 (1.5%) of patients exposed to TOPAMAX during its development reported the occurrence of kidney stones, an incidence about 10 times that expected in a similar, untreated population (M/F ratio: 27/1,092 male; 5/623 female). In the general population, risk factors for kidney stone formation include gender (male), ages between 20-50 years, prior stone formation, family history of nephrolithiasis, and hypercalciuria. Based on logistic regression analysis of the clinical trial data, no correlation between mean TOPAMAX dosage, duration of TOPAMAX therapy, or age and the occurrence of kidney stones was established; of the risk factors evaluated, only gender (male) showed a correlation with the occurrence of kidney stones. In the pediatric patients studied, there were no kidney stones observed.

Carbonic anhydrase inhibitors, e.g. acetazolamide, 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 and associated signs and symptoms such as renal colic, renal pain or flank pain. 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.

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}< 70 mL/min/1.73m^2) 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, Dosing Considerations**).

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. Patients also should be instructed to increase and maintain fluid intake prior to and during activities such as exercise and exposure to warm temperatures to help prevent complications from decreased sweating.

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 TOPAMAX to gauge whether it adversely affects their mental and/or motor performance.

Acute Myopia and Secondary Angle Closure Glaucoma

Patients taking TOPAMAX should be told to immediately contact their doctor and/or go to the Emergency Room if they/their child experience(s) sudden worsening of vision, blurred vision or painful/red eye(s).

Special Populations

Pregnant Women:

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.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed *in utero* to TOPAMAX, with or without other anticonvulsants; however, a causal relationship with TOPAMAX has not been established.

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

Nursing Women:

Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Since the potential for serious adverse reactions in nursing infants exposed to TOPAMAX exists, the prescriber should decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother and the risks to the infant.

Pediatrics (<2 years of age):

Safety and effectiveness in children under 2 years of age have not been established.

Weight Loss in Pediatrics (>2 years of age)

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

Geriatrics (>65 years of age):

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.

Monitoring and Laboratory Tests

It has been observed in clinical trials that topiramate treated subjects experienced an average decrease in serum bicarbonate level of 4 mmol/L and an average increase in serum chloride level of 4 mmol/L.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adults

The most commonly observed adverse events associated with the adjunctive use of TOPAMAX (topiramate) at dosages of 200 to 400 mg/day in controlled trials in adults that were seen at greater frequency in patients treated with TOPAMAX 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 1).

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 2).

Pediatrics

Adverse events associated with the use of TOPAMAX at dosages of 5 to 9 mg/kg/day in worldwide pediatric clinical trials that were seen at greater frequency in patients treated with TOPAMAX were: fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease (See Table 3).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials in ADULTS [a,b]

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

Body System/ Adverse Event	TOPAMAX Dosage (mg/day) 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 2: Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Add-On Trials in ADULTS

Adverse Event	TOPAMAX Dosage (mg/day) Placebo (n=216)	200 (n=45)	400 (n=68)	600 - 1,000 (n=414)
Fatigue	13.4	11.1	11.8	29.7
Nervousness	7.4	13.3	17.6	19.3
Difficulty with Concentration/Attention	1.4	6.7	8.8	14.5
Confusion	4.2	8.9	10.3	13.8
Depression	5.6	8.9	7.4	13.0
Anorexia	3.7	4.4	5.9	12.3
Language problems	0.5	2.2	8.8	10.1
Anxiety	6.0	2.2	2.9	10.4
Mood problems	1.9	0	5.9	9.2

In six double-blind clinical trials, 10.6% of subjects (n=113) assigned to a TOPAMAX 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 TOPAMAX in the double-blind trials discontinued due to adverse events, compared to 4% of the subjects (n=216) receiving placebo.

Table 3 lists treatment-emergent adverse events that occurred in at least 2% of children treated with 5 to 9 mg/kg/day TOPAMAX in controlled trials that were numerically more common than in patients treated with placebo.

Table 3: Incidence (%) of Treatment-Emergent Adverse Events in Worldwide Pediatric Clinical Trials Experience (2-16 years of Age)[a,b]
(Events that Occurred in ≥ 2% of Patients Treated with TOPAMAX and Occurred More Frequently in Patients Treated with TOPAMAX Than Placebo-Treated Patients)

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

[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.

[c] Not otherwise specified

None of the pediatric patients who received TOPAMAX adjunctive therapy at 5 to 9 mg/kg/day in controlled clinical trials discontinued due to adverse events. In open extensions of the controlled clinical trials, approximately 9% of the 303 pediatric patients who received TOPAMAX at dosages up to 30 mg/kg/day discontinued due to adverse events. Adverse events associated with discontinuing therapy included aggravated convulsions (2.3%), language problems (1.3%), and difficulty with concentration/attention (1.3%).
When the safety experience of patients receiving TOPAMAX as adjunctive therapy in both double-blind and open-label trials (1,446 adults and 303 children) was analyzed, a similar pattern of adverse events emerged.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse events that occurred less frequently but were considered potentially medically relevant included: taste perversion, cognitive problems (not otherwise specified) and psychosis/psychotic symptoms.
In adult and pediatric patients, nephrolithiasis was reported rarely. Isolated cases of thromboembolic events have also been reported; a causal association with the drug has not been established.
In clinical trials with topiramate, the occurrence rate for all potential cases of oligohidrosis (decreased sweating) was 0.25%.

Post-Market Adverse Drug Reactions

In addition to the adverse experiences reported during clinical trial testing of TOPAMAX, the following adverse experiences have been reported in patients receiving marketed TOPAMAX from worldwide use since approval. There are insufficient data to support an estimate of their incidence or to establish causation.
The most frequently reported adverse events in spontaneous post-marketing reports on TOPAMAX include:
Psychiatric: somnolence or sedation, hallucination(s), depression, anorexia, aggressive reaction, psychosis, thinking abnormal, insomnia, emotional lability, suicide attempt, delusion, amnesia, confusion, nervousness, agitation, concentration impaired, personality disorder, anxiety
Central and Peripheral Nervous System: convulsions aggravated, paresthesia, speech disorder, ataxia, dizziness, convulsions, headache, hyperkinesia, convulsions grand mal
Metabolic and Nutritional: weight decrease, metabolic acidosis, hypokalemia, hyperchloremia
Vision: vision abnormal (includes vision decreased, vision blurred, visual disturbance, visual impairment, amblyopia); rarely reported: diplopia, glaucoma, myopia, eye pain
Gastrointestinal: nausea, diarrhea, abdominal pain, constipation, vomiting
Body as a Whole - General Disorders: fatigue, fever, dehydration, flushing, hot flushes
Urinary System: renal calculus
Skin and Appendages: *rash, alopecia*
White Cell and RES Disorders: leucopenia, thrombocytopenia
Oligohidrosis (decreased sweating) has been rarely reported with the use of TOPAMAX. The majority of spontaneous post-marketing reports have been in children. Adverse events that may be related to potential cases of oligohidrosis include dehydration, hyperthermia, and heat intolerance. Adequate hydration prior to activities such as exercise or exposure to warm temperatures is recommended (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).
To date, there have been rare spontaneous, post-marketing reports of metabolic acidosis. In some cases, acidosis resolved after dosage reduction or upon discontinuation of topiramate.
Rare reports of encephalopathy with or without hyperammonemia have been received for patients treated with TOPAMAX while also taking valproate or other antiepileptic medications (see **DRUG INTERACTIONS**).
Reports of increases in liver function tests in patients taking TOPAMAX with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with TOPAMAX.
Very rare reports have also been received for bullous skin and mucosal reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and pemphigus). The majority of these reports have occurred in patients taking other medications that can be associated with bullous skin and mucosal reactions.

DRUG INTERACTIONS

Drug-Drug Interactions

Antiepileptic Drugs

Effects of TOPAMAX on Other Antiepileptic Drugs

Potential interactions between TOPAMAX and standard AEDs were measured in controlled clinical pharmacokinetic studies in patients with epilepsy. The addition of TOPAMAX to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of TOPAMAX to phenytoin may result in an increase of plasma concentrations of phenytoin.
The effect of TOPAMAX 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 (CYP2C$_{max}$)*.
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.

Effects of Other Antiepileptic Drugs on TOPAMAX

Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX may require adjustment of the dose of TOPAMAX. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of topiramate, and therefore, does not warrant dosage adjustment of TOPAMAX.
Rare post-marketing reports of encephalopathy with or without hyperammonemia have been received for patients treated with TOPAMAX while also taking valproate or other antiepileptic medications. Thus, caution is advised when polytherapy with valproate is necessary (see **ADVERSE REACTIONS, Post-Market Adverse Reactions**).
The effects of these interactions on plasma concentrations are summarized in Table 4.

Table 4: Drug Interactions with TOPAMAX Therapy

AED Co-administered	AED Concentration	Topiramate 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 (< 15% change)
** 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

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 a pharmacokinetic interaction study, epileptic patients received TOPAMAX as adjunctive therapy with valproic acid and a combination oral contraceptive product containing norethindrone (1 mg) plus ethinyl estradiol (35μ). In this study, 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 of topiramate, respectively. Consequently, the efficacy of low-dose (e.g. 20 μ oral contraceptives may be reduced in this situation. Patients taking oral contraceptives should receive a preparation containing not less than 30 μ of estrogen. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.
Metformin: A drug-drug interaction study conducted in 18 healthy volunteers, ages 18-37, evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin (500 mg b.i.d.) was given alone and when metformin and topiramate (50, 75 and 100 mg) were given simultaneously for 6 consecutive days. The results of this study indicated that metformin mean C_{ss} and mean AUC_{0-12h} increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with TOPAMAX (up-titrated to 100 mg b.i.d.). TOPAMAX did not affect metformin $t_{1/2}$. The effects of higher doses of topiramate (>100 mg b.i.d.) on metformin are unknown. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When TOPAMAX is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.
Others: Concomitant use of TOPAMAX, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g. acetazolamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided if possible.

Drug-Food Interactions

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

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients with renal impairment
- Patients undergoing hemodialysis
- Patients with hepatic disease

Recommended Dose and Dosage Adjustment

TOPAMAX (topiramate) Tablets or Sprinkle Capsules can be taken without regard to meals.

Adults (Age 17 years and older)

It is recommended that TOPAMAX as adjunctive therapy be initiated at 50 mg/day, followed by titration as needed and tolerated to an effective dose. At weekly intervals, the dose may be increased by 50 mg/day and taken in two divided doses. Some patients may benefit from lower initial doses, e.g. 25 mg and/or a slower titration schedule. Some patients may achieve efficacy with once-a-day dosing.
The recommended total daily maintenance dose is 200–400 mg/day in two divided doses. Doses above 400 mg/day have not been shown to improve responses and have been associated with a greater incidence of adverse events. The maximum recommended dose is 800 mg/day. Daily doses above 1,600 mg have not been studied.

Children (Ages 2-16 years)

It is recommended that TOPAMAX as adjunctive therapy be initiated at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week followed by titration as needed and tolerated to an effective dose. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses). Some patients may benefit from lower initial doses and/or a slower titration schedule.
The recommended total daily maintenance dose is approximately 5 to 9 mg/kg/day in two divided doses. Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

Geriatrics

See **WARNINGS AND PRECAUTIONS** section.

Patients with Renal Impairment

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

Patients Undergoing Hemodialysis

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

Patients with Hepatic Disease

In hepatically impaired patients, topiramate plasma concentrations are increased approximately 30%. This moderate increase is not considered to warrant adjustment of the TOPAMAX 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.

Missed Dose

The missed dose should be taken as soon as possible. If it is almost time for the next dose, the missed dose should not be taken. Instead, the next scheduled dose should *be taken. Doses should not be doubled.*

Administration

Tablets should not be broken. TOPAMAX Sprinkle Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use. The sprinkle formulation is provided for those patients who cannot swallow tablets, e.g. pediatric and the elderly.

OVERDOSAGE

Ingestion of between 6 and 40 g topiramate has been reported in a few patients. Signs and symptoms included: headache, agitation, drowsiness, lethargy, metabolic acidosis and hypokalemia. The clinical consequences were not severe. All patients recovered.
A patient who ingested a dose calculated to be between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.
General supportive measures are indicated and an attempt should be made to remove undigested drug from the gastrointestinal tract using gastric lavage or activated *charcoal. Hemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.*

DOSAGE FORMS AND PACKAGING

Availability of Dosage Forms

TOPAMAX (topiramate) is available as embossed, round, coated tablets in the following strengths and colours: 25 mg white, 100 mg yellow and 200 mg salmon. They are marked as follows:

25 mg:	"TOP" on one side; "25" on the other.
100 mg:	"TOP" on one side; "100" on the other.
200 mg:	"TOP" on one side; "200" on the other.
Supplied:	25 mg tablets in bottles of 100 with desiccant.
	100 and 200 mg tablets in bottles of 60 with desiccant.

TOPAMAX (topiramate) Sprinkle Capsules contain small white to off-white spheres. The gelatin capsules are white and clear. They are marked as follows:

15 mg:	"TOP" and "15 mg" on the side.
25 mg:	"TOP" and "25 mg" on the side.
Supplied:	Bottles of 60 capsules without desiccant.

TOPAMAX is a Schedule F drug.
Product Monograph available upon request.

JANSSEN-ORTHO

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TXBP041005A 8011

See pages A-8, A-9

Brief Prescribing Information

BETASERON®

Interferon beta-1b

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

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

General: Interferons are a family of naturally occurring proteins, which have molecular weights ranging from 15,000 to 21,000 daltons. Three major classes of interferons have been identified: alpha, beta, and gamma. Interferon beta-1b, interferon alpha, and interferon gamma have overlapping yet distinct biologic activities. The activities of interferon beta 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.

INDICATIONS AND CLINICAL USE

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

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

The safety and efficacy of BETASERON in primary progressive MS have not been evaluated.

CONTRAINDICATIONS

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

WARNINGS

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

In the RR-MS clinical trial, one suicide and four attempted suicides were observed among 372 study patients during a 3-year period. All five patients received BETASERON (interferon beta-1b) (three in the 0.05 mg [1.6 MIU] group and two in the 0.25 mg [8.0 MIU] group). There were no attempted suicides in patients on study who did not receive BETASERON. In the SP-MS study there were 5 suicide attempts in the placebo group and 3 in the BETASERON group including one patient in each group who committed suicide. Depression and suicide have been reported to occur in patients receiving interferon alpha, a related compound. Patients treated with BETASERON should be informed that depression and suicidal ideation may be a side effect of the treatment and should report these symptoms immediately to the prescribing physician. Patients exhibiting depression should be monitored closely and cessation of therapy should be considered.

PRECAUTIONS

General: Rare cases of cardiomyopathy have been reported. If this occurs, and a relationship to BETASERON (interferon beta-1b) is suspected, treatment should be discontinued.

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

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

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

Instruction on Self-injection Technique and Procedures: It is recommended that the first injection be administered by, or under the direct supervision of, a physician. Appropriate instructions for reconstitution of BETASERON and self-injection, using aseptic techniques, should be given to the patient. A careful review of the **BETASERON® INFORMATION FOR THE PATIENT** section is also recommended.

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

Overall, 80% of patients in the two controlled clinical trials reported injection site reactions at one or more times during therapy. Post-marketing experience has been consistent with this finding, with infrequent reports of injection site necrosis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

Laboratory abnormalities included:

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

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

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

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

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

- injection site reaction (85%),
- lymphocyte count < 1500/mm^3 (82%),
- ALT (SGPT) > 5 times baseline value (19%),
- absolute neutrophil count < 1500/mm^3 (18%),
- menstrual disorder (17%),
- WBC < 3000/mm^3 (16%),
- palpitation (8%),
- dyspnea (8%),
- cystitis (8%),
- hypertension (7%),
- breast pain (7%),
- tachycardia (6%),
- gastrointestinal disorders (6%),
- total bilirubin > 2.5 times baseline value (6%),
- somnolence (6%),
- laryngitis (6%),
- pelvic pain (6%),
- menorrhagia (6%),
- injection site necrosis (5%), and
- peripheral vascular disorders (5%).

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

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

The table that follows enumerates adverse events and laboratory abnormalities that occurred at an incidence of 2% or more among the 124 MS patients treated with 0.25 mg (8 MIU) BETASERON every other day for periods of up to 3 years in the controlled trial and at an incidence that was at least 2% more than that observed in the 123 placebo patients. Reported adverse events have been re-classified using the standard COSTART glossary to reduce the total number of terms employed in Table 1. In the following table, terms so general as to be uninformative, and those events where a drug cause was remote have been excluded.

Table 1: Adverse Events and Laboratory Abnormalities

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

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

* significantly associated with BETASERON treatment ($p<0.05$)

It should be noted that the figures cited in Table 1 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. The cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

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

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

Adverse Event	Placebo n=358	0.25 mg (8 MIU) n=360
Body as a Whole		
Asthenia	58%	63%
Flu syndrome*	40%	61%
Pain	25%	31%
Fever*	13%	40%
Back pain	24%	26%
Accidental injury	17%	14%
Chills*	7%	23%
Pain in Extremity	12%	14%
Infection	11%	13%
Abdominal pain*	6%	11%
Malaise	5%	8%
Neck pain	6%	5%
Abscess*	2%	4%
Laboratory test abnormal	1%	3%
Allergic reaction	3%	2%
Chills and fever*	0%	3%
Thorax pain	2%	1%

*significantly associated with BETASERON treatment ($p<0.05$)

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

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

Lymphopenia ($<1500/mm^3$) was observed in 90.9% of BETASERON patients compared to 74.3% of placebo patients and neutropenia ($<1400/mm^3$) was noted in 18.0% BETASERON and 5.1% placebo patients.

DOSAGE AND ADMINISTRATION FOR SUBCUTANEOUS USE ONLY

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

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

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

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

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

Withdraw 1 mL of reconstituted solution from the vial into a sterile syringe fitted with a 27-gauge ½-inch 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 (See **BETASERON® [interferon beta-1b] INFORMATION FOR THE PATIENT** section for **SELF-INJECTION PROCEDURE**.)

AVAILABILITY OF DOSAGE FORMS

BETASERON (interferon beta-1b) is presented in single-use vials of lyophilized powder containing 0.3 mg (9.6 MIU) interferon beta-1b, 15 mg Albumin Human USP, and 15 mg Mannitol, 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).

Product Monograph available upon request.
B10204E5

REFERENCES:

1. Data on file. Berlex Canada Inc., 1999.
2. Product Monograph of PrBETASERON® (interferon beta-1b), Berlex Canada, June 1999.
3. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomised controlled trial. *Neurology* 1995; 45:1227-1285.

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power you can **trust**™

®LIPITOR®
(atorvastatin calcium)
10 mg, 20 mg, 40 mg and 80 mg tablets

THERAPEUTIC CLASSIFICATION: Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

LIPITOR (atorvastatin calcium) is a synthetic lipid-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake and catabolism of Low Density Lipoprotein (LDL).

LIPITOR reduces LDL-Cholesterol (LDL-C) and the number of LDL particles. LIPITOR also reduces Very Low Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated serum cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Low serum concentration of HDL-C is also an independent risk factor. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Epidemiologic, clinical and experimental studies have established that high LDL-C, low HDL-C and high plasma TG promote human atherosclerosis and are risk factors for developing cardiovascular disease. Some studies have also shown that the ratio of total cholesterol (total-C) to HDL-C (total-C/HDL-C) is the best predictor of coronary artery disease. In contrast, increased levels of HDL-C are associated with decreased cardiovascular risk. Drug therapies that reduce levels of LDL-C or decrease TG while simultaneously increasing HDL-C have demonstrated reductions in rates of cardiovascular mortality and morbidity.

Pharmacokinetics

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions.

Mean distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. Atorvastatin is extensively metabolized by cytochrome P-450 3A4 to ortho- and para-hydroxylated derivatives and to various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites.

INDICATIONS AND CLINICAL USE

LIPITOR (atorvastatin calcium) is indicated as an adjunct to lifestyle changes, including diet, (at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet), for the reduction of elevated total cholesterol, (total-C), LDL-C, TG and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

- Primary hypercholesterolemia (Type IIa);
- Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern;
- Dysbetalipoproteinemia (Type III);
- Hypertriglyceridemia (Type IV);
- Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.

LIPITOR also raises HDL-cholesterol and therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios in patients with primary hypercholesterolemia and combined (mixed) hyperlipidemia (Fredrickson Type IIa and IIb dyslipidemia). In pooled data from 24 controlled clinical trials, LIPITOR raised HDL-C levels 5%-7% in primary hypercholesterolemic (type IIa) patients and 10%-15% in mixed (type IIb) dyslipidemic patients.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly to moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25 - 56%) and LDL-C levels (23 - 40%). LIPITOR has not been studied in conditions where the major abnormality is elevation of chylomicrons (TG levels > 11 mmol/L), i.e. types I and V.

In an open-label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and IDL-C + VLDL-C levels (34-58%).

In an open label study in patients with homozygous familial hypercholesterolemia (FH) LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients (see PHARMACOLOGY, Clinical Studies).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACOLOGY, Clinical Studies.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

$$\text{LDL-C (mmol/L)} = \text{total-C} - [(0.37 \times \text{(TG)}) + \text{HDL-C})]$$

$$\text{LDL-C (mg/dL)} = \text{total-C} - [(0.2 \times \text{(TG)}) + \text{HDL-C})]^1$$

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

Patients with high or very high triglyceride levels, i.e. > 2.2 mmol/L (200 mg/dL) or > 5.6 mmol/L (500 mg/dL), respectively, may require triglyceride-lowering therapy (fenofibrate, bezafibrate or nicotinic acid) alone or in combination with LIPITOR.

In general, combination therapy with fibrates must be undertaken cautiously and only after risk-benefit analysis (see WARNINGS, Muscle Effects; PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions).

Elevated serum triglycerides are most often observed in patients with the metabolic syndrome (abdominal obesity, atherogenic dyslipidemia [elevated triglycerides, small dense LDL particles and low HDL-cholesterol], insulin resistance with or without glucose intolerance, raised blood pressure and prothrombic and proinflammatory states).

(For the treatment of specific dyslipidemias refer to the Report of the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias or to the US NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III], under SELECTED BIBLIOGRAPHY).

When drugs are prescribed attention to therapeutic lifestyle changes (reduced intake of saturated fats and cholesterol, weight reduction, increased physical activity, ingestion of soluble fibers) should always be maintained and reinforced.

The Atorvastatin Versus Revascularization Treatments (AVERT) study examined the effect of intensive lipid-lowering in patients with stable coronary artery disease and LDL-C at least 3.0 mmol/L in patients referred for percutaneous transluminal coronary angioplasty (PTCA). Patients were randomised for 18 months to LIPITOR 80 mg daily or to PTCA with usual medical care which could include lipid metabolism regulators. The results of the AVERT study should be considered as exploratory since several limitations may affect its design and conduct. In the medical-treated group with LIPITOR there was a trend for a reduced incidence of ischemic events and a delayed time to first ischemic event. The results also suggest that intensive treatment to target LDL-C levels with LIPITOR is **additive and complementary** to angioplasty and would benefit patients referred for this procedure (see SELECTED BIBLIOGRAPHY).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme. (See WARNINGS, Muscle effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450-mediated Interactions).

Hepatic Effects

In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in <1% of patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR; if such a condition should develop during therapy, the drug should be discontinued.

Muscle Effects

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatinine phosphokinase (CPK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of pharmacokinetic studies conducted in healthy subjects with erythromycin and clarithromycin, the benefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions).

Rhabdomyolysis has been reported in very rare cases with LIPITOR (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been reported with HMG-CoA reductase inhibitors. LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

Effect on the Lens

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Effect on Ubiquinone (CoQ_{10}) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY).

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) lipoprotein concentrations. Present knowledge suggests the importance of high Lp(a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high risk patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY).

Hypersensitivity

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

Use in Pregnancy

LIPITOR is contraindicated during pregnancy (see CONTRAINDICATIONS).

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause harm to the fetus when administered to pregnant women.

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

Nursing Mothers

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Geriatric Use

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see PHARMACOLOGY, Human Pharmacokinetics; SELECTED BIBLIOGRAPHY).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects; PRECAUTIONS, Drug Interactions).

Refer also to DOSAGE AND ADMINISTRATION.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

1. Friedewald WT, *et al. Clin Chem* 1972;18(6):489-502.

Pharmacokinetic Interaction Studies and Potential Drug Interactions

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see also Geriatric Use; Renal Insufficiency; Patients with Severe Hypercholesterolemia).

Concomitant Therapy with Other Lipid Metabolism Regulators: Combined drug therapy should be approached with caution as information from controlled studies is limited.

Bile Acid Sequestrants:

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to that with LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone.

However, the combination drug therapy was less effective in lowering the triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid): Although there is limited experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class, including atorvastatin, is increased with concurrent administration (see WARNINGS, Muscle Effects and SELECTED BIBLIOGRAPHY).

Coumarin Anticoagulants: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTED BIBLIOGRAPHY).

Digoxin: In healthy subjects, digoxin pharmacokinetics at steady-state were not significantly altered by coadministration of digoxin 0.25 mg and LIPITOR 10 mg daily. However, digoxin steady-state concentrations increased approximately 20% following *coadministration of digoxin 0.25 mg and LIPITOR 80 mg daily (see Human Pharmacokinetics). Patients taking digoxin should be* monitored appropriately.

Antihypertensive agents (amlodipine): In clinical studies, LIPITOR was used concomitantly with antihypertensive agents without evidence to date of clinically significant adverse interactions. In healthy subjects, atorvastatin pharmacokinetics were not altered by the coadministration of LIPITOR 80 mg and amlodipine 10 mg at steady state (see Human Pharmacokinetics).

(quinapril): In a randomized, open-label study in healthy subjects, steady-state quinapril dosing (80 mg QD) did not significantly affect the pharmacokinetic profile of atorvastatin tablets (10 mg QD) (see Human Pharmacokinetics).

Oral Contraceptives and Hormone Replacement Therapy: Coadministration of LIPITOR with an oral contraceptive, containing 1 mg norethindrone and 35 µg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive. In clinical studies, LIPITOR was used concomitantly with estrogen replacement therapy without evidence to date of clinically significant adverse interactions.

Antacids: Administration of aluminum and magnesium based antacids, such as Maalox, TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Cimetidine: Administration of cimetidine with LIPITOR did not alter plasma concentrations or LDL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, some macrolide antibiotics (i.e. erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), protease inhibitors, or the antidepressant, nefazodone, may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY). Caution should thus be exercised with concomitant use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Endocrine Function; DOSAGE AND ADMINISTRATION; SELECTED BIBLIOGRAPHY).

In healthy subjects, coadministration of maximum doses of both atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g. preexisting prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION).

Antipyrine: Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin): In healthy adults, coadministration of LIPITOR (10 mg QD) and azithromycin (500 mg QD) did not significantly alter the plasma concentrations of atorvastatin. However, coadministration of atorvastatin (10 mg QD) with erythromycin (500 mg QID) or clarithromycin (500 mg BID), which are both CYP 3A4 inhibitors, increased plasma concentrations of atorvastatin approximately 40% and 80%, respectively (see WARNINGS, Muscle Effects; Human Pharmacokinetics).

Protease Inhibitors (nelfinavir mesylate): In healthy adults, coadministration of nelfinavir mesylate (1250 mg BID), a known CYP 3A4 inhibitor, and atorvastatin (10 mg QD) resulted in increased plasma concentrations of atorvastatin. AUC and Cmax of atorvastatin were increased by 74% and 122% respectively.

Patients with Severe Hypercholesterolemia: Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions; DOSAGE AND ADMINISTRATION).**

Drug/Laboratory Test Interactions

LIPITOR may elevate serum transaminase and creatinine phosphokinase levels (from skeletal muscle). In the differential diagnosis *of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined.*

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

TABLE 1. Associated Adverse Events Reported in ≥1% of Patients in Placebo-Controlled Clinical Trials

	Placebo % (n=270)	LIPITOR % (n=1122)
GASTROINTESTINAL		
Constipation	1	1
Diarrhea	1	1
Dyspepsia	2	1
Flatulence	2	1
Nausea	0	1
NERVOUS SYSTEM		
Headache	2	1
MISCELLANEOUS		
Pain	<1	1
Myalgia	1	1
Asthenia	<1	1

The following additional adverse events were reported in clinical trials; not all events listed below have been associated with a causal relationship to LIPITOR therapy: Muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia.

Post-marketing experience: Very rare reports: severe myopathy with or without rhabdomyolysis (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Drug Interactions). Isolated reports: thrombocytopenia, arthralgia and allergic reactions including urticaria, angioneurotic edema, anaphylaxis and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis)]. These may have no causal relationship to atorvastatin.

Ophthalmologic observations: see PRECAUTIONS.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet] before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented.

Primary Hypercholesterolemia and Combined (Mixed) Dyslipidemia, Including Familial Combined Hyperlipidemia

The recommended starting dose of LIPITOR is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of LIPITOR is 10 to 80 mg once daily. Doses can be given at any time of the day, with or without food, and should preferably be given in the evening. Doses should be individualized according to the level of risk; the baseline LDL-C and/or TG levels; the LDL-C, TG and/or total-C/HDL-C targets (see the Detection and Management of Hypercholesterolemia, Working Group on Hypercholesterolemia and other Dyslipidemias [Canada] and/or the US National Cholesterol Education Program [NCEP Adult Treatment Panel III]); the goal of therapy; and the patient's response. A significant therapeutic response is evident within two weeks, and the maximum response is usually achieved within two to four weeks. The response is maintained during chronic therapy. Adjustments of dosage, if necessary, should be made at intervals of two to four weeks. The maximum dose is 80 mg/day.

Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

The following reductions in total cholesterol and LDL-C levels have been observed in 2 dose-response studies, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia:

TABLE 2. Dose-Response in Patients With Mild to Moderate Hypercholesterolemia
(Mean Percent Change from Baseline)[a]

Lipid Parameter	LIPITOR Dose (mg/day)			
	10 (N=22)	20 (N=20)	40 (N=21)	80 (N=23)
Total-C: 7.1 mmol/L[b] (273 mg/dL)[b]	-29	-33	-37	-45
LDL-C: 4.9 mmol/L[b] (190 mg/dL)[b]	-39	-43	-50	-60

a. Results are pooled from 2 dose-response studies.
b. Mean baseline values.

Severe Dyslipidemias

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions).

Concomitant Therapy

See PRECAUTIONS, Drug Interactions.

Dosage in Patients With Renal Insufficiency

See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance

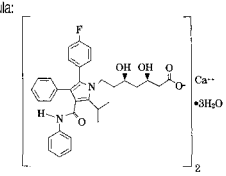
Proper Name: Atorvastatin calcium

Chemical Name: [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Empirical Formula: $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$

Molecular Weight: 1209.42

Structural Formula:



Description: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Tablet Composition:

Each tablet contains either 10 mg, 20 mg, 40 mg or 80 mg atorvastatin as the active ingredient. Each tablet also contains the following non-medicinal ingredients: calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, polysorbate 80 and simethicone emulsion.

Stability and Storage Recommendations:

Store at controlled room temperature 15 to 30°C.

AVAILABILITY OF DOSAGE FORMS

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg, 40 mg and 80 mg atorvastatin per tablet.

10 mg: White, elliptical, film-coated tablet, coded "10" on one side and "PD 155" on the other. Available in bottles of 90 tablets.

20 mg: White, elliptical, film-coated tablet, coded "20" on one side and "PD 156" on the other. Available in bottles of 90 tablets.

40 mg: White, elliptical, film-coated tablet, coded "40" on one side and "PD 157" on the other. Available in bottles of 90 tablets.

80 mg: White, elliptical, film-coated tablet, coded "80" on one side and "PD 158" on the other. Available in blisters of 30 tablets (3 strips X 10).

References:

1. LIPITOR (atorvastatin calcium) Product Monograph, Pfizer Canada Inc., August 2003. **2.** IMS Health MIDAS, March 1997-March 2003. **3.** Pitt B, Waters D, Brown WV *et al.* Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. *N Engl J Med* 1999;341:70-76. **4.** Data on File, Pfizer Canada Inc. **5.** Simon Day. Dictionary for Clinical Trials, 1999, John Wiley & Sons Ltd. Pages 137-38.

For a copy of the Product Monograph or full Prescribing Information, please contact:

Pfizer

Life is our life's work

Pfizer Canada Inc.
Kirkland, Quebec
H9J 2M5

See page A-25

NEW

Pr Keppra® levetiracetam

CONNECTING EXCELLENT PROFILES IN EFFICACY AND TOLERABILITY

PRESCRIBING INFORMATION

Tablets of 250 mg, 500 mg, and 750 mg
Therapeutic classification: Antiepileptic

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

Levetiracetam is a drug of the pyrrolidine class chemically unrelated to existing antiepileptic drugs (AEDs). Levetiracetam exhibits anti-seizure and antiepileptogenic activity in several models of chronic epilepsy in both mice and rats, while being devoid of anticonvulsant activity in the classical screening models of acute seizures.

The mechanism of action of levetiracetam has not yet been fully established, however, it appears to be unlike that of the commonly used AEDs. *In vitro* studies show that levetiracetam, at concentrations of up to 10 μM did not result in significant ligand displacement at known receptor sites such as benzodiazepine, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites or second messenger systems. Furthermore, levetiracetam does not modulate neuronal voltage-gated sodium and T-type calcium currents and does not induce conventional facilitation of the GABAergic system.

Pharmacokinetics

Summary: Single- and multiple-dose pharmacokinetics of levetiracetam have included healthy volunteers, adult and pediatric patients with epilepsy, elderly subjects, and subjects with renal and hepatic impairment. Results of these studies indicate that levetiracetam is rapidly and almost completely absorbed after oral administration. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. Food does not affect the extent of absorption of levetiracetam, although the rate is decreased. Levetiracetam is not protein-bound (< 10% bound) and its volume of distribution is close to the volume of intracellular and extracellular water. Sixty-six percent (66%) of the dose is renally excreted unchanged. The major metabolic pathway of levetiracetam (24% of the dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The metabolites have no known pharmacodynamic activity and are renally excreted. Plasma half-life of levetiracetam across studies is 6-8 hours. Plasma half-life is increased in subjects with renal impairment, and in the elderly primarily due to impaired renal clearance.

Based on its pharmacokinetic characteristics, levetiracetam is unlikely to produce or to be subject to metabolic interactions.

The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight. Therefore, there is no need for plasma level monitoring of levetiracetam.

Human Pharmacology

Pharmacokinetics: The pharmacokinetics of levetiracetam have been characterized in single and multiple dose PK studies, with doses up to 5000 mg; these studies included healthy volunteers (n = 98), patients with epilepsy (n = 58 adult patients and n = 24 pediatric patients), elderly subjects (n = 16) and subjects with renal and hepatic impairment (n = 36 and 16, respectively).

Absorption and Distribution: Levetiracetam is rapidly and almost completely absorbed after oral administration. The oral bioavailability of levetiracetam tablets is 100%. Plasma peak concentrations (C_{max}) are achieved at 1.3 hours after dosing. The extent of absorption is independent of both dose and the presence of food, but the latter delays T_{max} by 1.5 hours and decreases C_{max} by 20%. The pharmacokinetics of levetiracetam are linear over the dose range of 500 – 5000 mg. Steady-state is achieved after two days of a twice daily administration schedule. Mean peak concentrations (C_{max}) are 31 and 43 μg/mL, respectively, following a single 1000 mg dose, and a repeated 1000 mg twice daily dose.

Neither levetiracetam nor its primary metabolite is significantly bound to plasma proteins (< 10%). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 L/kg, a value that is close to the total body water volume. No tissue distribution data for humans are available.

Metabolism: Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the pharmacologically inactive carboxylic acid metabolite, ucb L057 (24% of dose). The production of this metabolite is not dependent on any liver cytochrome P450 isoenzymes and is mediated by serine esterase(s) in various tissues, including blood cells. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no evidence for enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination: Levetiracetam plasma half-life in adults is 7 ± 1 hours and was unaffected by dose, route of administration or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug, which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. Approximately 93% of the dose was excreted within 48 hours. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The primary metabolite, ucb L057, is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance and clearance is thus reduced in patients with impaired renal function (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Special Populations: *Elderly:* Pharmacokinetics of levetiracetam were evaluated in 16 elderly patients, ranging in age from 61-88 years, with 11 of the 16 patients aged 75 years of age or over with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of 500 mg bid for 10 days, total body clearance decreased by 38% and the half-life was increased about 40% (10 to 11 hours) when compared to healthy adults. This is most likely due to the decrease in renal function in these subjects. *Pediatrics (6 to 12 years):* Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6-12 years) after a single dose. The apparent clearance of levetiracetam adjusted to body weight was approximately 40% higher than in epileptic adults. *Gender:* Levetiracetam C_{max} and AUC were 20% higher in women (n = 11) compared to men (n = 12). However, clearances adjusted for body weight were comparable. *Race:* Formal pharmacokinetic studies of the effects of race have not been conducted. Because levetiracetam is primarily renally excreted and there are no known important racial differences in creatinine clearance, significant pharmacokinetic differences due to race are not expected.

Renal Impairment: Single dose pharmacokinetics were performed in 20 subjects with renal impairment (n = 7 mild/CL_{cr} of 50-79 mL/min; n = 8 moderate/CL_{cr} of 30-49 mL/min; n = 5 severe/CL_{cr} <30 mL/min), and n = 11 matching healthy volunteers. Clearance of levetiracetam is correlated with creatinine clearance and levetiracetam pharmacokinetics following repeat administration were well predicted from single dose data. The apparent body clearance of the parent drug levetiracetam is reduced in patients with impaired renal function by approximately 40% in the mild group, 50% in the moderate group, and 60% in the severe renal impairment group. For the primary metabolite ucb L057, the decrease in clearance values from baseline was greater than that seen for the parent drug in all subject groups.

In anuric (end stage renal disease) patients, the apparent body clearance was approximately 30% compared to that of normal subjects. Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure.

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment: A single-dose pharmacokinetic study was performed in 16 subjects with hepatic impairment (n = 5 mild/Child-Pugh Grade A; n = 6 moderate/Grade B; n = 5 severe/Grade C vs 5 healthy controls). For the mild and moderate subgroups neither mean nor individual pharmacokinetic values were clinically different from those of controls. In patients with severe hepatic impairment, mean apparent body clearance was 50% that of normal subjects, with decreased renal clearance accounting for most of the decrease. Patients with severe hepatic impairment thus require a reduced dosage of Keppra® (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND CLINICAL USE

Keppra® (levetiracetam) is indicated as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in Keppra® (levetiracetam) tablets.

WARNINGS

Central Nervous System Adverse Events

Keppra® (levetiracetam) use is associated with the occurrence of central nervous system (CNS) adverse events; the most significant of these can be classified into the following categories: 1) somnolence and fatigue, 2) behavioral/psychiatric symptoms and 3) coordination difficulties.

There was no clear dose response relationship for any of the three categories of CNS adverse events, within the recommended dose range of up to 3000 mg/day. Somnolence/asthenia and coordination difficulties occurred most frequently within the first four weeks of treatment and usually resolved while patients remained on treatment. In the case of behavioral/psychiatric symptoms (including such adverse events as aggression, agitation, anger, anxiety, emotional lability, hostility, irritability), approximately half of the patients reported these events within the first four weeks, with the remaining events occurring throughout the duration of the trials. See also **PRECAUTIONS,** ***Central Nervous System Adverse Events***.

Withdrawal of Anti-Epileptic Drugs

As with all antiepileptic drugs, Keppra® should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

General

Hematological Abnormalities: Minor but statistically significant decreases compared to placebo were seen in total mean RBC count, mean hemoglobin, and mean hematocrit in Keppra®-treated patients in controlled trials. For hemoglobin values, the percentage of Keppra® or placebo treated patients with possibly clinically significant abnormalities were less than 0.5% each. For hematocrit values, a total of 5.1% of Keppra® treated versus 3.2% of placebo patients had at least one possibly significant decrease in hematocrit (≤ 37% in males and 32% in females).

For white blood cells (WBC), 2.9% of treated versus 2.3% of placebo patients had at least one possibly clinically significant decrease in WBC count (≤ 2.8 x 10^9/L), while 2.6% of treated vs. 1.7% of placebo patients had at least one possibly significant decrease in neutrophil count (≤ 1.0 x 10^9/L). Of the Keppra®-treated patients with a low neutrophil count, all but one rose towards or reached baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Central Nervous System Adverse Events **(See WARNINGS):** Keppra® (levetiracetam) use is associated with the occurrence of central nervous system (CNS) adverse events; the most significant of these can be classified into the following categories: 1) somnolence and fatigue, 2) behavioral/psychiatric symptoms and 3) coordination difficulties.

The following CNS adverse events were observed in controlled clinical trials.

Table 1:
Total Combined Incidence Rate for Each of the Three Categories of CNS Adverse Events in Placebo-controlled Add-on Clinical Trials.

Category of CNS adverse event	Keppra®* + AED therapy (n = 672)	Placebo + AED therapy (n = 351)
Somnolence and fatigue		
Somnolence	15%	10%
Asthenia	14%	10%
Behavioral/psychiatric symptoms		
Nonpsychotic[1]	14%	6%
Psychotic[2]	1%	0%
Coordination difficulties[3]	3%	2%

* Reflects Keppra® doses of 1000 mg, 2000 mg, 3000 mg, and 4000 mg per day.

[1] "Non-psychotic behavioral/psychiatric symptoms" encompasses the following terms: agitation, antisocial reaction, anxiety, apathy, depersonalization, depression, emotional lability, euphoria, hostility, nervousness, neurosis, personality disorder and suicide attempt.

[2] "Psychotic behavioral/psychiatric symptoms" encompasses the following terms: hallucinations, paranoid reaction, psychosis and psychotic depression.

[3] "Coordination difficulties" encompasses the following terms: ataxia, abnormal gait, incoordination.

See **ADVERSE EVENTS, Table 2,** for incidence rate of individual AEs contained within the categories.

Behavioral/psychiatric symptoms (including agitation, emotional lability, hostility, anxiety, etc.) have been reported approximately equally in patients with and without a psychiatric history.

There was no clear dose response relationship for any of the three categories of CNS adverse events, within the recommended dose range of up to 3000 mg/day. In a controlled study including a dose of 4000 mg, administered without titration, the incidence rate of somnolence during the first four weeks of treatment for patients receiving the high dose was 42%, compared to 21% for patients receiving 2000 mg/day.

Special Populations

Patients with Renal Impairment: Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, pharmacokinetic studies in renally-impaired patients indicate that apparent clearance is significantly reduced in subjects with renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY,** ***Special Populations***).

In patients with renal impairment Keppra® dosage should be appropriately reduced. Patients with end stage renal disease, i.e. those undergoing dialysis, should be given supplemental doses after dialysis (See **DOSAGE AND ADMINISTRATION**).

Pregnancy and Nursing: There are no adequate and well-controlled studies on the use of Keppra® in pregnant women. Levetiracetam and/or its metabolites cross the placental barrier in animal species. In reproductive toxicity studies in rats and rabbits, levetiracetam induced developmental toxicity at exposure levels similar to or greater than the human exposure. There was evidence of increased skeletal variations/minor anomalies, retarded growth, embryonic death, and increased pup mortality. In the rat, fetal abnormalities occurred in the absence of overt maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure. The potential risk for humans is unknown. Keppra® should not be used during pregnancy unless potential benefits to mother and fetus are considered to outweigh potential risks to both. Discontinuation of antiepileptic treatments may result in disease worsening, which can be harmful to the mother and the fetus.

Pregnancy Exposure Registry: To facilitate monitoring of fetal outcomes of pregnant women exposed to Keppra®, physicians should encourage patients to register, before fetal outcome is known (e.g., ultrasound, results of amniocentesis, etc.), in the Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

Nursing Mothers: Levetiracetam is excreted in breast milk. Therefore, there is a potential for serious adverse reactions from Keppra® in nursing infants. Recommendations regarding nursing and epilepsy medication should take into account the importance of the drug to the mother, and the as yet uncharacterized risks to the infant. Typically, recommendations are made in the context of the necessary prior risk-benefit judgement, regarding pregnancy and epilepsy medication.

Use in Pediatric Patients: Safety and efficacy in patients below the age of 18 have not been established.

Use in the Elderly: Renal function can be decreased in the elderly and levetiracetam is known to be substantially excreted by the kidney, the risk of adverse reactions to the drug may be greater in patients with impaired renal function. A pharmacokinetic study in 16 elderly subjects (age 61-88 years) showed a decrease in clearance by about 40% with oral administration of both single dose and 10 days of multiple twice-daily dosing. This decrease is most likely due to the expected decrease in renal function in these elderly subjects. Care should therefore be taken in dose selection for elderly patients, and it may be useful to monitor renal function.

There were insufficient numbers of elderly patients in controlled trials of epilepsy to adequately assess the efficacy or safety of Keppra® in these patients. Nine of 672 patients treated with Keppra® were 65 or over.

Drug Interactions

In Vitro **Studies on Metabolic Interaction Potential** *In vitro*, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C8/9/10, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (paracetamol UGT, i.e. UGT1A6, ethinyl estradiol UGT, i.e.UGT1A1, and *p*-nitrophenol UGT, i.e.UGT [pI6.2]) and epoxide hydrolase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid. In human hepatocytes in culture, levetiracetam did not cause enzyme induction.

Levetiracetam circulates largely unbound (< 10% bound) to plasma proteins; therefore clinically significant interactions with other drugs through competition for protein binding sites are unlikely.

Thus *in-vitro* data, in combination with the pharmacokinetic characteristics of the drug, indicate that Keppra® is unlikely to produce, or be subject to, pharmacokinetic interactions.

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Clinical Pharmacokinetic Data

Other Antiepileptic Drugs (AEDs): Potential drug interactions between Keppra® and other AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) were assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data suggest that levetiracetam may not significantly influence the plasma concentrations of these other AEDs, and that the other AEDs may not significantly influence the plasma *concentrations of levetiracetam.*

For two of these AEDs — phenytoin and valproate — formal pharmacokinetic interaction studies with Keppra® were performed. Keppra® was co-administered with either phenytoin or valproate at doses of 3000 mg/day and 1000 mg/day respectively. No clinically significant interactions were observed.

Other Drug Interactions

Oral Contraceptives: A pharmacokinetic clinical interaction study has been performed in healthy subjects between the oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgesterol, and the lowest therapeutic dose of Keppra® (500 mg bid). No clinically significant pharmacokinetic interactions were observed.

However, pharmacokinetic interaction studies using Keppra® as adjunctive therapy and covering the recommended dosage range, have not been conducted. Therefore, physicians should advise their female patients to be alert to any irregular vaginal bleeding or spotting, and to immediately report to them any occurrences.

Digoxin: Keppra® (1000 mg bid) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin: Keppra® (1000 mg bid) did not influence the pharmacokinetics of R and S warfarin (2.5 mg, 5 mg, or 7.5 mg daily). Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

Probenecid: Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg bid. C_{ssmax} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid and the renal clearance of the metabolite ucb L057 was decreased by 60%; this alteration is likely related to competitive inhibition of tubular secretion of ucb L057. The effect of Keppra® on probenecid was not studied.

ADVERSE EVENTS

Commonly Observed

In well-controlled clinical studies, the most frequently reported adverse events associated with the use of Keppra® in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, dizziness and infection. Of the most frequently reported adverse events, asthenia, somnolence and dizziness appeared to occur predominantly during the first four weeks of treatment with Keppra®.

Incidence of AEs in Controlled Clinical Trials

Table 2:

Incidence (%) of Treatment-emergent Adverse Events in Placebo-controlled, Add-on Studies by Body System. (Adverse Events Occurred in at least 1% of Keppra®-treated Patients and Occurred More Frequently than Placebo-treated Patients.) (Studies N051, N052, N132 and N138)

Body system/ adverse event	Keppra®+ AED therapy (*n* = 672) (%)	Placebo + AED therapy (*n* = 351) (%)
Body as a whole		
Asthenia	14	10
Infection*	13	7
Digestive system		
Tooth disorders	2	1
Hemic and lymphatic system		
Ecchymosis	2	1
Nervous system		
Amnesia	2	0
Anxiety	2	1
Ataxia	3	1
Depression	4	2
Dizziness	9	4
Emotional lability	2	0
Hostility	2	1
Nervousness	4	2
Personality disorders	1	0
Somnolence	15	10
Thinking abnormal	2	1
Vertigo	3	1
Respiratory system		
Pharyngitis	6	4
Rhinitis	4	3
Sinusitis	2	1

* In levetiracetam-treated patients, the majority of "infection" events (93%) were coded to reported terms of "common cold" or "infection upper respiratory".

Additional Events Observed in Placebo Controlled Trials

Lack of Dose-related Incidence within Therapeutic Range: Based on the data from the controlled clinical trials, there was no evidence of dose relationship within the recommended dose range of 1000 to 3000 mg/day.

Discontinuation or Dose Reduction in Well-controlled Clinical Studies: In well-controlled clinical studies, 14.3% of patients receiving Keppra® and 11.7% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events most commonly associated (>1%) with discontinuation or dose reduction in either treatment group are presented in **Table 3.**

Table 3:

Adverse Events Most Commonly Associated with Discontinuation or Dose Reduction in Placebo-controlled Studies in Patients with Epilepsy

	Keppra® (n = 672)	Placebo (n = 351)
Asthenia	9 (1.3%)	3 (0.9%)
Headache	8 (1.2%)	2 (0.6%)
Convulsion	16 (2.4%)	10 (2.8%)
Dizziness	11 (1.6%)	0
Somnolence	31 (4.6%)	6 (1.7%)
Rash	0	5 (1.4%)

The overall adverse experience profile of Keppra® was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse experience reports by age and race.

Post-marketing Experience

In post-marketing experience, nervous system and psychiatric disorders have most frequently been reported. In addition to adverse reactions during clinical studies, and listed above, the following adverse reactions have been reported in post-marketing experience. Data are insufficient to support an estimate of their incidence in the population to be treated.

Blood and lymphatic disorders: leukopenia, neutropenia, pancytopenia, thrombocytopenia.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms

The highest reported Keppra® overdose is approximately 10 times the therapeutic dose. In the majority of overdose cases, multiple drugs were involved. Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression, and coma were observed with Keppra® overdoses. The minimal lethal oral dose in rodents is at least 233 times the maximum clinically studied dose.

Treatment

There is no antidote for overdose with Keppra®; treatment is symptomatic and may include hemodialysis. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

Standard hemodialysis procedures result in significant removal of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

General

Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, reduced doses are recommended for patients with renal impairment.

Keppra® is given orally with or without food.

Adults

Treatment should be initiated at a dose of 1000 mg/day, given as twice daily dosing (500 mg bid). Depending on clinical response and tolerability, the daily dose may be increased every two weeks by increments of 1000 mg, to a maximum recommended daily dose of 3000 mg.

In clinical trials, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice a day dosing, were shown to be effective. Although there was a tendency toward greater response rate with higher dose, a consistent statistically significant increase in response with increased dose has not been shown. There are limited safety data from controlled clinical trials at doses higher than 3000 mg/day (approximately 40 patients), therefore these doses are not recommended.

Patients with Impaired Renal Function

Keppra® dosage should be reduced in patients with impaired renal function (see **Table 4** below). Patients with end stage renal disease should receive supplemental doses following dialysis. To use this dosing table, an estimate of the patient's CL_{cr} in mL/min is needed. CL_{cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$CL_{cr} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Table 4:

Dosing Adjustment for Patients with Impaired Renal Function

Group	Creatinine clearance (mL/min)	Dosage and frequency
Normal	≥ 80	500 to 1500 mg twice daily
Mild	50-79	500 to 1000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe*	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis[1]	—	500 to 1000 mg once daily

[1] Following dialysis, a 250 to 500 mg supplemental dose is recommended.
* or according to best clinical judgement

Patients with Impaired Hepatic Function

No dose adjustment is needed in patients with mild-to-moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is < 70 mL/min.

Elderly Patients

Dose selection and titration should proceed cautiously in elderly patients, as renal function decreases with age.

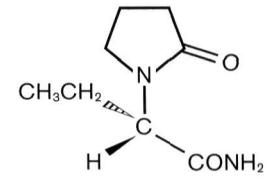
PHARMACEUTICAL INFORMATION

Drug Substance

U.S.A.N: levetiracetam

Chemical Name: (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide

Structural Formula:



Molecular Formula: $C_8H_{14}N_2O_2$

Molecular Weight: 170.21

Physical Form: A white to off-white crystalline powder with a faint odor and a bitter taste.

Solubility: It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane.

pKa and pH values: The pKa of levetiracetam is < -2 and cannot be determined with accuracy due to the chemical instability of the protonated form.

The protonation of ucb L059 starts at H_0 values between -1 and -2.

Partition Co-efficient: Δ log P (log $P_{octanol}$ - Log $P_{cyclohexane}$) was calculated at pH 7.4 using phosphate buffered saline and at pH 1.0 using KCl/HCl. The Δ log P at pH 7.4 is 3.65 and at pH 1.0 is 3.10.

Melting Range: 115-119°C

Composition: Keppra® tablets contain the labeled amount of levetiracetam. Inactive ingredients include colloidal silicon dioxide, corn starch, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 4000, povidone, talc, titanium dioxide and coloring agents.

The individual tablets contain the following coloring agents:
250 mg tablets: FD&C Blue No. 2,
500 mg tablets: FD&C Blue No. 2 and yellow iron oxide,
750 mg tablets: FD&C Blue No. 2, FD&C Yellow No. 6 and red iron oxide.

Stability and Storage Recommendations

Store between 15-30°C (59-86°F).

AVAILABILITY OF DOSAGE FORMS

Keppra® (levetiracetam) tablets, 250 mg are blue, oblong-shaped, film-coated tablets debossed with "ucb" and "250" on one side. They are supplied in bottles of 120 tablets.

Keppra® (levetiracetam) tablets, 500 mg are yellow, oblong-shaped, film-coated tablets debossed with "ucb" and "500" on one side. They are supplied in bottles of 120 tablets.

Keppra® (levetiracetam) tablets, 750 mg are orange, oblong-shaped, film-coated tablets debossed with "ucb" and "750" on one side. They are supplied in bottles of 120 tablets.

For more information, please refer to the complete Keppra® Product Monograph.

References: 1. Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. *Neurology* 2000;55:236-4. **2.** Keppra Product Monograph. UCB Pharma, Inc.

Lundbeck

Keppra® is distributed by Lundbeck Canada Inc.,
413 St-Jacques St. West, Suite FB-230, Montreal, Quebec H2Y 1N9

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See pages A-32, A-33

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Immune Globulin Intravenous (Human), 10%

GAMUNEX™

Manufactured by Chromatography

THERAPEUTIC CLASSIFICATION

PASSIVE IMMUNIZING AGENT

ACTION AND CLINICAL PHARMACOLOGY

General

GAMUNEX™ (Immune Globulin Intravenous [Human], 10%) manufactured by a patented chromatography process is a ready-to-use sterile solution of human immune globulin protein for intravenous administration. GAMUNEX™ consists of 9%–11% protein in 0.16–0.24 M glycine. GAMUNEX™ contains no preservative.

GAMUNEX™ is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography. The protein is stabilized during the process by adjusting the pH of the solution to 4.0-4.5. Isotonicity is achieved by the addition of glycine.

The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled down process model using relevant and model viruses. In the GAMUNEX™ manufacturing process, virus inactivation and/or removal is achieved by way of caprylate precipitation and cloth filtration, caprylate incubation, column chromatography, and final container low pH incubation, evaluated independently and in combination to identify those steps which are mechanistically distinct. Each step was verified to provide robust virus reduction across the production range for key operating parameters. (See PHARMACEUTICAL INFORMATION).

Furthermore, data derived from prion spiking studies have shown that the GAMUNEX™ process has the potential to remove animal model prions.[1,2] (See PHARMACEUTICAL INFORMATION).

The buffering capacity of GAMUNEX™ is 35.0 mEq/L (0.35 mEq/g protein). A dose of 1000 mg/kg body weight therefore represents an acid load of 0.35 mEq/kg body weight. The total buffering capacity of whole blood in a normal individual is 45–50 mEq/L of blood, or 3.6 mEq/kg body weight.[3] Thus, the acid load delivered with a dose of 1000 mg/kg of GAMUNEX™ would be neutralized by the buffering capacity of whole blood alone, even if the dose was infused instantaneously. Glycine (aminoacetic acid) is a nonessential amino acid normally present in the body. Glycine is a major ingredient in amino acid solutions employed in intravenous alimentation.[4]

In patients with limited or compromised acid-base compensatory mechanisms, and in patients in whom there is already an expanded fluid volume (e.g. during pregnancy) consideration should be given to the effect the additional acid and/or protein load that may occur.

The pharmacokinetic parameters AUC and C_{max} of GAMUNEX™ in a randomized clinical trial involving Primary Immunodeficiency (PID) patients were determined to be approximately 6746 mg*h/mL and 19 mg*h/mL respectively. The IgG concentration/time curve follows a biphasic slope with a distribution phase of about 5 days characterized by a fall in serum IgG levels to about 65-75% of the peak levels achieved immediately post-infusion. This phase is followed by the elimination phase with a half-life of approximately 35 days.[5,6]

Primary Humoral Immunodeficiency

Immune Globulin Intravenous (Human), 10% supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria, viruses or their toxins, that have been demonstrated to be effective in the prevention or attenuation of lethal infections in animal models. Immune Globulin Intravenous (Human), 10% has proven to be effective in preventing infections in patients with Primary Humoral Immunodeficiency (PID). In randomized pharmacokinetic trials, GAMUNEX™ has demonstrated bioequivalence to GAMIMUNE® N, 10% (Immune Globulin Intravenous [Human], 10% - Solvent/ Detergent Treated).

Idiopathic Thrombocytopenic Purpura

The mechanism of action of high doses of immunoglobulins in the treatment of Idiopathic Thrombocytopenic Purpura (ITP) has not been fully elucidated. It is postulated that the mechanisms of action may be the Fc-receptor blockade of phagocytes as well as the down regulation of auto-reactive B-cells by antiidiotypic antibodies provided by human immune globulin.[7-12]

Allogeneic Bone Marrow Transplantation

The mechanism of action of Immune Globulin Intravenous (Human), 10% in protecting immune-compromised patients with Allogenic Bone Marrow Transplantation (BMT) from serious bacterial infections is similar to the anti-infective mechanism of action in PID.[21] The immunomodilatory mechanism of action of Immune Globulin Intravenous (Human), 10% in suppressing acute graft versus host reaction in patients with immune cells involving Fab and Gc functions of the immunoglobulin molecules is similar to the discussed mode of action in ITP.[8,9,12,27,44]

Pediatric HIV Infection

Children with HIV infections, particularly when acquired through vertical transmission, are prone to recurrent serious bacterial infections. Types of infection seen in these children are similar to those with primary hypogammaglobulinemia The replacement of opsonic and neutralizing IgG antibodies has been shown to be effective in pediatric HIV infections. The anti-infective mechanism of action of Immune Globulin Intravenous (Human), 10% in the Pediatric HIV is comparable to that in PID.

INDICATIONS AND USAGE

GAMUNEX™ (Immune Globulin Intravenous [Human],10%) is indicated in:

Primary Humoral Immunodeficiency

GAMUNEX™ is indicated as replacement therapy of primary humoral immunodeficiency states in which severe impairment of antibody forming capacity has been shown, such as congenital agammaglobulinemia, common variable immunodeficiency, X-linked immunodeficiency with hyper IgM, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[13-20]

In a double-blind, randomized, parallel group clinical trial in patients with primary humoral immunodeficiencies GAMUNEX™ was demonstrated to be at least as efficacious as GAMIMUNE® N, 10% in the prevention of infections during a nine month treatment period. The annual rate of validated infections was 0.18 and rate for any infection was 2.76 in the group treated with GAMUNEX™ compared to 0.43 (p=0.023) and 3.26 (p=0.287) respectively with the control group.

Idiopathic Thrombocytopenic Purpura

GAMUNEX™ is indicated in Idiopathic Thrombocytopenic Purpura (ITP) to rapidly raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery.[7-17]

A double-blind, randomized, parallel group clinical trial with 97 acute or chronic ITP patients (adults and children), GAMUNEX™ was at least as effective as GAMIMUNE® N, 10% in increasing platelet counts from less than or equal to $20*10^9$/L to more than $50*10^9$/L within 7 days after treatment. A 2000 mg/kg dose of GAMUNEX™ successfully raised platelet counts in 90% of ITP patients by day 7 and day 23 compared to 83% and 86% respectively, in the control group. A sustained 7 day response was observed in 74% of patients treated with GAMUNEX™ compared to 60% in the control group.

Allogeneic Bone Marrow Transplantation

GAMUNEX™ is indicated for the reduction of septicemia and other infections, interstitial pneumonia and acute graft versus host *disease in the first 100 days posttransplant in Allogeneic Bone Marrow Transplantation (BMT) patients of at least 20 years of age.*

Shortly before, and for varying times after bone marrow transplantation, patients are immunosuppressed. The benefit of Immune Globulin Intravenous [Human] in these patients during the recovery period is similar to that of replacement therapy in PID. The utility of Immune Globulin Intravenous (Human) in BMT had been confirmed by long-term experience and in peer-reviewed published reports.[21-24]

Graft-versus-host-disease (GvHD) is a frequent complication of BMT. Immune Globulin Intravenous (Human) has been demonstrated to significantly reduce the incidence of acute GvHD.[21, 22]

Pediatric HIV Infection

GAMUNEX™ is indicated for the reduction of recurrent serious bacterial infections in those children who do not respond to or cannot tolerate antiretroviral combination therapy. Children with HIV infections, particularly when acquired through vertical transmission, are prone to recurrent serious bacterial infections, although they have apparently normal or supranormal IgG levels.

In well controlled clinical trials, Immune Globulin Intravenous (Human) has been shown to significantly decrease serious and minor bacterial infections and to decrease the number of hospitalizations for acute care in children with CD4 counts greater than or equal to $0.2*10^9$/L (200 cells/mm^3) at entry.[25] The benefit of Immune Globulin Intravenous (Human) is still present for children who cannot be treated with trimethoprim-sulfamethoxazole and are receiving zidovudine.[25]

CONTRAINDICATIONS

GAMUNEX™ (Immune Globulin Intravenous [Human],10%) is contraindicated in individuals with known anaphylactic or severe systemic response to human immune globulin. Individuals with severe, selective IgA deficiencies (serum IgA <0.05 g/L) who have known antibody against IgA (anti-IgA antibody) should only receive GAMUNEX™ with utmost cautionary measures. Recent reports claim that IgA exposure to individuals with severe, selective IgA deficiency and high levels of anti-IgA antibodies was not, or only in a few cases, associated with adverse reactions.[27,28] Two groups have reported that human immune globulin intravenous preparations with an IgA content less than 50 mg/L could be given safely to patients with severe selective IgA deficiency despite a history of repeated severe infusion reactions to Immune Globulin Intravenous (Human).[29,30] GAMUNEX™ has a markedly reduced IgA content (46 mg/L) compared to GAMIMUNE® N, 10% (210 mg/L). However, no experience is available on tolerability of GAMUNEX™ in patients with selective IgA deficiency since they were excluded from participation in clinical trials with GAMUNEX™.

WARNINGS

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death.[31] Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, human immune globulin products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed human immune globulin products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. GAMUNEX™ [Immune Globulin Intravenous (Human), 10%] does not contain sucrose.

See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

GAMUNEX™ is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C.

All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Bayer Inc. [1-800-265-7382]. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

GAMUNEX™ should be administered intravenously only. On rare occasions, treatment with an immune globulin preparation may cause a precipitous fall in blood pressure and a clinical picture of anaphylaxis, even when the patient is not known to be sensitive to immune globulin preparations. Epinephrine should be available for the treatment of an acute anaphylactic reaction.

PRECAUTIONS

General

Any vial that has been punctured should be used promptly. Partially used vials should be discarded. Visually inspect each bottle before use. Do not use if turbid. If the solution has been frozen, it must not be used.

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) treatment. The syndrome usually begins within several hours to two days following Immune Globulin Intravenous (Human) treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting. AMS may occur more frequently in association with high dose (2000 mg/kg) Immune Globulin Intravenous (Human) treatment. Discontinuation of Immune Globulin Intravenous (Human) treatment has resulted in remission of AMS within several days without sequelae.[32-34]

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion of GAMUNEX™ and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing GAMUNEX™ (Immune Globulin Intravenous [Human], 10%) at a rate less than 8 mg/kg/min (0.08 mL/kg/min).

Assure that all patients are not volume depleted prior to the initiation of the infusion of Immune Globulin Intravenous [Human], 10%.

In some patients, administration of GAMUNEX™ results in a transitory rise of passively transferred antibodies which may produce misleading serological findings such as positive direct anti-globulin and anti-HBc results in the absence of viral transmission.

There is a possible association between thrombo-embolic (TE) events and administration of Immune Globulin Intravenous (Human) (IGIV) products. Caution should be exercised in administration of IGIV in patients with coagulopathies, cardiovascular disease, thrombophilia, restricted mobility, and the elderly. The etiology of TE events related to IGIV therapy is not clear and may reflect IGIV dose and hyperosmolality[45, 46]. GAMUNEX™ is an iso-osmolar solution. In clinical trials to date, no thromboembolic events were reported for any patient treated with GAMUNEX™.

Drug Interactions

Antibodies in GAMUNEX™ may interfere with the response to live viral vaccines such as measles, mumps and rubella. Therefore, use of such vaccines should be deferred until approximately 6 months after GAMUNEX™ administration. (See DOSAGE AND ADMINISTRATION for other relevant interactions).

Pregnancy

Animal reproduction studies have not been conducted with GAMUNEX™. It is not known whether GAMUNEX™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMUNEX™ should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

General

Increases in creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following infusion, predominantly with other human immune globulin products, stabilized with sucrose. Progression to oliguria and anuria requiring dialysis has been observed, although some patients have improved spontaneously following cessation of treatment.[35] GAMUNEX™ (Immune Globulin Intravenous [Human], 10%) does not contain sucrose. Glycine, a natural amino acid, is used as a stabilizer. In the studies undertaken to date with GAMUNEX™, no increase in creatinine and blood urea nitrogen was observed.

Although not all adverse effects previously reported with intravenous and intramuscular immunoglobulin administration have been observed for GAMUNEX™, adverse effects may be expected to be similar to those reported with these products. Potential reactions may include anxiety, flushing, wheezing, abdominal cramps, myalgias, arthralgia, dizziness, and rash.

True anaphylactic reactions to GAMUNEX™ may occur in recipients with documented prior histories of severe allergic reactions to intramuscular immunoglobulin, but some patients may tolerate cautiously administered intravenous immunoglobulin without adverse effects.[36] Very rarely an anaphylactoid reaction may occur in patients with no prior history of severe allergic reactions to either intramuscular or intravenous immunoglobulin.

Direct antiglobin tests (DAT or direct Coombs tests), which are carried out in some centers as a safety check prior to red blood cell transfusions may show a positive result following treatment with GAMUNEX™. This may be due to the fact that GAMUNEX™ may contain low levels of anti Blood Group A and B antibodies primarily of the IgG4 class. However, there was no evidence of hemolysis or significant clinical effect in association with positive DAT findings in clinical trials.[5,6,37-39]

In some patients in the clinical trial program, administration with GAMUNEX™ resulted in a transitory decrease in RBC, hematocrit and hemoglobin with no evidence of hemolysis or significant clinical outcome.

Primary Humoral Immunodeficiency

Adverse events were monitored in three randomized clinical trials, involving more than 200 primary humoral immunodeficiency patients. In two trials, involving 18-20 patients each, patients received 100-600 mg/kg GAMUNEX™ or GAMIMUNE® N, 10% for three subsequent infusions on a 3 or 4 week infusion interval and were then crossed over to three infusions of the alternate product. In the third trial, 172 patients were randomized to GAMUNEX™ or GAMIMUNE® N, 10% for a nine-month double-blinded treatment with either of the two products at a dose between 100 and 600 mg/kg on a 3 or 4 week infusion interval. In a pooled analysis across the three studies, the infusion rate (0.08 mL/kg/min) was reduced for 11 of 210 exposed patients (7 GAMUNEX™, 4 GAMIMUNE® N, 10%) at 17 occasions. In most instances, mild to moderate hives/urticaria, itching, pain or reaction at infusion site, anxiety or headache was the main reason for reduction in infusion rate. There was one case of severe chills. There were no anaphylactic or anaphylactoid reactions.

In the pivotal clinical trial, the most frequently recorded drug related adverse events (≥0.5%) normalized per patient and infusion are given in the table below:

Drug Related Adverse Events	GAMUNEX™ No. of Infusions: 825	GAMIMUNE® N, 10% No. of Infusions: 865
Cough increased	14 (1.7%)	11 (1.3%)
Headache	7 (0.8%)	11 (1.3%)
Fever	1 (0.1%)	9 (1.0%)
Pharyngitis	7 (0.8%)	9 (1.0%)
Nausea	4 (0.5%)	4 (0.5%)
Urticaria	4 (0.5%)	5 (0.6%)

At various time points after the infusion of Immune Globulin Intravenous (Human), 10%, serum samples were drawn to monitor the viral safety of the PID patients. Viral markers of hepatitis C, hepatitis B, HIV-1, and parvovirus B19 were monitored by nucleic acid testing (NAT, Polymerase Chain Reaction [PCR]), and serological testing. There were no treatment related emergent findings of viral transmission.[5, 6, 37]

Similar adverse reactions as for **PID** are expected for the Immune Globulin Intravenous [Human],10% treatment of patients with **pediatric HIV** infection or **Allogeneic Bone Marrow Transplantation** due to the similar mechanism of action and dose schedule.

Idiopathic Thrombocytopenic Purpura (ITP)

Adverse reactions were monitored in two randomized clinical trials with more than 100 patients with acute or chronic ITP.

In the first study (randomized and double-blind), 97 ITP patients were randomized to a single dose of 2000 mg/kg of GAMUNEX™ or GAMIMUNE® N ,10%. The total dose was divided into two 1000 mg/kg doses given on two consecutive days at a maximum infusion rate of 0.08 mL/kg/min.

As expected, the adverse event rate for Immune Globulin Intravenous [Human],10% in this ITP trial was higher than observed in the replacement therapy for Primary Humoral Immunodeficiencies (PID), but was within the range reported earlier for Immune Globulin Intravenous (Human).[40] It should be noted that the dose is 4-5 fold higher than in PID and that the total dose was given on two consecutive days rather than on five consecutive days, which is associated with a higher adverse event rate.[7] Finally, no pre-medication with corticosteroids was permitted in the study protocol. More than 90% of the observed drug related adverse events were of mild to moderate severity and of transient nature.

The most frequently recorded drug related adverse events (≥2.0%) are given in the table below:

Incidence of drug related adverse events	GAMUNEX™ (n = 48)	GAMIMUNE® N 10% (n = 49)
Headache	24 (50%)	24 (49%)
Mild	25%	18%
Moderate	21%	20%
Severe	4%	12%
<Day 3	46%	49%
>Day 3	4%	0%
Vomiting	6 (13%)	8 (16%)
Mild	10%	10%
Moderate	2%	6%
Severe	0%	0%
< Day 3	10%	16%
>Day 3	2%	0%
Fever	5 (10%)	5 (10%)
Nausea	5 (10%)	4 (8%)
Rash	3 (6%)	0 (0%)
Back Pain	3 (6%)	2 (4%)
Asthenia	2 (4%)	3 (6%)
Arthralgia	2 (4%)	0 (0%)
Pruritus	2 (4%)	0 (0%)
Dizziness	1 (2%)	3 (6%)
Neck Pain	0 (0%)	2 (4%)

The infusion rate was reduced for only 4 of the 97 treated patients (1 GAMUNEX™, 3 GAMIMUNE® N, 10%) on 4 occasions. Mild to moderate headache, nausea, and fever were the reported reasons. There were no anaphylactic or anaphylactoid reactions.

At various time points after the infusion of Immune Globulin Intravenous (Human), 10%, serum samples were drawn to monitor the viral safety of the ITP patients. Viral markers of hepatitis C, hepatitis B, HIV-1, and parvovirus B19 were monitored by nucleic acid testing (NAT, PCR), and serological testing. There were no treatment related emergent findings of viral transmission.[38]

A second trial was carried out in 28 chronic ITP patients who received 1000 mg/kg GAMUNEX™ on three occasions for treatment of relapses to determine tolerability of various infusion rates. The maximum infusion rate on the three occasions was randomly assigned to 0.08, 0.11, or 0.14 mL/kg/min (8, 11 or 14 mg/kg/min) in which each patient was to receive Immune Globulin Intravenous (Human), 10%, at all 3 rates. No pre-medication with corticosteroids to alleviate infusion-related intolerability was permitted. Seven patients did not complete the study for the following reasons: one adverse event (hives) at the 0.08 mL/kg/min level, one patient withdrew because he refused to participate without a forbidden concomitant medication (prednisone) and five patients did not require additional treatment.

The number of patients who experienced at least one adverse event for the 0.08, 0.11, and 0.14 mL/kg/min infusion rates was 12 (46%), 13 (59%), and 11 (46%), respectively. The most commonly reported adverse event was headache, which occurred more frequently during the higher infusion rates (4% in 0.08 mL/kg/min patients vs. 23% in 0.11 mL/kg/min patients vs. 13% in 0.14 mL/kg/min patients). Importantly, all of the headaches were mild except for one severe headache at the 0.08 mL/kg/min rate. Otherwise, the incidence rates of adverse events and drug-related adverse events generally appeared to be similar among the three infusion groups. No patients experienced a drug related serious adverse event. There were no other abnormal safety results except for slightly decreased heart rates following all infusion rates.[39]

DOSAGE AND ADMINISTRATION

General

For intravenous use only. Dosages for specific indications are indicated below, but in general, it is recommended that Immune Globulin Intravenous (Human), 10% be infused by itself at an initial rate of 0.01 to 0.02 mL/kg body weight per minute for 30 minutes; if well-tolerated, the rate may be **gradually** increased to a maximum of 0.14 mL/kg body weight per minute. Clinical investigations indicate that Immune Globulin Intravenous (Human), 10% is well-tolerated and less likely to produce side effects when infused at the recommended rate. If side effects occur, the rate may be reduced, or the infusion interrupted until symptoms subside. The infusion may then be resumed at the rate which is comfortable for the patient. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For patients judged to be at increased risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing GAMUNEX™ (Immune Globulin Intravenous [Human], 10%) at a rate less than 8 mg/kg/min (0.08 mL/kg/min). No prospective data are presently available to identify a maximum safe dose, concentration, and rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate should be the minimum level practicable. Reduction in dose, concentration, and/or rate of administration in patients at risk of acute renal failure is suggested in order to reduce the risk of *acute renal failure.*[41]

Primary Humoral Immunodeficiency

GAMUNEX™ doses between 100 and 600 mg/kg (1 and 6 mL/kg administered every 3 or 4 weeks) may be used for infection prophylaxis. The dose should be individualized taking into account dosing intervals (e.g. 3 or 4 weeks) and GAMUNEX™ dose (between 100 and 600 mg/kg). The goal should be to achieve serum IgG levels at trough (i.e. prior to the next infusion) of at least 5 g/L[18]

Idiopathic Thrombocytopenic Purpura

GAMUNEX™ may be administered at a total dose of 2000 mg/kg, divided into two doses of 1000 mg/kg (10 mL/kg) given on two consecutive days, or into five doses of 400 mg/kg (4 mL/kg) given on five consecutive days. If after administration of the first of two daily 1000 mg/kg (10 mL/kg) doses, an adequate increase in the platelet count is observed at 24 hours, the second dose of 1000 mg/kg body weight may be withheld.

The high dose regimen (1000 mg/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Allogeneic Bone Marrow Transplantation (BMT)

An equivalent dosage of 500 mg/kg GAMUNEX™ (5 mL/kg) is recommended beginning on days 7 and 2 prior to transplantation (or at the time conditioning therapy for transplantation is begun), then weekly through 90 days after transplantation. GAMUNEX™ should be administered by itself through a Hickman line while it is in place, and thereafter through a peripheral vein.

Pediatric HIV Infection

An equivalent dosage of GAMUNEX™ is recommended in doses of 400 mg/kg (4 mL/kg) body weight every 28 days.

Administration

It is recommended that GAMUNEX™ should initially be infused at a rate of 0.01 to 0.02 mL/kg per minute (1 to 2 mg/kg per minute) for the first 30 minutes. If well tolerated, the rate may be gradually increased to a maximum of 0.14 mL/kg per minute (14 mg/kg per minute). If side effects occur, the rate may be reduced, or the infusion interrupted until symptoms subside. The infusion may then be resumed at the rate, which is comfortable for the patient.

In a clinical trial with 28 chronic adult ITP patients receiving 1000 mg/kg GAMUNEX™ to treat relapses, the infusion rate could be safely increased up to 0.14 mL/kg per minute (14 mg/kg per minute).[35] Caution should be exercised when an infusion rate higher than 0.08 mL/kg per minute (8 mg/kg per minute) is administered for the first time.

Only 18 gauge needles should be used to penetrate the stopper for dispensing product from 10 mL vial sizes; 16 gauge needles or dispensing pins should only be used with 20 mL vial sizes and larger. Needles or dispensing pins should only be inserted within the stopper area delineated by the raised ring. The stopper should be penetrated perpendicular to the plane of the stopper within the ring.

Content of vials may be pooled under aseptic conditions into sterile infusion bags and infused within 8 hours after pooling.

It is recommended to infuse GAMUNEX™ using a separate line by itself, without mixing with other intravenous fluids or medications the patient might be receiving. GAMUNEX™ should not be mixed with any other Immune Globulin Intravenous (Human) formulation.

GAMUNEX™ is not compatible with saline. If dilution is required, GAMUNEX™ may be diluted with 5% dextrose in water (D5W). No other drug interactions or compatibilities have been evaluated.

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use.

PHARMACEUTICAL INFORMATION

GAMUNEX™ (Immune Globulin Intravenous [Human], 10%) manufactured by a patented Chromatography Process is a ready-to-use sterile solution of human immune globulin protein for intravenous administration. GAMUNEX™ consists of 9%–11% protein in 0.16–0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma globulin. GAMUNEX™ typically has low levels of IgA (average of 0.046 g/L). IgM levels were at or below the limit of quantitation (0.002 g/L). The distribution of IgG subclasses is similar to that found in normal serum. The measured buffer capacity is 35 mEq/L and the osmolality is 258 mOsmol/kg solvent, which is close to physiological osmolality (285- 295 mOsmol/kg). GAMUNEX™ contains no preservative.

GAMUNEX™ is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography. Part of the fractionation may be performed by another licensed manufacturer. Two ethanol fractionation steps of the classical Cohn-Oncley process have been replaced by tandem anion-exchange chromatography. The IgG proteins are not subjected to heating or chemical or enzymatic modification steps. Fc and Fab functions of the IgG molecule are retained, but do not activate complement or pre-Kallikrein activity in an unspecific manner. The protein is stabilized during the process by adjusting the pH of the solution to 4.0-4.5. Isotonicity is achieved by the addition of glycine. GAMUNEX™ is incubated in the final container (at the low pH of 4.0 – 4.3), for a minimum of 21 days at 23° to 27°C. The product is intended for intravenous administration.

The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled down process model, using the following enveloped and non-enveloped viruses:

Spiking Study Virus used:	As a model for:
Human Immunodeficiency Virus Type 1 (HIV-1)	HIV-1 and HIV-2
Bovine Viral Diarrhea Virus (BVDV)	Hepatitis C virus
Pseudorabies Virus (PRV)	Hepatitis B and herpes virus
Reo virus type 3 (Reo)	non enveloped virus
Hepatitis A virus (HAV)	non enveloped virus
porcine parvovirus (PPV)	human parvovirus B19

The following process steps contribute to virus inactivation and/or removal: caprylate precipitation and cloth filtration, caprylate incubation, column chromatography, and final container low pH incubation. The table below indicates how the viruses are affected by the different steps. A number of virus removal steps were evaluated independently and in combination to identify those steps which are mechanistically distinct. Overall virus reduction was calculated only from steps that are mechanistically independent from each other and truly additive. In addition, each step was verified to provide robust virus reduction across the production range for key operating parameters.

Process step	Enveloped viruses	Non-enveloped viruses
Caprylate precipitation and cloth filtration	Robust removal of BVDV; not claimed for other enveloped viruses[1]	Robust removal
Caprylate incubation	Dedicated step, robust inactivation*	No effect
Depth Filtration	Not claimed[2]	Not claimed[3]
Column chromatography	Robust removal*	Robust removal*
Final container low pH incubation	Dedicated step, robust inactivation*	No effect

1 Although removal of all viruses is likely to occur at this step, BVDV is the only enveloped virus for which reduction is claimed. The presence of caprylate prevents detection of other, less resistant enveloped viruses and therefore their removal cannot be assessed.

2 The presence of caprylate in the process at this step prevents detection of enveloped viruses, and their removal cannot be assessed.

3 Some mechanistic overlap occurs between depth filtration and other steps. Therefore we have chosen to exclude this step from our overall virus reduction calculations.

* The steps marked by an asterisk indicate that the step fulfills the criteria of a significant reduction step, i.e. removal is in the order of magnitude of 4 log or greater and/or the spiked virus is removed to the detection limit.

Data derived from prion spiking studies have shown that the GAMUNEX™ process has the potential to remove animal model prions.[1,2]

Glycine (aminoacetic acid) is a nonessential amino acid normally present in the body. Glycine is a major ingredient in amino acid solutions employed in intravenous alimentation.[4] While toxic effects of glycine administration have been reported,[42] the doses and rates of administration were 3 – 4 fold greater than those for GAMUNEX™. In another study it was demonstrated that intravenous bolus doses of 0.44 g/kg glycine were not associated with serious adverse effects.[43] GAMUNEX™ doses of 1000 mg/kg, usually infused over 2-3 hours, amount to corresponding glycine concentrations of 0.15 g/kg. 0.2M Glycine stabilizer has been used safely in other Bayer Immune Globulin Intravenous (Human), 10% preparations since 1992.

The buffering capacity of GAMUNEX™ is 35.0 mEq/L (0.35 mEq/g protein). A dose of 1000 mg/kg body weight therefore represents an acid load of 0.35 mEq/kg body weight. The total buffering capacity of whole blood in a normal individual is 45–50 mEq/L of blood, or 3.6 mEq/kg body weight.[3] Thus, the acid load delivered with a dose of 1000 mg/kg of GAMUNEX™ would be neutralized by the buffering capacity of whole blood alone, even if the dose was infused instantaneously.

Storage

GAMUNEX™ may be stored for 36 months at 2-8°C (36-46°F), AND product may be stored at room temperature not to exceed 25°C (77°F) for up to 5 months during the first 18 months from the date of manufacture, after which the product must be immediately used or discarded. Do not freeze. Do not use after expiration date.

AVAILABILITY OF DOSAGE FORMS

GAMUNEX™ (Immune Globulin Intravenous [Human], 10%) is supplied in the following sizes:

Size	Protein (g)
10 mL	1.0
25 mL	2.5
50 mL	5.0
100 mL	10.0
200 mL	20.0

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Product Monograph available upon request.

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1. Gamunex™ Product Monograph, August 11, 2003. Bayer Inc.
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See pages A-26, A-27

Pr Axert*

almotriptan malate tablets

AXERT
almotriptan malate tablets
6.25 mg and 12.5 mg
almotriptan

5-HT_1 Receptor Agonist
Migraine Therapy

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AXERT (almotriptan malate) is a selective 5-hydroxytryptamine $_{1}$ (5-$HT_{1B/1D}$) receptor agonist. Almotriptan binds with high affinity to 5-HT_{1D}, 5-HT_{1B} and 5-HT_{1F} receptors. Almotriptan has a weak affinity for 5-HT_{1A} and 5-HT_7 receptors, but has no significant affinity or pharmacological activity at 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, alpha or beta adrenergic, adenosine (A_1, A_2); angiotensin (AT_1, AT_2); dopamine (D_1, D_2); endothelin (ET_A, ET_B); or tachykinin (NK, NK_2, NK_3) binding sites.

Current theories on the etiology of migraine headaches suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from the sensory nerve endings in an activated trigeminal system. The therapeutic activity of almotriptan in migraine can most likely be attributed to agonist effects at 5-$HT_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack, and on the nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of the neuropeptide release, and reduced transmission in the trigeminal pain pathways.

Pharmacokinetics

Absorption

Almotriptan is well absorbed following oral administration. The mean oral absolute bioavailability is approximately 70%, and peak plasma concentrations of approximately 40 ng/mL are reached 1 to 3 hours after a single 12.5 mg dose. The rate and extent of absorption are not affected by food intake or by administration during a migraine attack. Almotriptan does not undergo substantial first-pass elimination.

Distribution

Almotriptan is extensively distributed. Almotriptan is minimally protein bound (approximately 35%), and the mean apparent volume of distribution is approximately 180 to 200 litres.

Metabolism

Almotriptan is metabolized by one minor and two major pathways. Monoamine oxidase (MAO)-mediated oxidative deamination (approximately 27% of the dose) and cytochrome P450-mediated oxidation (approximately 12% of the dose) are the major routes of metabolism, while flavin mono-oxygenase is the minor route. MAO-A is responsible for the formation of the indoleacetic acid metabolite, whereas cytochrome P450 (3A4 and 2D6) catalyzes the hydroxylation of the pyrrolidine ring to an intermediate that is further oxidized by aldehyde dehydrogenase to the gamma-aminobutyric acid derivative. Both metabolites are inactive.

Excretion

The mean half-life of almotriptan is between 3 and 4 hours. The primary route of elimination is via renal clearance, accounting for 75% of the administered dose. Approximately 40% of an administered dose is excreted unchanged in urine. Renal clearance exceeds the glomerular filtration rate by approximately 3-fold, indicating an active mechanism. Approximately 13% of the administered dose is excreted via feces, both unchanged and metabolized.

Special Populations

Geriatric

Renal and total clearance, and amount of drug excreted in the urine (10 L/h, 33 L/h and 30% respectively) were lower in elderly non-migraineur volunteers (aged 65 to 76 years) than in younger non-migraineur volunteers (aged 19 to 34 years), resulting in longer terminal half-life (3.7 h vs. 3.2 h) and higher area under the plasma concentration-time curve (405 ng.h/mL vs. 325 ng.h/mL) in the elderly subjects. However, the differences do not appear to be clinically significant.

Pediatric

The pharmacokinetics of almotriptan have not been evaluated in pediatric patients.

Gender

No significant gender differences have been observed in pharmacokinetic parameters.

Race

No significant differences have been observed in the pharmacokinetic parameters between Caucasian and African-American volunteers.

Hepatic Impairment

The pharmacokinetics of almotriptan have not been assessed in this population. Based on the known mechanisms of the clearance of almotriptan, the maximum decrease in expected almotriptan clearance due to hepatic impairment would be 60% (see DOSAGE AND ADMINISTRATION and Hepatic Impairment in PRECAUTIONS).

Renal Impairment

The clearance of almotriptan was approximately 65% lower in patients with severe renal impairment (Cl/F = 19.8 L/h; creatinine clearance between 10 and 30 mL/min) and approximately 40% lower in patients with moderate renal impairment (Cl/F = 34.2 L/h; creatinine clearance between 31 and 71 mL/min) compared to healthy volunteers. Maximum plasma concentrations of almotriptan increased by approximately 80% in these patients (see DOSAGE AND ADMINISTRATION and Renal Impairment in PRECAUTIONS).

CLINICAL STUDIES

The pharmacological activity of almotriptan in the treatment of migraine has been assessed in Phase II and Phase III clinical trials.

The efficacy of AXERT (almotriptan malate) tablets was established in 3 multicentre, randomized, double-blind, placebo-controlled trials. Patients enrolled in these studies were primarily female (86%) and Caucasian (more than 98%), with a mean age of 41 years (range of 18 to 72). Patients were instructed to treat a moderate to severe migraine headache. Two hours after taking one dose of study medication, patients evaluated their headache pain. If the pain had not decreased in severity to mild or to no pain, the patient was allowed to take an escape medication. If the pain had decreased to mild or to no pain at 2 hours but subsequently increased in severity between 2 and 24 hours, it was considered a relapse and the patient was instructed to take a second dose of study medication. Associated symptoms of nausea, vomiting, photophobia, and phonophobia were also evaluated.

In these studies, the percentage of patients achieving a response (mild or no pain) 2 hours after treatment was significantly greater in patients who received either AXERT 6.25 mg or 12.5 mg, compared with those who received placebo. In study 1, almotriptan 12.5 mg was superior to placebo as early as 30 minutes after drug administration (pairwise comparison, p = 0.0485). A higher percentage of patients reported pain relief after treatment with the 12.5 mg dose than with the 6.25 mg dose. Doses greater than 12.5 mg did not lead to significantly better response. These results are summarized in Table 1.

Table 1. Pain Relief Rates 2 Hours Following Treatment of Initial Headache

	Placebo	AXERT 6.25 mg	AXERT 12.5 mg
Study 1	32.5% (n=80)	56.3%* (n=167)	58.5%† (n=164)
Study 2	42.4% (n=98)	–	56.5%‡ (n=184)
Study 3	33.9% (n=176)	57.3% (n=360)	64.6%† (n=373)

* p value 0.002 in comparison to placebo
† p value < 0.001 in comparison to placebo
‡ *p value 0.008 in comparison to placebo*

These results cannot be validly compared with results of anti-migraine treatments in other studies. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment responses and the timing of responses may be expected to vary considerably from study to study.

For patients with migraine-associated photophobia, phonophobia, nausea, and vomiting at baseline, there was a decreased incidence of these symptoms following administration of AXERT compared with placebo.

Two to 24 hours following the initial dose of study medication, patients were allowed to take an escape medication or a second dose of study medication for pain response. Escape medication was taken more frequently by patients in the placebo groups than by those in the active almotriptan treatment groups.

The efficacy of AXERT was unaffected by the presence of aura; by gender, weight, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g. beta-blockers, calcium channel blockers, tricyclic antidepressants), or oral contraceptives. There were insufficient data to assess the effect of race on efficacy.

INDICATIONS AND CLINICAL USE

AXERT (almotriptan malate) tablets are indicated for the acute treatment of migraine with or without aura in adults.

AXERT is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, ophthalmoplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of AXERT have not been established for cluster headache, which presents in an older, predominantly male population.

CONTRAINDICATIONS

AXERT (almotriptan malate) 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 AXERT. 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 AXERT may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

AXERT should not be administered within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication, such as dihydroergotamine or methylsergide.

AXERT should not be given to patients with hemiplegic, ophthalmoplegic or basilar migraine.

AXERT is contraindicated in patients who are hypersensitive to almotriptan or any other ingredients in AXERT.

WARNINGS

AXERT (almotriptan malate) tablets 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

Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, AXERT should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that 5-HT_1 agonists (including AXERT) not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors such as: hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age, unless a cardiovascular examination 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 diseases or predisposition to coronary artery vasospasm is modest at best. If, during the cardiovascular evaluation, the patient's medical history, electrocardiogram (ECG) or other evaluations reveal findings indicative of, or consistent with, coronary artery vasospasm, or myocardial ischemia, AXERT should not be administered (see CONTRAINDICATIONS).

These evaluations, however, may not identify every patient who has cardiac disease, and in very rare cases, serious cardiac events, such as myocardial infarction or coronary ischemia have occurred in patients without evidence of underlying cardiovascular disease.

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of AXERT take place in a clinical setting, such as the physician's office or a similarly staffed medical facility, unless the patient has previously received almotriptan. Because cardiac ischemia can occur in the absence of any clinical symptoms, consideration should be given to obtaining an ECG during the interval immediately following the first use of AXERT in a patient with risk factors. 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.

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

It is recommended that patients who are intermittent long-term users of AXERT and who have or acquire risk factors predictive of CAD as described above undergo periodic interval cardiovascular evaluation as they continue to use AXERT.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease are inadvertently exposed to AXERT.

Cardiac Events and Fatalities Associated with 5-HT_1 Agonists

Serious adverse cardiac events, including acute myocardial infarction have been reported within a few hours following administration of almotriptan. Life-threatening disturbances of cardiac rhythm and death have been reported within a few hours following the administration of other 5-HT_1 agonists. Due 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. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

AXERT can cause coronary vasospasm; at least one of these events occurred in a patient with no cardiac history and with documented absence of coronary artery disease.

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

Premarketing experience with almotriptan

Among the 3865 subjects/patients who received AXERT in premarketing clinical trials, one patient was hospitalized for observation after a scheduled ECG was found to be abnormal (negative T-waves on the left leads) 48 hours after taking a single 6.25 mg dose of AXERT. The patient, a 48-year-old female, had previously taken 3 other doses for earlier migraine attacks. Myocardial enzymes at the time of the abnormal ECG were normal. The patient was diagnosed as having had myocardial ischemia, and it was also found that she had a family history of coronary disease. An ECG performed 2 days later was normal, as was a follow-up coronary angiography. The patient recovered without incident.

Postmarketing experience with almotriptan

Serious cardiovascular events have been reported in association with the use of AXERT. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to definitely determine the proportion of the reported cases that were actually caused by almotriptan or to reliably assess causation in individual cases.

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 other 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 belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted, however, that patients who suffer from migraine may have an increased risk of certain cerebrovascular events such as stroke, hemorrhage or transient ischemic attack.

Other Vasospasm-Related Events

5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT_1 agonists.

Increases in Blood Pressure

Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT_1 agonists. AXERT is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). In volunteers, small increases in mean systolic and diastolic blood pressure relative to placebo were seen over the first 4 hours after administration of 12.5 mg of almotriptan (0.21 and 1.35 mm Hg, respectively). The effect of AXERT on blood pressure was also assessed in patients with hypertension controlled by medication. In this population, mean increases in systolic and diastolic blood pressure relative to placebo over the first 4 hours after administration of 12.5 mg of almotriptan were 4.87 and 0.26 mm Hg, respectively. The slight increases in blood pressure in both volunteers and controlled hypertensive patients were not considered clinically significant (see ADVERSE REACTIONS and PRECAUTIONS).

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 AXERT. 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 have occurred in patients receiving other 5-HT_1 agonists. 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, AXERT should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists. (see ADVERSE REACTIONS and PRECAUTIONS).

PRECAUTIONS

General

AXERT should be administered with caution to patients with diseases that may alter the absorption, metabolism or excretion of drugs, such as those with impaired hepatic or renal function (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

Cardiovascular

As with other 5-HT_1 agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck and jaw have been reported after treatment with AXERT (almotriptan malate). These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials. Because drugs in this class,

including AXERT, may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of the medication, 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 the use of any 5-HT_1 agonist, are candidates for further evaluation (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 headache 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 AXERT.

Corneal Opacities

Three male dogs (out of a total of 14 treated) in a 52-week toxicity study of oral almotriptan developed slight corneal opacities that were noted after 51, but not after 25, weeks of treatment. The doses at which this occurred were 2, 5, and 12.5 mg/kg/day. The opacity reversed in the affected dog at 12.5 mg/kg/day after a 4-week drug-free period. Systemic exposure (plasma AUC) to parent drug at 2 mg/kg/day was approximately 2.5 times the exposure in humans receiving the maximum recommended daily dose of 25 mg. A no-effect dose was not established.

Binding to Melanin-Containing Tissues

When pigmented rats were given a single oral dose of 5 mg/kg of radiolabelled almotriptan, the elimination half-life of radioactivity from the eye was 22 days, suggesting that almotriptan and/or its metabolites may bind to the melanin of the eye. Because almotriptan could accumulate in the melanin-rich tissues over time, there is the possibility that it could cause toxicity in these tissues over extended use. However, no adverse ocular effects related to treatment with almotriptan were noted in any of the toxicity studies. Although no systemic monitoring of ophthalmic function was undertaken in clinical trials, and no specific recommendations for ophthalmic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmic effects.

Carcinogenesis

The carcinogenic potential of almotriptan was evaluated by oral gavage for up to 103 weeks in mice at doses of up to 250 mg/kg/day, and in rats for up to 104 weeks at doses up to 75 mg/kg/day. These doses were associated with plasma exposures (AUC) to parent drug that were approximately 40 and 78 times, in mice and rats respectively, the plasma AUC observed in humans receiving the MRDD of 25 mg. Because of high mortality rates in both studies, which reached statistical significance in high-dose female mice, all female rats, all male mice and high-dose female mice were terminated between weeks 96 and 98. There was no increase in tumors related to almotriptan administration.

Mutagenesis

Almotriptan was not mutagenic, with or without metabolic activation, when tested in two gene mutation assays, the Ames test and the *in vitro* thymidine locus mouse lymphoma assay. Almotriptan was not determined to be clastogenic in two *in vitro* cytogenetics assays in human lymphocytes and an *in vivo* mouse micronucleus assay. Almotriptan produced an equivocal weakly positive response in *in vitro* cytogenetics assays in human lymphocytes.

Impairment of Fertility

When female rats received almotriptan by oral gavage prior to and during mating and up to implantation at doses of 25, 100, and 400 mg/kg/day, prolongation of the estrous cycle was observed at a dose of 100 mg/kg/day (exposure, based on mg/m^2, was approximately 40 times exposure in humans receiving the maximum recommended daily dose (MRDD) of 25 mg). No effects on fertility were noted in female rats at 25 mg/kg/day (exposure approximately 10 times human exposure at MRDD). No adverse effects were noted in male rats at 400 mg/kg/day (160 times the human exposure based on mg/m^2).

Pregnancy

When almotriptan was administered orally during organogenesis to pregnant rats at doses of 125, 250, 500 and 1000 mg/kg/day, an increase in embryolethality was seen at the 1000 mg/kg/day dose (maternal exposure [based on plasma AUC of parent drug] was approximately 958 times the human exposure at MRDD of 25 mg). Increased incidences of fetal skeletal variations (decreased ossification) were noted at doses greater than the no-observed-effect level in rats of 125 mg/kg/day (maternal exposure 80 times human exposure at MRDD). Similar studies in rabbits conducted with almotriptan at doses of 5, 20 and 60 mg/kg/day demonstrated increases in embryolethality at 60 mg/kg/day (maternal exposure, based on mg/m^2, 50 times human exposure at MRDD). When almotriptan was administered to rats throughout the periods of gestation and lactation at doses of 25, 100 and 400 mg/kg/day, gestation length was increased and litter size and offspring body weight were decreased at the high dose (maternal exposure, based on mg/m^2, 160 times human exposure at MRDD). The decrease in pup weight persisted throughout lactation. The no-observed-effect level in this study was 100 mg/kg/day (maternal exposure 40 times human exposure at MRDD).

There have been no adequate and well-controlled studies in pregnant women; therefore AXERT should only be used during pregnancy if the potential benefit justifies the risk to the fetus.

Hepatic Impairment

AXERT should be used with caution in patients with hepatic impairment. The maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg is recommended (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

Renal Impairment

AXERT should be used with caution in patients with severe renal impairment. The maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

Psychomotor Effect

Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that AXERT does not affect them adversely.

Use in the Elderly

Clinical studies of AXERT did not include sufficient numbers of subjects over 65 years of age to determine whether they respond differently from younger subjects. Renal and total clearance, and amount of drug excreted in the urine were lower in elderly non-migraineur volunteers (age 65 to 76 years) than in younger non-migraineur volunteers (age 19 to 34 years), resulting in longer terminal half-life and higher area under the plasma concentration-time curve. Although clearance of almotriptan was lower in elderly volunteers, there were no differences in the safety and tolerability between the two populations (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal, cardiac, and hepatic function, and of concomitant disease or other drug therapy.

Use in Children

The safety and effectiveness of AXERT in pediatric patients has not been established; therefore, AXERT is not recommended for use in patients under 18 years of age.

Post-marketing experience with other triptans include a limited number of reports that describe pediatric (under 12 years of age) and adolescent (12 - 17 years of age) patients who have experienced clinically serious adverse events that are similar in nature to those reported as rare occurrences in adults.

Use during Lactation

It is not known whether almotriptan is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when AXERT is administered to a nursing woman.

Dependence Liability

Although the abuse potential of AXERT has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behaviour was observed in patients who received AXERT in clinical trials or their extensions. The 5-$HT_{1B/1D}$ agonists, as a class, have not been associated with drug abuse.

Drug Interactions

All drug interaction studies were performed in healthy volunteers using a single 12.5 mg dose of almotriptan and multiple doses of the other drug.

Ergot-containing drugs

These drugs have been reported to cause prolonged vasospastic reactions. As there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (dihydroergotamine or methylsergide) and AXERT within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

Monoamine oxidase inhibitors

Coadministration of almotriptan and moclobemide (150 mg b.i.d. for 8 days) resulted in a 27% decrease in almotriptan clearance and an increase in C_{max} of approximately 6%. No dose adjustment is necessary.

Propranolol

Coadministration of almotriptan and propranolol (80 mg b.i.d. for 7 days) resulted in no significant changes in the pharmacokinetics of almotriptan.

Selective serotonin reuptake inhibitors (SSRIs)

Coadministration of almotriptan and fluoxetine (60 mg daily for 8 days), a potent inhibitor of CYP2D6, had no effect on almotriptan clearance, but maximal concentrations of almotriptan were increased by 18%. This difference is not clinically significant. SSRIs (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline) have been rarely reported to cause weakness, hyperreflexia and incoordination when coadministered with 5-HT$_1$ agonists. If concomitant treatment with AXERT and an SSRI is clinically warranted, appropriate observation of the patient, for both acute and long term adverse events, is advised.

Verapamil

Coadministration of almotriptan and verapamil (120 mg sustained-release tablets b.i.d. for 7 days), an inhibitor of CYP4503A4, resulted in a 20% increase in the area under the plasma concentration-time curve, and in a 24% increase in maximal plasma concentrations of almotriptan. Neither of these changes is clinically significant.

Other 5-$HT_{1B/1D}$ agonists

Concomitant use of other 5-$HT_{1B/1D}$ agonists within 24 hours of treatment with AXERT is contraindicated (see CONTRAINDICATIONS).

Ketoconazole and other potent CYP3A4 inhibitors

Coadministration of almotriptan and the potent CYP3A4 inhibitor ketoconazole (400 mg q.d. for 3 days) resulted in an approximately 60% increase in the area under the plasma concentration-time curve and maximal plasma concentrations of almotriptan. Although the interaction between almotriptan and other potent CYP3A4 inhibitors (e.g. itraconazole, ritonavir, and erythromycin) has not been studied, increased exposures to almotriptan may be expected when almotriptan is used concomitantly with these medications.

Laboratory Tests

Almotriptan is not known to interfere with any commonly employed clinical laboratory tests. No specific laboratory tests are recommended for monitoring patients.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of other 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 vasospasms, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Serious cardiac events, including myocardial infarction, coronary artery vasospasm and intermediate coronary syndrome, have occurred following the use of AXERT tablets. These events are extremely rare and have been reported mostly in patients with cardiovascular risk factors (see WARNINGS and POST-MARKETING ADVERSE REACTIONS).

Experience in Controlled Clinical Trials with AXERT (almotriptan)

Typical 5-HT_1 Agonist Adverse Reactions

As with other 5-HT$_1$ agonists, AXERT 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 limbs.

Increases in Blood Pressure

Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT_1 agonists. AXERT is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). In volunteers, small increases in mean systolic and diastolic blood pressure relative to placebo were seen over the first 4 hours after administration of 12.5 mg of almotriptan (0.21 and 1.35 mm Hg, respectively). The effect of AXERT on blood pressure was also assessed in patients with hypertension controlled by medication. In this population, mean increases in systolic and diastolic blood pressure relative to placebo over the first 4 hours after administration of 12.5 mg of almotriptan were 4.87 and 0.26 mm Hg, respectively. The slight increases in blood pressure in both volunteers and controlled hypertensive patients were not considered clinically significant (see also CONTRAINDICATIONS and WARNINGS).

Acute Safety

Adverse events were assessed in controlled clinical trials that included 1840 patients who received one or two doses of AXERT (almotriptan malate) tablets and 386 patients who received placebo.

The most common adverse events during treatment with AXERT were nausea, somnolence, headache, paresthesia, and dry mouth. In long-term, open-label studies where patients were allowed to treat multiple attacks for up to one year, 5% (63 out of 1347 patients) withdrew due to adverse experiences.

Table 2 lists the adverse events that occurred in at least 1% of the patients treated with AXERT, and at an incidence greater than in patients treated with placebo, regardless of drug relationship. These events 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 behaviour, and the kinds of patients treated may differ.

Table 2. Incidence of Adverse Events in Controlled Clinical Trials (Reported in at Least 1% of Patients Treated with AXERT, and at an Incidence Greater than Placebo)

Adverse Event	Percentage of Patients Reporting the Event		
	AXERT 6.25 mg (n=527)	AXERT 12.5 mg (n=1313)	Placebo (n=386)
Digestive			
Nausea	1	2	1
Dry Mouth	1	1	0.5
Nervous			
Paresthesia	1	1	0.5

AXERT is generally well tolerated. Most adverse events were mild in intensity and were transient, and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, age, presence of aura, or use of prophylactic medications or oral contraceptives. There were insufficient data to assess the effect of race on the incidence of adverse events.

Other Events

The frequencies of less commonly reported adverse events are presented below. However, the role of AXERT 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 AXERT in controlled clinical trials and reported an event, divided by the total number of patients exposed to AXERT in these studies. All reported events are included, except the ones already listed in the previous table, and those unlikely to be drug related. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; and *rare* adverse events are those occurring in fewer than 1/1000 patients.

Total Body System: *Frequent* was headache. *Infrequent* were abdominal cramp or pain, asthenia, chills, back pain, chest pain, neck pain, fatigue, and rigid neck. *Rare* were fever and photosensitivity reaction.

Cardiovascular: *Infrequent* were vasodilation, palpitations, and tachycardia. *Rare* were intermediate coronary syndrome, abnormal cardiac rhythm, hypertension, and syncope.

Digestive: *Infrequent* were diarrhea, vomiting, and dyspepsia. *Rare* were decreased appetite, increased appetite, colitis, gastritis, gastroenteritis, esophageal reflux, increased thirst, and increased salivation.

Metabolic: *Infrequent* were hyperglycemia and increased serum creatine phosphokinase. *Rare* were increased gamma glutamyl transpeptidase and hypercholesteremia.

Musculoskeletal: *Infrequent* were myalgia and muscular weakness. *Rare* were arthralgia, arthritis, and myopathy.

Nervous: *Frequent* were dizziness and somnolence. *Infrequent* were tremor, vertigo, anxiety, hypesthesia, restlessness, CNS stimulation, insomnia, and shakiness. *Rare* were change in dreams, impaired concentration, abnormal coordination, depressive symptoms, euphoria, hyperreflexia, hypertonia, nervousness, neuropathy, nightmares, and nystagmus.

Respiratory: *Infrequent* were pharyngitis, rhinitis, dyspnea, laryngismus, sinusitis, bronchitis, and epistaxis. *Rare* were hyperventilation, laryngitis, and sneezing.

Skin: *Infrequent* were diaphoresis, dermatitis, erythema, pruritus, and rash.

Special Senses: *Infrequent* were ear pain, conjunctivitis, eye irritation, hyperacusis, and taste alteration. *Rare* were diplopia, dry eyes, eye pain, otitis media, parosmia, scotoma, and tinnitus.

Urogenital: Dysmenorrhea was *infrequent*.

Long-Term Safety

In a long term open label study, 762 patients treated 13,751 migraine attacks with AXERT over a period of up to 1 year. Migraine headaches could be treated with either a single dose of 12.5 mg AXERT or an initial 12.5 mg dose followed by a second 12.5 mg dose if needed. In this study, 3% (24 of 762) of patients withdrew due to an adverse experience. The most common adverse events (defined as occurring in more than 3% of patients) in descending order frequency were as follows: back pain (8%), bronchitis (6.4%), influenza like symptoms (5.8%), pharyngitis (4.6%), vomiting (4.2%), rhinitis (4.1%), skeletal pain (3.4%) and sinusitis (3.4%). Due to the lack of placebo control in this study, the role of AXERT in causation cannot be reliably determined.

POST-MARKETING ADVERSE REACTIONS

In addition to the adverse experiences reported during clinical trials of AXERT, the following adverse events have been reported in patients receiving marketed AXERT from worldwide use since approval. Due to the uncontrolled nature of post-marketing surveillance, it is not possible to definitely determine the proportion of the reported cases that were actually caused by AXERT or to reliably assess causation.

Serious cardiovascular adverse events, including acute myocardial infarction, coronary vasospasm and angina pectoris have been reported within a few hours following administration of AXERT.

Although very rare, AXERT can cause coronary vasospasm; at least one of these events occurred in a patient with no cardiac history and with documented absence of coronary artery disease (see CONTRAINDICATIONS, WARNINGS, ADVERSE REACTIONS and PRECAUTIONS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Patients and volunteers receiving single oral doses of 100 to 150 mg of AXERT did not experience significant adverse events. During the clinical trials, one patient ingested 62.5 mg in a five-hour period, and another patient ingested 100 mg in a 38-hour period. Neither patient experienced adverse reactions.

Based on the pharmacology of 5-HT_1 agonists, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination (i.e. gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with AXERT. Clinical and electrocardiographic monitoring should be continued for at least 20 hours, even if clinical symptoms are not observed.

The effects of hemodialysis or peritoneal dialysis on plasma concentrations of almotriptan are unknown.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 6.25 mg and 12.5 mg of AXERT (almotriptan malate) were effective for the acute treatment of migraine in adults, with the 12.5 mg dose tending to be a more effective dose (see CLINICAL STUDIES). Individuals may vary in response to doses of AXERT. The choice of dose should therefore be made on an individual basis.

If the headache returns, the dose may be repeated after 2 hours, but no more than two doses should be given within a 24-hour period. Controlled trials have not adequately established the effectiveness of a second dose if the initial dose is ineffective. The safety of treating an average of more than four headaches in a 30-day period has not been established.

Continued on page A-65

PRESCRIBING INFORMATION

PrReminyl*

Galantamine hydrobromide tablets

PrREMINYL*

galantamine hydrobromide tablets
4 mg, 8 mg, 12 mg galantamine base
Cholinesterase Inhibitor

CLINICAL PHARMACOLOGY

Although the etiology of cognitive impairment in Alzheimer's Disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's Disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's Disease).

REMINYL (galantamine hydrobromide), a tertiary alkaloid, is a competitive and reversible cholinesterase inhibitor. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible cholinesterase inhibition. It has also been postulated, based on *in vitro* data, that galantamine enhances the action of acetylcholine through binding to an allosteric site on the nicotinic receptors (see PRECAUTIONS). The clinical relevance to humans of these *in vitro* findings is unknown.

If these mechanisms are correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

Pharmacokinetics

Absorption

The summary of related pharmacokinetic parameters in healthy subjects is presented in Table 1. After oral intake of a single 8 mg galantamine solution in 12 healthy males, absorption is rapid, with a peak plasma concentration (C_{max}) of 43 ± 13 ng/mL, which is reached after 1.2 hours (T_{max}), and a mean AUC_∞ of 427 ± 102 ng.h/mL.

The absolute oral bioavailability of galantamine is 88.5%. Bioavailability of the tablet was the same as the bioavailability of an oral solution in 27 healthy males. Food did not affect the AUC of galantamine but C_{max} decreased by 25% and T_{max} was delayed by 1.5 hours after repeated oral dosing of 12 mg galantamine b.i.d. in 24 healthy elderly subjects.

The maximum inhibition of anticholinesterase activity of about 40% was achieved about one hour after a single oral dose of 8 mg galantamine in healthy male subjects.

Table 1. Pharmacokinetic parameters of galantamine after single or multiple dose administration

	C_{max} (ng/mL)	t_{max} (h)	$C_{ss,av}$ (ng/mL)	C_{min} (ng/mL)	AUC† (ng.h/mL)	$T_{1/2}$ (h)
Single dose, 12 healthy males						
8 mg, solution p.o.	42.6 ± 13.1	1.2 ± 0.6	-	-	427 ± 102	7.3 ± 1.7
8 mg, 1 hr i.v. infusion	-	-	-	-	482 ± 112	7.4 ± 1.7
Food effect, single dose, 24 healthy elderly						
Fasted, 8 mg p.o.	57.5 ± 15.8	1.1 ± 0.5	-	-	562 ± 180	9.7 ± 3.1
Non-fasted, 8 mg p.o.	42.5 ± 7.5	2.6 ± 1.4	-	-	543 ± 176	9.7 ± 3.3
Multiple oral dose, 27 healthy males						
12 mg b.i.d. tablet	89.4 ± 18.3	1.0 ± 0.6	51.9 ± 12.2	30.7 ± 10.3	623 ± 147	-
12 mg b.i.d. solution	87.6 ± 20.5	1.1 ± 0.5	50.5 ± 13.0	29.8 ± 10.2	606 ± 156	-
Dose-proportionality, multiple oral dose, 18 healthy subjects						
4 mg b.i.d. tablet	30.7 ± 6.2	1.9 ± 0.8	17.7 ± 4.6	10.6 ± 4.0	212 ± 56	-
8 mg b.i.d. tablet	63.8 ± 14.2	1.7 ± 0.8	36.6 ± 9.8	20.6 ± 6.8	439 ± 117	-
12 mg b.i.d. tablet	97.4 ± 31.4	1.9 ± 1.1	53.1 ± 12.7	29.1 ± 9.3	637 ± 152	-
16 mg b.i.d. tablet	137 ± 36	1.7 ± 0.9	76.5 ± 20.3	41.5 ± 14.2	918 ± 244	7.9 ± 0.8

† $AUC = AUC_\infty$ after single dose and $AUC = AUC_\tau$ after multiple dose

Distribution

Galantamine is a low-clearance drug (plasma clearance of approximately 300 mL/min) with a moderate volume of distribution (average Vd_{ss} of 175 L) after a one-hour i.v. infusion of 8 mg galantamine in 12 healthy males.

The plasma protein binding of galantamine is 18% at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%) and plasma water (39.0%), whereas the fraction of galantamine bound to plasma proteins is only 8.4%. The blood-to-plasma concentration ratio of galantamine is 1.2.

Metabolism

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 are the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly (see PRECAUTIONS, Drug-Drug Interactions). O-demethylation, mediated by CYP2D6 is greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity.

Elimination

The elimination of galantamine is bi-phasic, with a terminal half-life in the order of 7-8 hours in young healthy subjects (n=4 males). Two studies in healthy elderly subjects indicated that the terminal half-life of galantamine is 8.5 hours (n=13 males and 16 females) and 9.7 hours (n=10 males and 14 females) after administering a single oral dose of 10 mg galantamine. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide accounted for 14-24%. Seven days after a single oral dose of 4 mg ^{3}H-galantamine, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose, and that of galantamine glucuronide for another 12% on average.

After i.v. and oral administration, about 20% of the dose was excreted as unchanged galantamine in the urine in 24 hours, with a renal clearance of about 65 mL/min, which represents 20-25% of the total plasma clearance of about 300 mL/min.

CYP2D6 Poor Metabolizers

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of the CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar C_{max} and about 35% AUC_∞ increase of unchanged galantamine compared to extensive metabolizers.

A total of 356 patients with Alzheimer's disease enrolled in two Phase III studies were genotyped with respect to CYP2D6 (n=210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability due to observed inter-patient variability.

Hepatic Impairment

Following a single 4 mg dose of galantamine, the pharmacokinetics of galantamine in subjects with mild hepatic impairment (n=8; Child-Pugh score of 5-6) were similar to those in healthy subjects. In patients with moderate hepatic impairment (n=8; Child-Pugh score of 7-9), AUC and half-life of galantamine were increased by about 30% compared to normal subjects (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment

In patients with renal insufficiency, elimination of galantamine decreases with decreasing creatinine clearance. Following a single 8 mg dose of galantamine, AUC increased by 37% and 67% in moderately (n=8; creatinine clearance of 30 to 60 mL/min/1.73 m^2) and severely (n=9; creatinine clearance of 5 to 29 mL/min/1.73 m^2) renal-impaired patients compared to normal volunteers (n=8) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Patients with Alzheimer's Disease

Data from clinical trials in patients indicate that there is a difference in total clearance after oral administration between patients with Alzheimer's Disease and healthy subjects (13.2 L/h versus 19.4 L/h) based on pooled population analysis. Therefore, the plasma concentrations of galantamine in elderly patients (median age 75) with Alzheimer's Disease are 30-40% higher than in healthy young subjects (median age 28).

Gender and Race

No specific pharmacokinetic study was performed to investigate the gender differences. A population pharmacokinetic analysis (n=539 males and 550 females) suggests that galantamine clearance is about 20% lower in females than in males, which is explained by lower body weight in females.

Pharmacokinetic differences due to race have not been identified in a population pharmacokinetic analysis (n=1029 White, 24 Black, 13 Asian and 23 other).

Clinical Trials

Efficacy data for REMINYL (galantamine hydrobromide) in the symptomatic treatment of patients with Alzheimer's Disease were derived from 4 randomized, double-blind, placebo-controlled clinical trials in patients with probable Alzheimer's Disease [diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination Scores that were ≥10 and ≤24]. Doses studied were 8-32 mg/day given as twice daily doses. In 3 of the 4 studies, patients were started on a low dose of 8 mg, then titrated weekly by 8 mg/day to 24 or 32 mg as assigned (GAL-USA-1, GAL-INT-1, GAL-INT-2). In the fourth study (U.S. 4-week Dose-Escalation Fixed-Dose Study, GAL-USA-10) dose escalation of 8 mg/day occurred over 4 week intervals. The mean age of patients participating in the 4 REMINYL trials was 75 years with a range of 41 to 100. Approximately 62% of patients were women and 38% were men. The racial distribution was White 94%, Black 3% and other races 3%. Two other studies examined a three times daily dosing regimen; these also showed or suggested benefit but did not suggest an advantage over twice daily dosing.

Results for 2 of these studies are presented in this section. The data shown below 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).

Study Outcome Measures: In each study, the primary efficacy of REMINYL was evaluated using a dual outcome assessment strategy as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change (CIBIC-plus).

The ability of REMINYL to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance, including elements of memory, orientation, attention, reasoning, language and praxis.

The patients recruited as participants in each study had mean scores on the ADAS-cog of approximately 27 units, with a range from 5 to 69. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's Disease suggests that they gain 6 to 12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in REMINYL trials was approximately 4.5 units per year.

The ability of REMINYL to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-plus. The CIBIC-plus used in the trials was a semi-structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of 4 major areas of patient function: general, cognitive, behavioural and activities of daily living. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-plus evaluations from other clinical trials.

Among the secondary measures of efficacy, the Alzheimer's Disease Cooperative Study, Activities of Daily Living Inventory (ADCS/ADL) was used. The ADCS/ADL is a caregiver-rated evaluation which yields a compound score derived from a categorical scale of 23 items concerning participation in activities of daily living.

U.S. Twenty-One-Week Fixed-Dose Study (GAL-USA-10)

In a study of twenty-one weeks' duration, 978 patients were randomized to doses of 8, 16, or 24 mg of REMINYL per day, or to placebo, each given in 2 divided doses. Treatment was initiated at 8 mg/day for all patients randomized to REMINYL, and increased by 8 mg/day every 4 weeks. Therefore, the maximum dose-escalation phase was 8 weeks and the minimum maintenance phase was 13 weeks (in patients randomized to 24 mg/day of REMINYL).

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all four dose groups over the 21 weeks of the study. At 21 weeks of treatment, the mean differences in the ADAS-cog change scores for the REMINYL-treated patients compared to the patients on placebo were 0.8, 2.9 and 2.9 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo and to the 8 mg/day treatment. There was no statistically significant difference between the 16 mg/day and 24 mg/day dose groups.

Figure 1: Time-course of the Changes from Baseline in ADAS-cog Score (ITT Population)

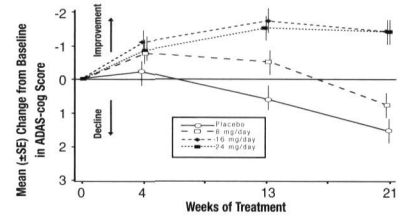
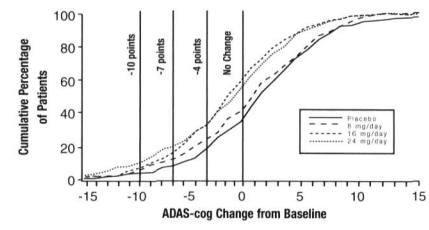


Figure 2 illustrates the cumulative percentages of patients from each of the four treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percentage of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL groups are more likely to show the greater improvements.

Figure 2: Cumulative Percentage of Patients with Specified Changes from Baseline in ADAS-cog Scores (ITT Population)



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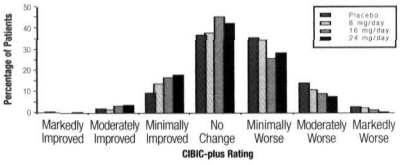
Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	3.7%	7.8%	19.0%	43.9%
8 mg/day	4.5%	11.4%	22.7%	47.7%
16 mg/day	6.4%	15.0%	33.1%	67.3%
24 mg/day	8.8%	19.8%	32.4%	62.6%

Effects on the CIBIC-plus: Figure 3 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the four treatment groups. The REMINYL-placebo differences for these groups of patients in the mean rating were 0.10, 0.32 and 0.38 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo. The differences vs. the 8 mg/day treatment for the 16 and 24 mg/day treatments were 0.22 and 0.28, respectively. There were no statistically significant differences between the 16 mg/day and 24 mg/day dose groups.

Figure 3: Distribution of CIBIC-plus Ratings at Week 21 (ITT Population)



Effects on ADCS/ADL Inventory: The Alzheimer's Disease Cooperative Study, Activities of Daily Living Inventory was used as a secondary efficacy measure. At baseline, mean ADCS/ADL scores (mean ± SE) were for the placebo group: 52.3 ± 0.89 units; for the 16 mg/day group: 51.6 ± 0.93 units; for the 24 mg/day group: 51.9 ± 0.98 units. At Week 21, the placebo group declined an average of 3.9 ± 0.55 units, and the 16 mg/day and 24 mg/day groups deteriorated minimally at 1.0 ± 0.51 units and 1.6 ± 0.56 units, respectively. The difference between the placebo group and the galantamine treatment groups (16 mg/day or 24 mg/day) was statistically significant.

U.S. Twenty-Six-Week Fixed-Dose Study (GAL-USA-1)

In a study of 26 weeks' duration, 636 patients were randomized to either a dose of 24 mg or 32 mg of REMINYL per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose-escalation phase and a 23-week maintenance phase.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog score for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean difference in the ADAS-cog change scores for the REMINYL-treated patients compared to the patients on placebo were 3.2 and 2.8 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not statistically significantly different from each other.

Figure 4: Time-course of the Changes from Baseline in ADAS-cog Score (ITT Population)

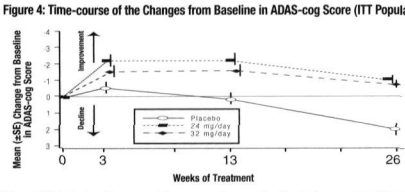
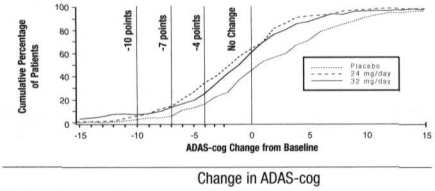


Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL groups are more likely to show the greater improvements. Curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

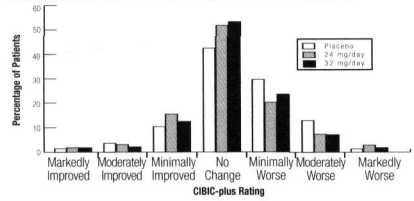
Figure 5: Cumulative Percentage of Patients with Specified Changes from Baseline in ADAS-cog Scores (ITT Population)



Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	2.3%	5.6%	16.4%	45.5%
24 mg/day	5.8%	14.0%	34.3%	63.8%
32 mg/day	7.7%	13.4%	25.8%	61.2%

Effects on the CIBIC-plus: Figure 6 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups. The mean REMINYL-placebo differences for these groups of patients in the mean rating were 0.22 and 0.17 units for 24 and 32 mg/day of REMINYL, respectively. The mean ratings for both groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 6: Distribution of CIBIC-plus Ratings Week 26 (ITT Population)



Age, gender and race: Patient's age, gender or race did not predict outcome of treatment.

INDICATIONS AND CLINICAL USE

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

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

CONTRAINDICATIONS

REMINYL (galantamine hydrobromide) is contraindicated in patients with known hypersensitivity to galantamine hydrobromide, other tertiary alkaloid derivatives or to any excipients used in the formulation.

WARNINGS

Anesthesia

REMINYL (galantamine hydrobromide), as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Neurological Conditions

Seizures: In placebo-controlled trials with REMINYL, cases of seizure were reported; there was no increase in incidence compared with placebo. Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's Disease. The risk/benefit of REMINYL treatment for patients with a history of seizure disorder must therefore be carefully evaluated.

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

Pulmonary Conditions

Like other cholinomimetic drugs, REMINYL should be prescribed with care for patients with a history of asthma or obstructive pulmonary disease.

Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and heart block. These actions may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction disorders, or to patients taking other drugs concomitantly which significantly slow heart rate. In clinical trials, patients with serious cardiovascular disease were excluded. Caution should be exercised in treating patients with active coronary artery disease or congestive heart failure. It is recommended that REMINYL 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.

In randomized controlled trials, bradycardia was reported at 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo, and it rarely led to treatment discontinuation. No increased incidence of heart block was observed at the recommended doses. Patients treated with galantamine up to 24 mg/day at the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo, 0.7% [2/286]; 4 mg b.i.d., 0.4% [3/692]; 8 mg b.i.d., 1.3% [7/552]; 12 mg b.i.d., 2.2% [6/273]).

A 6-week cardiovascular safety clinical trial (GAL-USA-16; n=139) was performed to investigate the effect of galantamine at doses up to 32 mg/day. This dosing regimen was: 8 mg/day in Week 1, 16 mg/day in Week 2, 24 mg/day in Weeks 3 and 4, and 32 mg/day in Weeks 5 and 6. Heart block/pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients. It should be noted that a forced 1-week dose escalation was used in this study, which is not recommended. Whether these cardiac effects are attenuated by slower titration rates is not known. Particular *caution is warranted during titration where the majority of pauses occurred in the* above study.

Gastrointestinal Conditions

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g. those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). In controlled clinical studies with REMINYL, patients with symptomatic peptic ulceration were excluded. Clinical studies of REMINYL have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see ADVERSE REACTIONS).

REMINYL, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting and diarrhea, anorexia and weight loss. These effects appeared more frequently at higher doses (see ADVERSE REACTIONS), with nausea and vomiting being *more prevalent in women and patients with lower body weight and* correspondingly higher plasma drug concentrations. Females are more sensitive to the cholinergic adverse effects associated with cholinesterase inhibitors and in general are more likely to experience nausea and vomiting than are males. In most cases, these effects were of mild to moderate intensity and transient and have resolved during continued REMINYL treatment or upon treatment discontinuation.

Weight Loss

Cholinesterase inhibitors as well as Alzheimer's Disease can be associated with significant weight loss. In controlled clinical trials, the use of REMINYL was associated with weight loss. Weight decrease occurred early during treatment and was related to dose. Weight loss of ≥7% occurred more frequently in patients treated with REMINYL and in female patients than in patients receiving placebo. Where weight loss may be of clinical concern, body weight should be monitored.

Genitourinary

Although not observed in clinical trials of REMINYL, 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 the REMINYL (galantamine hydrobromide) clinical trials received neuroleptics, antidepressants or anticonvulsants, there is thus limited information concerning the interaction of REMINYL with these drugs.

Use in Patients ≥85 Years Old

In controlled clinical studies, the number of patients aged 85 years or over who received REMINYL at therapeutic doses of 16 or 24 mg/day was 123. Of these patients, 70 received the maximum recommended dose of 24 mg/day. There is limited safety information for REMINYL in this patient population.

Since cholinomimetics as well as Alzheimer's Disease can be associated with significant weight loss, caution is advised regarding the use of REMINYL in elderly patients with low body weight, especially in those ≥85 years old.

Use in Elderly Patients with Serious Comorbid Disease

There is limited information on the safety of REMINYL treatment in patients with mild to moderate Alzheimer's Disease and serious/significant comorbidity. The use of REMINYL 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. Dose escalation in this patient population should proceed with caution.

Renally and Hepatically Impaired Patients

There is limited information on the pharmacokinetics of REMINYL in renally and hepatically impaired patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics). It is therefore recommended that dose escalation with REMINYL in Alzheimer's Disease patients with renal impairment (creatinine clearance of 9 to 60 mL/min) or hepatic impairment be undertaken with caution and under conditions of close monitoring for adverse effects (see DOSAGE AND ADMINISTRATION, Special Populations). Since no data are available on the use of REMINYL in patients with a creatinine clearance of less than 9 mL/min and in *patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL* is not recommended for these populations.

Drug-Drug Interactions

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide.

Effect of Other Drugs on the Metabolism of REMINYL

Pharmacokinetic studies to assess the potential of REMINYL for interaction with cimetidine, ranitidine, ketoconazole, erythromycin, paroxetine, warfarin and digoxin were limited to short-term, mostly single-dose studies in young healthy volunteers. Similar studies in elderly patients were not done.

In vitro

CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of *galantamine. CYP3A4 mediates the formation of galantamine-N-oxide, whereas* CYP2D6 is involved in the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged in urine, no single pathway appears predominant.

In vivo

Cimetidine and Ranitidine: Galantamine was administered as a single dose of 4 mg on Day 2 of a 3-day treatment with either cimetidine (800 mg daily; n=6 males and 6 females) or ranitidine (300 mg daily; n=6 males and 6 females). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the pharmacokinetics of galantamine.

Ketoconazole: Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg b.i.d. for 4 days, increased the AUC of galantamine by 30% when subjects were treated with galantamine 4 mg b.i.d. for 8 days (n=8 males and 8 females).

Erythromycin: Erythromycin, a moderate inhibitor of CYP3A4 at a dose of 500 mg q.i.d. for 4 days increased the AUC of galantamine by 10% when subjects received galantamine 4 mg b.i.d. for 6 days (n=8 males and 8 females).

Paroxetine: Paroxetine, a strong inhibitor of CYP2D6, increased the AUC of 4 mg b.i.d., 8 mg b.i.d. and 12 mg b.i.d. galantamine by 40%, 45% and 48%, respectively, in 16 healthy volunteers (8 males and 8 females) who received galantamine together with 20 mg/day paroxetine.

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Effect of Galantamine on the Metabolism of Other Drugs

In vitro

Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

In vivo

Warfarin: Galantamine at 12 mg b.i.d. had no effect on the pharmacokinetics of R- and S-warfarin (25 mg single dose) or on the prothrombin time (n=16 males). The protein binding of warfarin was unaffected by galantamine.

Digoxin: Galantamine at 12 mg b.i.d. had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were co-administered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia (n=8 males and 8 females).

Nicotinic Receptor Modulation

Single *in vitro* applications of galantamine dose-dependently modulate the effect on nicotinic receptors, having a positive allosteric (sensitizing) effect at concentrations below 0.28 µg/mL (1 µM) and an inhibitory effect at higher concentrations. Chronic *in vitro* or *in vivo* studies on nicotinic receptor modulation have not been conducted.

It is unknown whether galantamine has an effect on the pharmacodynamic action of other drugs that act on cholinergic nicotinic receptors (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times on an exposure [AUC] basis), and 30 mg/kg/day (12 times the MRHD on a mg/m² basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m² basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m² and AUC basis).

Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m² basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m² basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

Pregnancy

In a teratology study in which rats were dosed from Day 14 (females) or Day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the MRHD on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through Day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis.

The safety of REMINYL in pregnant women has not been established. REMINYL should not be used in women of childbearing potential unless, in the opinion of the physician, the potential benefit to the patient justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether REMINYL is excreted in human breast milk and therefore REMINYL should not be used in nursing mothers.

Pediatric Use

The safety and effectiveness of REMINYL in any illness occurring in pediatric patients have not been established.

ADVERSE REACTIONS

A total of 2287 patients with mild to moderate Alzheimer's Disease were treated with REMINYL (galantamine hydrobromide) in Phase III controlled clinical studies using either a 1-week or 4-week dose-escalation period, and 761 patients received REMINYL 24 mg/day, the maximum recommended maintenance dose. The number of patients who completed the studies was 1686 (72%). The mean duration of treatment for all REMINYL groups was 130 days (range 1-214 days).

Adverse Events Leading to Discontinuation

Overall, 19% (441/2287) of patients treated with REMINYL discontinued from Phase III controlled clinical trials due to adverse events compared to 8% (98/1159) in the placebo group. For patients treated with REMINYL, the rate of discontinuation due to adverse events was 14% for males and 22% for females.

In the 4-week dose-escalation fixed-dose study (GAL-USA-10), 8% (55/692) of patients treated with REMINYL withdrew due to adverse events compared to 7% (20/286) in the placebo group. During the dose-escalation phase of this study the incidence of discontinuations due to adverse events was 4% for placebo, 5% for REMINYL 16 mg/day and 6% for REMINYL 24 mg/day. During the maintenance phase, 4% of patients who received placebo, 3% of patients who received REMINYL 16 mg/day and 4% of patients who received REMINYL 24 mg/day withdrew from this study due to adverse events.

Table 1 shows the most frequent adverse events leading to discontinuation for study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used.

Table 1: Most frequent adverse events leading to discontinuation in a placebo-controlled, double-blind trial with a 4-week dose-escalation schedule (GAL-USA-10)

Adverse Events	Recommended 4-week dose escalation		
	Placebo n=286	16 mg/day n=279	24 mg/day n=273
Nausea	<1%	2%	4%
Vomiting	0%	1%	3%
Anorexia	<1%	1%	<1%
Dizziness	<1%	2%	1%
Syncope	0%	0%	1%

Most Frequent Adverse Clinical Events Seen in Association with the Use of REMINYL

The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate of placebo in study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used are shown in Table 2. These events were primarily gastrointestinal and tended to occur at a lower rate with 16 mg/day, the initial recommended maintenance dose.

Table 2: Most frequent adverse events in a randomized placebo-controlled clinical trial with a 4-week dose increment during dose-escalation and maintenance phases (GAL-USA-10)

Adverse Events	Week 1-12†			Week 13-21		
	Placebo n=286	16 mg/day n=279	24 mg/day n=273	Placebo n=259	16 mg/day n=243	24 mg/day n=241
Nausea	5%	11%	13%	<1%	4%	6%
Vomiting	<1%	5%	6%	<1%	2%	6%
Diarrhea	5%	9%	4%	2%	5%	2%
Anorexia	2%	5%	5%	1%	2%	5%

† Dose escalation occurred with 4 weeks per dose increment.

The majority of these adverse events occurred during the dose-escalation period. Nausea and vomiting, the most frequent adverse events, occurred more frequently at higher doses, lasted 5-7 days in most cases, and the majority of patients had one episode. The incidence of weight loss in this study was, during dose escalation (Weeks 1-12): placebo, 1%; 16 mg/day, 3%; 24 mg/day, 2%; and during the maintenance phase (Weeks 13-21): placebo, <1%; 16 mg/day, 3%; 24 mg/day, 3%.

Dose escalation should be cautious and maintenance dosing should remain flexible and be adjusted according to individual needs.

Adverse Events Reported in Controlled Trials

The reported adverse events in REMINYL trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour and the types of patients treated may differ.

Table 3 lists the most common adverse events (adverse events occurring with an incidence of 2% with REMINYL treatment and in which the incidence was greater than with placebo treatment) for four placebo-controlled trials for patients treated with 16 or 24 mg/day of REMINYL. The combined values presented in Table 3 were derived from trials using a 1-week or the recommended 4-week dose-escalation period.

Table 3: Adverse events reported in at least 2% of patients with Alzheimer's Disease administered REMINYL and at a frequency greater than with placebo (combined 1- and 4-week dose-escalation data)

Body System / Adverse Events	Placebo (n=801)	REMINYL† (n=1040)
Body as a whole - general disorders		
Fatigue	3%	5%
Syncope	1%	2%
Central & peripheral nervous system disorders		
Dizziness	6%	9%
Headache	5%	8%
Tremor	2%	3%
Gastro-intestinal system disorders		
Nausea	9%	24%
Vomiting	4%	13%
Diarrhea	7%	9%
Abdominal pain	4%	5%
Dyspepsia	2%	5%
Heart rate and rhythm disorders		
Bradycardia	1%	2%
Metabolic and nutritional disorders		
Weight decrease	2%	7%
Psychiatric disorders		
Anorexia	3%	9%
Depression	5%	7%
Insomnia	4%	5%
Somnolence	3%	4%
Red blood cell disorders		
Anemia	2%	3%
Respiratory system disorders		
Rhinitis	3%	4%
Urinary system disorders		
Urinary tract infection	7%	8%
Hematuria	2%	3%

† Adverse events in patients treated with 16 or 24 mg/day of REMINYL in three placebo-controlled trials with a 1-week dose-escalation period and a 26-week fixed-dose REMINYL treatment, and one placebo-controlled trial with the recommended 4-week dose-escalation period and a 21-week fixed-dose REMINYL treatment are included.

No clinically relevant abnormalities in laboratory values were observed. In a cardiovascular safety clinical trial (GAL-USA-16), pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients during the dose-escalation period (see WARNINGS).

Other Adverse Events Observed During Clinical Trials

REMINYL has been administered to 3055 patients with Alzheimer's Disease during clinical trials worldwide.

A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's Disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years. To establish the rate of adverse events, data from all patients for any dose of REMINYL in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All events occurring in approximately 0.1% of patients are included, except for those already listed elsewhere in labelling, WHO terms too general to be informative, or relatively minor events. Events are classified by body system and listed using the following definitions: *frequent adverse events* - those occurring in at least 1/100 patients; *infrequent adverse events* - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to REMINYL treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole - General Disorders: *Frequent:* chest pain.

Cardiovascular System Disorders: *Frequent:* hypertension; *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure.

Central & Peripheral Nervous System Disorders: *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia.

Gastrointestinal System Disorders: *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *Rare:* esophageal perforation.

Heart Rate & Rhythm Disorders: *Infrequent:* AV block, palpitation, atrial fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T-wave inversion, ventricular tachycardia.

Metabolic & Nutritional Disorders: *Infrequent:* hyperglycemia, alkaline phosphatase increased, NPN increased.

Platelet, Bleeding & Clotting Disorders: *Infrequent:* purpura, epistaxis, thrombocytopenia.

Psychiatric Disorders: *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium.

Urinary System Disorders: *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi.

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.

In a postmarketing report, one patient who had been taking 4 mg of galantamine daily inadvertently ingested eight 4 mg tablets (32 mg total) on the tenth day of treatment. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment. ECG obtained just prior to initiation of galantamine treatment was normal.

Treatment

REMINYL (galantamine hydrobromide) has a plasma half-life of approximately 7-8 hours. It is recommended that, in case of asymptomatic overdose, no further dose of REMINYL should be administered and the patient should be monitored.

As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the following signs of cholinergic crisis may develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Tertiary anticholinergics such as atropine may be used as an antidote for REMINYL overdosage. Intravenous atropine sulphate titrated to effect is recommended at an initial dose of 0.5 to 1.0 mg i.v., 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. It is not known whether REMINYL and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.

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COPAXONE®
(glatiramer acetate injection)

20 mg, single use vials and 20 mg/1.0 mL, pre-filled syringes for Subcutaneous Injection

THERAPEUTIC CLASSIFICATION Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

COPAXONE® [glatiramer acetate for injection (formerly known as copolymer-1)] is a sterile, lyophilized mixture of synthetic polypeptides containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine with an average molar fraction of 0.141, 0.427, 0.095 and 0.338, respectively.

The mechanism(s) by which glatiramer acetate exerts its effect on Multiple Sclerosis (MS) is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in animals that is generally accepted as an experimental model of MS.

Studies in animals and *in vitro* systems suggest that upon its administration glatiramer acetate specific suppressor T cells are induced and activated in the periphery.

Because the immunological profile of glatiramer acetate remains to be fully elucidated, concerns exist about its potential to alter naturally occurring immune responses (see **PRECAUTIONS**).

Pharmacokinetics: Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support the assumption that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Nevertheless, larger fragments of glatiramer acetate can be recognized by glatiramer acetate reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some, may enter the systemic circulation intact.

Clinical Studies: The efficacy of COPAXONE® (glatiramer acetate for injection) was evaluated in two placebo-controlled trials in patients with Relapsing-Remitting MS (RR-MS). In a third placebo-controlled study the effects of glatiramer acetate on MRI parameters were assessed. In these studies, a dose of 20 mg/day was used. No other dose or dosing regimen has been studied in placebo-controlled trials of RR-MS.

The first trial was a pilot study Trial 1 (Trial BR-I) which was conducted at a single-center and was a double-blind, randomized, *matched-pair, parallel group placebo-controlled trial. Fifty patients with RR-MS were randomized to receive 20 mg/day* glatiramer acetate (n=25) or placebo (n=25) subcutaneously. The protocol-specified primary outcome measure was the proportion of patients who were relapse free during the 2-year duration of the trial, but two additional relevant outcomes were also specified as endpoints: frequency of attacks during the trial, and the change in the number of attacks compared to the rate of attacks in the 2 years prior to study entry. Results from this study (see Table 1) show that there was a statistically significant effect of glatiramer acetate on number of relapses.

TABLE 1 – Trial BR-1: Efficacy Results

Outcome	Trial I[a]		
	Glatiramer acetate n=25	Placebo n=25	p-Value
% Relapse Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate compared to pre-study	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

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

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

Trial II (01-9001) was a multicenter double-blind, randomized, placebo-controlled trial. Two hundred and fifty-one patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n=125) or placebo (n=126) subcutaneously. Patients were diagnosed with RR-MS by standard criteria, and had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients had a score of no more than 5 on the Kurtzke Expanded Disability Scale Score (EDSS), a standard scale ranging from 0 (normal) to 10 (death due to MS). A score of 5 is defined as one at which a patient is still ambulatory but for whom full daily activities are impaired due to disability, a score of 6 is defined as one at which the patient is still ambulatory but requires assistance and a score of 7 on this scale means that the patient requires a wheelchair.

Patients were seen every 3 months for 2 years, as well as within several days of a presumed exacerbation. In order for an exacerbation to be confirmed, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the lesion for at least 48 hours).

The protocol-specified primary outcome measure was the mean number of relapses during treatment. Table 2 shows results of the analysis of primary as well as several secondary outcome measures at two years based on the intent-to-treat population.

TABLE 2 – Core (24-month) Double-Blind Study: Effect on Relapse Rate

Outcome	Trial II[a]		
	Glatiramer acetate n=125	Placebo n=126	p-Value
Mean No. of Relapses/2 years[b]	1.19	1.68	0.055
% Relapse Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Patients Progression Free[c]	98/125 (78%)	95/126 (75%)	0.48
Mean Change in EDSS	-0.05	+0.21	0.023

[a] The primary efficacy measure for **Trial II** was the number of relapses during treatment. Analyses were based on the intent-to-treat population.

[b] Baseline adjusted mean.

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

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

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

The third study (9003) was a multi-national, multi-center, MRI-monitored study. A total of 239 patients with RR-MS (119 on glatiramer acetate and 120 on placebo) were randomized. Inclusion criteria were similar to those in Trial II (Study 01-9001) with the additional criteria that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated initially in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over nine months. Other MRI parameters were assessed as secondary endpoints. Table 3 summarizes the results for the parameters monitored during the nine-month double-blind phase for the intent-to-treat cohort. Because the link between MRI findings and the clinical status of patients is contentious, the prognostic value of the following statistically significant findings is unknown.

TABLE 3 – Nine-Month Double-Blind Phase: MRI Endpoints – Results

No.	Outcome	Glatiramer acetate n=113	Placebo n=115	p-Value
Primary Endpoint				
1.	Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	12	17	0.0037
Secondary Endpoints				
2.	Medians of the Cumulative Number of New T1 Gd-Enhancing Lesions	9	14	0.0347
3.	Medians of the Cumulative Number of New T2 Lesions	5	8	0.01
4.	Medians of the Cumulative Change from Baseline in volumes (mL) of T1 Gd-Enhancing Lesions	-0.309	0	0.0248
5.	Medians of the Cumulative Change from Baseline in volumes (mL) of T2 Lesions	8.852	13.566	0.0229
6.	Medians of the Cumulative Change from Baseline in volumes (mL) of T1 Hypointense Lesions	1.642	1.829	0.7311
7.	Proportion of T1 Gd-Enhancing Lesion-Free Patients	46.4%	32.2%	0.0653

The mean number of relapses in this 9-month study was 0.50 for the COPAXONE® group and 0.77 for the placebo group (p=0.0077).

INDICATIONS AND CLINICAL USE

For use in ambulatory patients with Relapsing-Remitting Multiple Sclerosis to reduce the frequency of relapses.

The safety and efficacy of COPAXONE® in chronic progressive MS have not been established.

CONTRAINDICATIONS

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

WARNINGS

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

Symptoms of Potentially Cardiac Origin: Approximately 26% of COPAXONE® patients in the pre-marketing multicenter controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain (see **ADVERSE REACTIONS: Chest Pain**). While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**), many did not. The pathogenesis of *this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New York Heart* Association Class I and II) and thus the risks associated with COPAXONE® treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown.

COPAXONE® has been associated with an Immediate Post-Injection Reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**).

COPAXONE® has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE® in such patients.

Anaphylactoid reactions associated with the use of COPAXONE® have been reported in rare instances (<1/1000) during the post-marketing period. Some cases required treatment with epinephrine and other appropriate medical treatment.

PRECAUTIONS

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

Considerations Involving the Use of a Product Capable of Modifying Immune Responses: COPAXONE® is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. Whether COPAXONE® can alter normal human immune responses, such as the recognition of foreign antigens is unknown. It is therefore possible that treatment with COPAXONE® may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done. Continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled clinical trial of 125 RR-MS patients given glatiramer acetate 20 mg for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype – and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested. Nevertheless, anaphylaxis can be associated with the administration of almost any foreign substance and, therefore, this risk cannot be excluded.

Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats do not suggest any evidence of carcinogenic potential related to glatiramer acetate administered subcutaneously at dose levels of up to 30 mg/kg/day in rats and 60 mg/kg/day in mice (see **TOXICOLOGY: Carcinogenicity**). The relevance of these findings for humans is unknown (see **PRECAUTIONS: Considerations Involving the Use of a Product Capable of Modifying Immune Responses**).

Drug Interactions: Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with Interferon beta. However, 246 patients who failed on or who did not tolerate therapy with Interferon beta and were later treated with COPAXONE® within the framework of an open clinical trial did not report any serious or unexpected adverse events thought to be related to treatment.

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

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

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

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

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

ADVERSE REACTIONS

In the pre-marketing clinical trials, approximately 900 individuals have received at least one dose of COPAXONE® (glatiramer acetate for injection) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE® in clinical trials ranged *from 6 months (693 patients) to 2 years (306 patients), and to over 7 years (69 patients) at a daily dose of 20 mg.*

In controlled clinical trials, the most commonly observed adverse events associated with the use of COPAXONE® which occurred at a higher frequency than in placebo treated patients were: injection site reactions, vasodilation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety and hypertonia.

Of a total of 844 patients who could be evaluated for safety, approximately 8% discontinued treatment due to an adverse event. The adverse events most commonly associated with discontinuation were: injection site reaction (6.5%), vasodilation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness and tremor. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE® treatment included a case of life-threatening serum sickness.

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

Chest Pain: Approximately 26% of glatiramer acetate patients in the multicenter pre-marketing controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. There has been only one episode of chest pain during *which a full ECG was performed; the ECG showed no evidence of ischemia. Patients in clinical trials were free of significant* cardiovascular disease (New York Heart Association Class I or II); therefore, the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown (see **WARNINGS: Symptoms of Potentially Cardiac Origin**).

Table 4 lists the adverse experiences after up to 35 months of treatment (>27-33 months: COPAXONE®, n=84; Placebo, n=75; >33 months: COPAXONE®, n=12; Placebo, n=24) in the pre-marketing multicenter placebo-controlled study (Trial II) in relapsing-remitting Multiple Sclerosis patients that occurred at an incidence of at least 2% among patients who received COPAXONE® and at an incidence that was at least 2% more than that observed in the same trial for placebo patients regardless of their causal relationship to treatment. No laboratory adverse experiences that met these criteria were reported.

It should be noted that the figures cited in Table 4 cannot be used to predict the incidence of side effects during the course of usual medical practice, where patient characteristics and other factors differ from those that prevailed in the clinical trials. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution *of drug and non-drug factors to the adverse event incidence rate in the population studied.*

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TABLE 4
Pre-marketing Controlled Trial in Patients with Multiple Sclerosis
Adverse Experiences ≥ 2% Incidence and ≥ 2% Above Placebo

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

Other events which occurred in at least 2% of patients but were present at equal or greater rates in the placebo group included: *Body as a whole:* Headache, injection site ecchymosis, accidental injury, abdominal pain, allergic rhinitis and malaise. *Digestive System:* Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth. *Musculo-Skeletal:* Myasthenia and myalgia. *Nervous System:* Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign, abnormal thinking, twitching, euphoria, and sleep disorder. *Respiratory System:* Pharyngitis, sinusitis, increased cough and laryngitis. *Skin and Appendages:* Acne, alopecia, and nail disorder. *Special Senses:* Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness. *Urogenital System:* Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender related differences. No clinically significant differences were identified. In these clinical trials 92% of patients were Caucasian, which is representative of the population of patients with Multiple Sclerosis. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE®. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE® and placebo groups in blinded clinical trials. No patient receiving COPAXONE® withdrew from any trial due to abnormal laboratory findings.

Other Adverse Events Observed During All Clinical Trials

COPAXONE® has been administered to approximately 900 individuals during clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using COSTART II dictionary terminology. All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and other events which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients. **Body as a whole:** *Frequent:* Injection site edema, injection site atrophy, abscess and injection site hypersensitivity. *Infrequent:* Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma and photosensitivity reaction. **Cardiovascular:** *Frequent:* Hypertension. *Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension and varicose veins. **Digestive:** *Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discolouration and duodenal ulcer. **Endocrine:** *Infrequent:* Goiter, hyperthyroidism, and hypothyroidism. **Gastrointestinal:** *Frequent:* Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis. **Hemic and Lymphatic:** *Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly. **Metabolic and Nutritional:** *Infrequent:* Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma. **Musculoskeletal:** *Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis. **Nervous:** *Frequent:* Abnormal dreams, emotional lability, and stupor. *Infrequent:* Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression and transient stupor. **Respiratory:** *Frequent:* Hyperventilation, hay-fever. *Infrequent:* Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration. **Skin and Appendages:** *Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy and warts. *Infrequent:* Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash. **Special Senses:** *Frequent:* Visual field defect. *Infrequent:* Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss. **Urogenital:** *Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious Papanicolaou smear, urinary frequency and vaginal hemorrhage. *Infrequent:* Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, breast pain, carcinoma cervix *in situ*, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Adverse Events Reported Post-Marketing and Not Previously Noted in Clinical Trials

Post-marketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE® (glatiramer acetate for injection) not mentioned above, that have been received since market introduction and that may have or not have causal relationship to the drug include the following: **Body as a whole:** Sepsis, LE syndrome, hydrocephalus, enlarged abdomen, injection site hypersensitivity, allergic reaction, anaphylactoid reaction, bacterial infection, fever, infection. **Cardiovascular:** Thrombosis, peripheral vascular disease, pericardial effusion, myocardial infarct, deep thrombophlebitis, coronary occlusion, congestive heart failure, cardiomyopathy cardiomegaly, arrhythmia, angina pectoris, tachycardia. **Digestive:** Tongue edema, stomach ulcer hemorrhage, liver function abnormality, liver damage, hepatitis, eructation, cirrhosis of the liver, cholelithiasis, diarrhea, gastrointestinal disorder. **Hemic and Lymphatic:** Thrombocytopenia, lymphoma-like reaction, acute leukemia. **Metabolic and Nutritional:** Hypercholesteremia. **Musculoskeletal:** Rheumatoid arthritis, generalized spasm. **Nervous:** Myelitis, meningitis, CNS neoplasm, cerebrovascular accident, brain edema, abnormal dreams, aphasia, convulsion, neuralgia, anxiety, foot drop, nervousness, speech disorder, vertigo. **Respiratory:** Pulmonary embolus, pleural effusion, carcinoma of lung, hay fever, laryngismus. **Skin and Appendages:** Herpes simplex, pruritis, rash, urticaria. **Special Senses:** Glaucoma, blindness, visual field defect. **Urogenital:** Urogenital neoplasm, urine abnormality, ovarian carcinoma, nephrosis, kidney failure, breast carcinoma, bladder carcinoma, urinary frequency.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

COPAXONE® should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Multiple Sclerosis.

The recommended dose of COPAXONE® (glatiramer acetate for injection or glatiramer acetate injection) for the treatment of relapsing-remitting MS is a daily injection of 20 mg given subcutaneously.

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

For the pre-filled syringe of COPAXONE®, please see the **INFORMATION FOR THE PATIENT: pre-filled syringe** for instructions on the preparation and injection of COPAXONE®.

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Glatiramer acetate

Chemical Name: Glatiramer acetate is the acetate salt of synthetic polypeptides.

Description: Glatiramer acetate is prepared by chemically reacting the activated derivatives of four amino acids: L-glutamic acid (L-Glu), L-alanine (L-Ala), L-tyrosine (L-Tyr), and L-lysine (L-Lys) in a specified ratio. The molar fraction of each amino acid residue ranges as follows: L-Glu 0.129-0.153, L-Ala 0.392-0.462, L-Tyr 0.086-0.100 and L-Lys 0.300-0.374.

Structural Formula: Poly[L-Glu$^{[3-15]}$, L-Ala$^{[39-46]}$, L-Tyr$^{[8-6-10]}$, L-Lys$^{[30-37]}$]•nCH_3CO_2H (n=15-24)

Molecular Weight: The average molecular weight of the polypeptide is between 4,700 and 11,000 daltons, with at least 68 percent of the material within the range of 2,500 to 22,500 daltons.

Physical Form: White to slightly yellowish lyophilized material.

Solubility: Sparingly soluble in water, insoluble in acetone.

pH: The pH of a 0.5% w/v solution of glatiramer acetate in water is in the range of 5.5-8.0.

Composition: COPAXONE® (glatiramer acetate for injection) is a sterile, lyophilized drug product, intended for subcutaneous injection following reconstitution with Sterile Water for Injection. Each vial of lyophilized drug product contains 20 mg glatiramer acetate, plus a 2 mg overage to allow for losses in reconstitution and transfer, and 40 mg mannitol. Each vial of Sterile Water for Injection contains 1.1 mL of Sterile Water for Injection plus a 0.35 mL overage to allow for losses in reconstitution and transfer.

COPAXONE® (glatiramer acetate injection) is a single-use 20 mg/1.0 mL pre-filled syringe containing a sterile solution equivalent with the COPAXONE® reconstituted solution (i.e., 20 mg/mL glatiramer acetate and 40 mg mannitol in sterile water for injection).

Stability and Storage Recommendations: Vials of lyophilized COPAXONE® should be stored under refrigeration (2° - 8°C). COPAXONE® may also be stored at room temperature (15° - 30°C) for up to 14 days. The vials of diluent (Sterile Water for Injection) should be stored at room temperature.

The pre-filled syringes of COPAXONE® should be refrigerated immediately upon receipt (between 2° - 8°C). DO NOT FREEZE. If you cannot have refrigerator storage, pre-filled syringes of COPAXONE® can be stored at room temperature (15° - 30°C) for up to one week. Do not store pre-filled syringes at room temperature for longer than one week. Note: this drug is light sensitive, do not expose to light when not injecting. Each pre-filled syringe is for single use only.

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

Parenteral Products: COPAXONE® should be reconstituted only with the provided diluent, Sterile Water for Injection.

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

AVAILABILITY OF DOSAGE FORMS

COPAXONE® (glatiramer acetate for injection) is supplied as a 20 mg dose of sterile lyophilized glatiramer acetate with mannitol, packaged in single use 2 mL amber vials. A separate vial, containing 1.1 mL of diluent (Sterile Water for Injection) plus 0.35 mL of overage of diluent is included in the Self Injection Administration Package for each vial of drug. COPAXONE® (glatiramer acetate for injection) is available in packs of 32 amber vials of sterile lyophilized material for subcutaneous injection. The diluent (Sterile Water for Injection) for COPAXONE® is supplied in packs of 32 clear vials and is located in the Self Injection Administration Package.

COPAXONE® (glatiramer acetate injection) is a single-use 20 mg/1.0 mL pre-filled syringe containing a sterile solution equivalent with the COPAXONE® reconstituted solution (i.e., 20 mg/mL glatiramer acetate and 40 mg mannitol in sterile water for injection). COPAXONE® (glatiramer acetate injection) is available in packs of 30 single-use 20 mg/1.0 mL pre-filled glass syringes with 33 alcohol preps (swabs).

REFERENCES

1. COPAXONE® (glatiramer acetate) Product Monograph, Teva Neuroscience.

Product monograph available upon request.

TEVA NEUROSCIENCE

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Montreal, Quebec H3A 3L4

PAAB

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See pages A-6, A-7

PCOPAXONE®
(acétate de glatiramère injectable)

20 mg, flacons unidoses et 20 mg/1,0 mL, seringues préremplies pour injection sous-cutanée

CLASSIFICATION THÉRAPEUTIQUE *Immunomodulateur*

ACTION ET PHARMACOLOGIE CLINIQUE

COPAXONE® [acétate de glatiramère pour injection (connu auparavant sous le nom de copolymère1)] est un mélange lyophilisé stérile de polypeptides synthétiques renfermant quatre acides aminés naturels : l'acide L-glutamique, la L-alanine, la L-tyrosine et la L-lysine dans une fraction molaire moyenne de 0,141, de 0,427, de 0,095 et de 0,338, respectivement.

Le mode d'action de l'effet de l'acétate de glatiramère dans la sclérose en plaques (SEP) n'est pas encore complètement élucidé. On croit cependant que l'acétate de glatiramère exercerait un effet modulateur sur les processus immuns que l'on associe actuellement à la pathogenèse de la SEP. Cette hypothèse est étayée par les résultats des essais menés pour explorer la pathogenèse de l'encéphalomyélite allergique expérimentale (EAE), affection qui peut être déclenchée chez plusieurs espèces animales et qui est généralement acceptée comme modèle expérimental de la SEP.

Les études expérimentales sur animaux et les systèmes *in vitro* laissent supposer que l'administration de l'acétate de glatiramère induit et active des lymphocytes T suppresseurs spécifiques dans le sang périphérique.

Comme le profil immunologique de l'acétate de glatiramère n'est pas encore complètement élucidé, il est possible que le produit puisse avoir des effets sur les réactions immunitaires naturelles (voir **PRÉCAUTIONS**).

Pharmacocinétique : Les résultats obtenus au cours des essais pharmacocinétiques menés chez les humains (*volontaires sains*) et les animaux étayent l'hypothèse selon laquelle une fraction importante de la dose thérapeutique délivrée au patient par voie sous-cutanée est hydrolysée localement. Néanmoins, de grands fragments d'acétate de glatiramère peuvent être reconnus par les anticorps réactifs contre l'acétate de glatiramère. Une certaine proportion de la dose injectée, intacte ou partiellement hydrolysée, passerait dans la circulation lymphatique, ce qui permettrait au produit d'atteindre les ganglions lymphatiques régionaux ; de plus, il est possible qu'une partie du produit intact passe dans la circulation générale.

Essais cliniques : L'efficacité de COPAXONE® (acétate de glatiramère pour injection) a été évaluée dans le cadre de deux essais comparatifs (avec placebo) chez des patients atteints de SEP rémittente. Un troisième essai comparatif (avec placebo) a évalué les effets de l'acétate de glatiramère sur les paramètres IRM. Dans ces essais, on a eu recours à une dose de 20 mg/jour. Aucune autre dose ou schéma posologique n'ont été étudiés dans des essais comparatifs (avec placebo) sur la SEP rémittente.

Le premier essai Essai I (Essai BR-1) était un essai pilote comparatif (avec placebo) à répartition aléatoire en paires appariées, à groupes parallèles et à double insu qui a été mené dans un seul centre[15]. Cinquante patients atteints de SEP rémittente ont reçu, au hasard, 20 mg/jour d'acétate de glatiramère (n=25) ou un placebo (n=25) par voie sous-cutanée. Selon le protocole, le paramètre primaire de l'essai consistait en la proportion de patients exempts de poussée pendant les deux ans de l'essai. Deux autres résultats pertinents ont également servi de paramètres dans le cadre de cet essai : la fréquence des poussées pendant l'essai et la variation de la fréquence des poussées par comparaison à la fréquence des poussées pendant les deux années précédant l'entrée à l'essai. Les résultats de cet essai (tableau 1) démontrent que l'acétate de glatiramère exercait un effet statistiquement significatif sur le nombre de poussées.

TABLEAU 1 – Essai BR-1 : résultats quant à l'efficacité

Résultats	Essai I[a]		
	Acétate de glatiramère n=25	Placebo n=25	Valeur de *p*
% de patients exempts de poussée	14/25 (56 %)	7/25 (28 %)	0,085
Fréquence moyenne des poussées	*0,6/2 ans*	*2,4/2 ans*	*0,005*
Réduction de la fréquence des poussées comparativement aux données avant l'essai	3,2	1,6	0,025
Délai médian avant la première poussée (jours)	> 700	150	0,03
% de patients exempts de progression*	20/25 (80 %)	13/25 (52 %)	0,07

[a] Le paramètre primaire de l'efficacité de l'**Essai I** consistait en la proportion de patients exempts de poussée pendant les deux ans de l'essai (**% de patients exempts de poussée**). Les analyses portaient sur l'ensemble des sujets retenus au début de l'essai.

* La progression se définissait comme une augmentation d'au moins un point de la cote DSS persistant pendant au moins trois mois consécutifs.

L'Essai II (01-9001) était un essai comparatif (avec placebo), multicentrique, à double insu et à répartition aléatoire. Deux cent cinquante et un patients atteints de SEP rémittente ont reçu, au hasard, 20 mg/jour d'acétate de glatiramère (n=125) ou un placebo (n=126) par voie sous-cutanée[16]. Les patients avaient fait l'objet d'un diagnostic de SEP rémittente selon les critères standards et avaient subi au moins deux poussées pendant les deux années précédant immédiatement l'entrée à l'essai. Les patients devaient présenter une cote maximale de 5 sur l'échelle élargie de l'état d'invalidité de Kurtzke (EDSS, *Expanded Disability Status Scale*), échelle standard de 0 (état normal) à 10 (décès secondaire à la SEP). Une cote de 5 définit un patient ambulatoire qui a des difficultés à vaquer à toutes ses activités habituelles en raison d'une invalidité ; une cote de 6 définit un patient ambulatoire qui a besoin d'aide pour vaquer à ses occupations, tandis qu'une cote de 7 signifie que le sujet est confiné à un fauteuil roulant.

Les patients ont été examinés tous les trois mois pendant deux ans ainsi que dans les quelques jours suivant une poussée possible. Toute poussée devait être confirmée par un neurologue qui ignorait le traitement reçu et qui devait noter la présence de signes neurologiques objectifs ainsi que d'autres critères (p. ex., la persistance de la lésion pendant au moins 48 heures).

Le protocole précisait que le paramètre primaire de l'essai était le nombre moyen de poussées pendant le traitement.

Le tableau 2 présente les résultats de l'analyse du paramètre primaire et de plusieurs paramètres secondaires de l'Essai II à deux ans, analyse portant sur l'ensemble des sujets retenus au début de l'essai.

TABLEAU 2 – Essai de base (24 mois) à double insu: effet sur la fréquence des poussées

Résultats	Essai II[a]		
	Acétate de glatiramère n=125	Placebo n=126	Valeur de *p*
Nombre moyen de poussées (2 ans)[b]	1,19	1,68	0,055
% de patients exempts de poussée	42/125 (34 %)	34/126 (27 %)	0,25
Délai médian avant la première poussée (jours)	287	198	0,23
% de patients exempts de progression[c]	98/125 (78 %)	95/126 (75 %)	0,48
Variation moyenne de la cote EDSS	-0,05	+0,21	0,023

[a] Le paramètre primaire de l'efficacité de l'**Essai II** était le nombre de poussées pendant le traitement. Les analyses portaient sur l'ensemble des sujets retenus au début de l'essai.

[b] Moyenne ajustée de départ

[c] La progression se définissait comme une augmentation d'au moins un point de la cote EDSS persistant pendant au moins trois mois consécutifs.

Les effets de l'acétate de glatiramère sur la gravité des poussées n'ont pas été évalués dans ces deux essais. Les deux essais ont révélé que l'acétate de glatiramère avait un effet bénéfique sur la fréquence des poussées ; on considère donc que l'acétate de glatiramère est un produit efficace à cet égard.

Le troisième essai (9003) était un essai multicentrique, multinational, avec surveillance IRM. Au total, 239 patients atteints de SEP rémittente (119 traités par l'acétate de glatiramère et 120 par un placebo) ont été répartis au hasard. Les critères d'inclusion étaient similaires à ceux de l'Essai II (Essai 01-9001) avec en plus le critère selon lequel les patients devaient présenter au moins une lésion rehaussée par le Gd à l'examen IRM de sélection. Les patients ont été d'abord traités à double insu pendant neuf mois, au cours desquels ils ont subi des examens IRM mensuels. Le paramètre primaire de la phase à double insu était le nombre cumulatif total de lésions rehaussées par le Gd en pondération T1 pendant les neuf mois. D'autres paramètres IRM ont été évalués à titre de paramètres secondaires. Le tableau 3 résume les résultats obtenus pour les paramètres surveillés pendant la phase à double insu de neuf mois pour l'ensemble des sujets retenus au début de l'essai. Compte tenu que le lien entre les résultats IRM et l'état clinique du patient fait l'objet d'une discussion, on ignore la valeur pronostique des résultats statistiquement significatifs suivants.

TABLEAU 3 – Phase à double insu de neuf mois : paramètres IRM - résultats

N°	Résultats	Acétate de glatiramère n=113	Placebo n=115	Valeur de *p*
Paramètre primaire				
1.	Médianes du nombre cumulatif de lésions rehaussées par le Gd en T1	12	17	0,0037
Paramètres secondaires				
2.	Médianes du nombre cumulatif de nouvelles lésions rehaussées par le Gd en T1	9	14	0,0347
3.	Médianes du nombre cumulatif de nouvelles lésions en T2	5	8	0,01
4.	Médianes de la variation cumulative par rapport aux valeurs de départ du volume (mL) des lésions rehaussées par le Gd en T1	-0,309	0	0,0248
5.	Médianes de la variation cumulative par rapport aux valeurs de départ du volume (mL) des lésions en T2	8,852	13,566	0,0229
6.	Médianes de la variation cumulative par rapport aux valeurs de départ du volume (mL) des lésions hypo-intenses en T1	1,642	1,829	0,7311
7.	*Proportion de patients exempts de lésion rehaussée par le Gd en T1*	*46,4 %*	*32,2 %*	0,0653

Le nombre moyen de poussées au cours de cet essai de neuf mois était de 0,50 pour le groupe COPAXONE® et de 0,77 pour le groupe placebo (p=0,0077).

INDICATIONS ET UTILISATION CLINIQUE Pour utilisation chez les patients ambulatoires atteints de sclérose en plaques rémittente en vue de réduire la fréquence des poussées.

L'innocuité et l'efficacité de COPAXONE® dans la sclérose en plaques chronique progressive n'ont pas été évaluées.

CONTRE-INDICATIONS COPAXONE® (acétate de glatiramère pour injection) est contre-indiqué chez les patients présentant une hypersensibilité avérée à l'acétate de glatiramère ou au mannitol.

MISES EN GARDE La seule voie d'administration recommandée de COPAXONE® (acétate de glatiramère pour injection) est la voie sous-cutanée. COPAXONE® ne doit pas être administré par voie intraveineuse. **Symptômes qui risquent d'avoir une origine cardiaque :** Environ 26 % des patients qui ont reçu COPAXONE® dans l'essai comparatif et multicentrique de précommercialisation (par comparaison à 10 % des patients ayant reçu un placebo) ont subi au moins un épisode de ce qui a été décrit comme une douleur thoracique transitoire (voir **EFFETS INDÉSIRABLES : Douleur thoracique**). Seulement certains de ces épisodes sont survenus dans le cadre de la réaction apparaissant immédiatement après l'injection (voir **EFFETS INDÉSIRABLES : Réaction suivant l'injection**), Aucune surveillance de l'ECG n'a été réalisée pendant l'un de ces épisodes, et la pathogenèse de ce symptôme demeure inconnue. Comme les patients des essais comparatifs ne présentaient pas de troubles cardiovasculaires significatifs (classe I ou II selon la *New York Heart Association*), on ignore les risques que courent les patients qui souffrent d'une atteinte cardiovasculaire et qui reçoivent COPAXONE® dans le traitement de la sclérose en plaques.

L'administration de COPAXONE® a été associée à une réaction suivant l'injection consistant en un ensemble de symptômes qui surviennent immédiatement après l'injection et qui peuvent comprendre les bouffées congestives, la douleur thoracique, les palpitations, l'anxiété, la dyspnée, la constriction de la gorge et l'urticaire (voir **EFFETS INDÉSIRABLES : Réaction suivant l'injection**).

COPAXONE® n'a pas été étudié chez des sujets présentant des antécédents de réactions anaphylactoïdes graves, de bronchopneumopathie chronique obstructive ou d'asthme ni chez des patients qui reçoivent des médicaments dans le traitement de l'une de ces deux dernières affections. Il convient donc de faire preuve de prudence pour ce qui est de l'utilisation de COPAXONE® chez ce type de patients.

De rares cas de réactions anaphylactoïdes (<1/1 000) ont été rapportés en association avec l'utilisation de COPAXONE® au cours de la période de postcommercialisation. Certains cas ont nécessité un traitement par l'épinéphrine et autre traitement médical approprié.

PRÉCAUTIONS Générales : Les patients doivent connaître les techniques de reconstitution et d'auto-injection respectant l'asepsie de sorte que COPAXONE® (acétate de glatiramère pour injection) soit administré de façon sûre (voir **INFORMATION À L'INTENTION DU PATIENT**). La première injection doit être effectuée sous la supervision d'un professionnel de la santé qualifié. Il convient de vérifier périodiquement si les patients comprennent et respectent les techniques d'auto-administration respectant l'asepsie. On doit avertir les patients de ne pas réutiliser les aiguilles et les seringues et leur expliquer les procédures de mise au rebut appropriées. Les patients doivent jeter les aiguilles et les seringues utilisées dans un contenant non perforable. On doit en outre expliquer aux patients comment mettre au rebut les contenants non perforables une fois remplis.

Considérations en matière d'utilisation d'un produit capable de modifier les réactions immunitaires : COPAXONE® étant une substance antigénique, son utilisation risque de déterminer des réactions délétères pour l'hôte. On ignore en outre si COPAXONE® peut modifier les réactions immunitaires normales de l'être humain, comme la reconnaissance des antigènes étrangers. Il est donc possible que le traitement par COPAXONE® puisse altérer les mécanismes de défense de l'organisme contre les infections ainsi que les mécanismes de surveillance des tumeurs. Aucune évaluation systématique de ces risques n'a encore été entreprise. L'altération continue de l'immunité cellulaire due au traitement chronique avec l'acétate de glatiramère pourrait entraîner des effets indésirables.

Des anticorps réactifs contre l'acétate de glatiramère sont formés chez presque tous les patients exposés au traitement quotidien avec la dose recommandée. Selon des essais menés chez le rat et le singe, des complexes immuns se déposent dans les glomérules rénaux. De plus, dans un essai comparatif portant sur 125 patients atteints de SEP rémittente qui ont reçu 20 mg d'acétate de glatiramère pendant deux ans, les taux sériques d'IgG ont atteint des taux au moins trois fois plus élevés que les taux de départ chez 80 % des patients trois mois après le début du traitement. Après 12 mois de traitement, cependant, 30 % des patients avaient toujours des taux d'IgG au moins trois fois plus élevés que les taux de départ et 90 % avaient des taux plus élevés que les taux de départ après 12 mois. Les anticorps sont uniquement de sous-type IgG, et surtout de sous-type IgG-1. Aucun anticorps de type IgE n'a été détecté chez aucun des 94 sérums testés. Néanmoins, compte tenu que l'anaphylaxie peut être associée à l'administration de presque toutes les substances étrangères, ce risque ne peut être exclu.

Des essais précliniques visant à évaluer le potentiel carcinogène de l'acétate de glatiramère chez la souris et le rat n'ont fait ressortir aucun signe de potentiel carcinogène associé à l'administration sous-cutanée de l'acétate de glatiramère à des doses allant jusqu'à 30 mg/kg/jour chez le rat et jusqu'à 60 mg/kg/jour chez la souris (voir **TOXICOLOGIE : Potentiel carcinogène**). On ignore si ces résultats sont extrapolables à l'humain (voir **PRÉCAUTIONS : Considérations en matière d'utilisation d'un produit capable de modifier les réactions immunitaires**).

Interactions médicamenteuses : Les interactions médicamenteuses entre COPAXONE® et d'autres produits n'ont pas fait l'objet d'une évaluation complète. Les résultats des essais cliniques à ce jour ne font pas ressortir d'interaction significative entre COPAXONE® et les traitements habituels de la SEP, y compris l'administration concomitante de corticostéroïdes pendant un maximum de 28 jours. COPAXONE® n'a pas été évalué de façon formelle en association à l'interféron bêta. En revanche, 246 patients chez lesquels le traitement par l'interféron bêta a échoué ou qui n'ont pas toléré le traitement et qui ont été par la suite traités avec COPAXONE® dans le cadre d'un essai clinique ouvert n'ont pas signalé l'apparition d'effets indésirables graves ou inattendus pouvant être liés au traitement.

Grossesse : Aucun essai comparatif rigoureux portant sur des femmes enceintes n'a été réalisé. Les essais précliniques n'ont pas fait ressortir de signe de toxicité liée à la reproduction (voir **TOXICOLOGIE : Reproduction et tératologie**). Étant donné que les essais de reproduction chez les animaux ne permettent pas toujours de prévoir les effets d'un produit chez l'être humain, ce médicament ne doit être administré pendant la grossesse que si son utilité a été clairement établie. Dans le cadre des essais cliniques de précommercialisation portant sur COPAXONE®, sept femmes sont devenues enceintes pendant le traitement par le produit actif. L'une de ces femmes a été perdue de vue pendant le suivi ; trois femmes ont choisi d'interrompre leur grossesse, et les trois autres ont cessé de prendre le produit un mois, un mois et demi et deux mois après avoir découvert qu'elles étaient enceintes. Ces trois femmes ont donné naissance à des enfants en bonne santé.

Allaitement : On ignore si le produit passe dans le lait maternel. Étant donné qu'un grand nombre de médicaments passent effectivement dans le lait maternel, l'administration de COPAXONE® à une femme qui allaite ne doit être envisagée qu'après une évaluation soigneuse du rapport risques-avantages, et le produit doit être utilisé avec prudence.

Enfants : L'innocuité et l'efficacité de COPAXONE® n'ont pas été établies chez les sujets de moins de 18 ans.

Patients âgés : COPAXONE® n'a fait l'objet d'aucune évaluation spécifique chez les personnes âgées (plus de 65 ans).

Insuffisants rénaux : Les paramètres pharmacocinétiques de COPAXONE® n'ont pas été déterminés chez les sujets souffrant d'un dysfonctionnement rénal.

EFFETS INDÉSIRABLES Au cours des essais cliniques de précommercialisation, environ 900 personnes ont reçu au moins une dose de COPAXONE® (acétate de glatiramère pour injection) dans le cadre d'essais cliniques comparatifs ou non. L'exposition totale des patients à COPAXONE® au cours d'essais cliniques s'échelonne de six mois (693 patients) à deux ans (306 patients), et à plus de sept ans (69 patients) à raison d'une dose quotidienne de 20 mg.

Au cours des essais comparatifs, les effets indésirables le plus fréquemment associés à l'utilisation de COPAXONE® et dont l'incidence était supérieure à celle qui a été observée chez les sujets qui recevaient le placebo étaient les suivants : réactions au point d'injection, vasodilatation, douleur thoracique, asthénie, infection, douleur, nausées,

arthralgie, anxiété et hypertonie.
Sur un total de 844 patients qui pouvaient faire l'objet d'une évaluation de l'innocuité du produit, environ 8 % des sujets ont abandonné le traitement en raison d'effets indésirables. Les effets indésirables le plus fréquemment associés à l'abandon du traitement étaient les suivants : réactions au point d'injection (6,5 %), vasodilatation, grossesse accidentelle, dépression, dyspnée, urticaire, tachycardie, étourdissements et tremblement. Au nombre des effets indésirables graves ayant entraîné l'abandon du traitement et que les chercheurs considéraient comme liés à l'administration de COPAXONE®, on compte un cas de maladie du sérum ayant menacé la survie du patient.

Réaction suivant l'injection : Environ 10 % des patients atteints de sclérose en plaques qui ont reçu COPAXONE® dans le cadre des essais précédant la commercialisation du produit ont signalé une réaction apparaissant immédiatement après l'injection sous-cutanée de COPAXONE®. Les symptômes ressentis pouvaient comprendre les bouffées congestives, la douleur thoracique, les palpitations, l'anxiété, la dyspnée, la constriction de la gorge et l'urticaire. Ces symptômes étaient toujours transitoires et spontanément résolutifs et n'exigeaient pas de traitement particulier. Ils survenaient en général plusieurs mois après l'établissement du traitement et parfois plus tôt. Un patient particulier pouvait subir un seul ou plusieurs de ces épisodes pendant son traitement par COPAXONE®. On ne sait pas si ces épisodes sont liés à des mécanismes immunologiques ou non, ni si plusieurs épisodes semblables survenant chez un même patient relèvent de mécanismes identiques. En fait, on ignore si cet ensemble de symptômes représente véritablement un syndrome spécifique. Au cours de la période de postcommercialisation, des patients ont signalé avoir subi des symptômes similaires et reçu des soins médicaux d'urgence (voir **MISES EN GARDE**).

Douleur thoracique : Environ 26 % des patients qui ont reçu de l'acétate de glatiramère dans l'essai comparatif multicentrique de précommercialisation (par comparaison à 10 % des patients ayant reçu un placebo) ont subi au moins un épisode de ce qui a été décrit comme une douleur thoracique transitoire. Seulement certains de ces épisodes sont survenus dans le cadre de la réaction apparaissant immédiatement après l'injection décrite dans le paragraphe précédent. Le lien temporel entre la douleur thoracique et l'injection d'acétate de glatiramère n'était pas toujours connu. La douleur était transitoire (elle ne durait habituellement que quelques minutes), apparaissait souvent seule et ne semblait pas laisser d'importantes séquelles cliniques. Aucune surveillance de l'ECG n'a été réalisée pendant l'un de ces épisodes. Certains patients ont subi plus d'un épisode de douleur thoracique, et ces épisodes commençaient à apparaître, en règle générale, au moins un mois après l'établissement du traitement. La pathogenèse de ce symptôme demeure inconnue. Il y a eu un seul épisode de douleur thoracique au cours duquel un ECG complet a été effectué; l'ECG n'a révélé aucun signe d'ischémie. Comme les patients des essais cliniques ne présentaient pas de troubles cardiovasculaires significatifs (classe I ou II selon la *New York Heart Association*), on ignore les risques que courent les patients qui souffrent d'une atteinte cardiovasculaire et qui reçoivent l'acétate de glatiramère dans le traitement de la sclérose en plaques (voir **MISES EN GARDE : Symptômes qui risquent d'avoir une origine cardiaque**).

Le tableau 4 dresse la liste des effets indésirables observés après un maximum de 35 mois de traitement (plus de 27 mois à 33 mois : COPAXONE®, n=84 ; placebo, n=75 ; plus de 33 mois : COPAXONE®, n=12 ; placebo, n=24) dans le cadre de l'Essai II (essai comparatif [avec placebo] multicentrique de précommercialisation portant sur des patients atteints de sclérose en plaques rémittente) et dont l'incidence était d'au moins 2 % parmi les sujets qui recevaient COPAXONE® et d'au moins 2 % de plus que l'incidence observée parmi les sujets du même essai qui recevaient le placebo, peu importe le lien de cause à effet entre la réaction et le traitement. Aucun résultat des épreuves de laboratoire répondant à ces critères n'a été signalé.

Il est à noter que les données du tableau 4 ne peuvent pas servir à prévoir l'incidence des effets indésirables du traitement dans le cadre de l'exercice normal de la médecine, étant donné que les caractéristiques des patients ainsi que d'autres facteurs risquent de ne pas être les mêmes que ceux des essais cliniques. Ces données fournissent tout de même au médecin traitant des points de repère lui permettant d'évaluer la contribution relative des facteurs liés au médicament et non liés au médicament en ce qui a trait à l'incidence des effets indésirables dans la population étudiée.

TABLEAU 4
Essai comparatif de précommercialisation chez des patients atteints de SEP
Effets indésirables dont l'incidence est ≥ 2 % et ≥ 2 % supérieure à celle du placebo

	COPAXONE® n=125		Placebo n=126	
Effets indésirables	**n**	**%**	**n**	**%**
Organisme dans son ensemble				
Douleur au point d'injection	83	66,4	46	36,5
Asthénie	81	64,8	78	61,9
Érythème au point d'injection	73	58,4	17	13,5
Prurit au point d'injection	48	38,4	5	4,0
Syndrome pseudo-grippal	38	30,4	34	27,0
Inflammation au point d'injection	35	28,0	9	7,1
Douleur dorsale	33	26,4	28	22,2
Douleur thoracique	33	26,4	13	10,3
Masse au point d'injection	33	26,4	10	7,9
Induration au point d'injection	25	20,0	1	0,8
Papule au point d'injection	19	15,2	5	4,0
Douleur au cou	16	12,8	9	7,1
Œdème du visage	11	8,8	2	1,6
Urticaire au point d'injection	9	7,2	0	0
Hémorragie au point d'injection	8	6,4	4	3,2
Frissons	5	4,0	1	0,8
Kyste	5	4,0	1	0,8
Réaction au point d'injection	4	3,2	1	0,8
Atrophie au point d'injection	3	2,4	0	0
Abcès	3	2,4	0	0
Appareil cardiovasculaire				
Vasodilatation	34	27,2	14	11,1
Palpitations	14	11,2	6	4,8
Migraine	9	7,2	5	4,0
Syncope	8	6,4	4	3,2
Appareil digestif				
Nausées	29	23,2	22	17,5
Vomissements	13	10,4	7	5,6
Anorexie	6	4,8	3	2,4
Gastro-entérite	6	4,8	2	1,6
Candidose orale	3	2,4	0	0
Carie dentaire	3	2,4	0	0
Systèmes hématopoïétique et lymphatique				
Adénopathie	23	18,4	12	9,5
Ecchymose	15	12,0	12	9,5
Troubles métaboliques et nutritionnels				
Œdème périphérique	14	11,2	7	5,6
Gain pondéral	7	5,6	0	0
Œdème	5	4,0	1	0,8
Appareil musculosquelettique				
Arthralgie	31	24,8	22	17,5
Système nerveux				
Hypertonie	44	35,2	37	29,4
Tremblement	14	11,2	7	5,6
Agitation	7	5,6	4	3,2
Confusion	5	4,0	1	0,8
Nystagmus	5	4,0	2	1,6
Appareil respiratoire				
Rhinite	29	23,2	26	20,6
Dyspnée	23	18,4	8	6,4
Bronchite	18	14,4	12	9,5
Peau et annexes cutanées				
Hypersudation	15	12,0	10	7,9
Érythème	8	6,4	4	3,2
Troubles dermatologiques	5	4,0	2	1,6
Nodule cutané	4	3,2	1	0,8
Verrue	3	2,4	0	0
Organes des sens				
Douleur auriculaire	15	12,0	12	9,5
Troubles oculaires	8	6,4	1	0,8
Voies urogénitales				
Miction impérieuse	20	16,0	17	13,5
Candidose vaginale	16	12,8	9	7,1
Dysménorrhée	12	9,6	9	7,1
Grossesse accidentelle	4	3,2	0	0
Impuissance	3	2,4	0	0

Voici les autres effets qui sont survenus chez au moins 2 % des patients mais dont l'incidence dans le groupe placebo était équivalente ou supérieure :
Organisme dans son ensemble : Céphalées, ecchymose au point d'injection, blessure accidentelle, douleur abdominale, rhinite allergique et malaise.
Appareil digestif : Dyspepsie, constipation, dysphagie, incontinence fécale, flatulence, nausées et vomissements, gastrite, gingivite, abcès périodontique et sécheresse de la bouche.
Appareil musculosquelettique : Myasthénie et myalgie.
Système nerveux : Étourdissements, hypoesthésie, paresthésie, insomnie, dépression, dysesthésie, troubles de la coordination, somnolence, troubles de la démarche, amnésie, instabilité émotionnelle, signe de Lhermitte, anomalies de la pensée, secousses musculaires, euphorie et troubles du sommeil.
Appareil respiratoire : Pharyngite, sinusite, aggravation de la toux et laryngite.
Peau et annexes cutanées : Acné, alopécie et troubles des ongles.
Organes des sens : Anomalies de la vision, diplopie, amblyopie, douleur oculaire, conjonctivite, acouphènes, dysgueusie et surdité.
Voies urogénitales : Infection des voies urinaires, augmentation de la fréquence des mictions, incontinence urinaire, rétention urinaire, dysurie, cystite, métrorragie, douleur mammaire et vaginite.

Les données portant sur les effets indésirables qui sont apparus au cours d'essais cliniques comparatifs ont été analysées dans l'optique d'évaluer les différences entre les sexes. Or, aucune différence cliniquement significative n'a été relevée. Dans ces essais cliniques, 92 % des patients étaient de race blanche, ce qui est représentatif de la population de patients atteints de sclérose en plaques. De plus, la vaste majorité des patients traités par COPAXONE® étaient âgés de 18 à 45 ans. Par conséquent, on disposait de trop peu de données pour effectuer une analyse de l'incidence des effets indésirables en fonction de groupes d'âge cliniquement pertinents.

Tous les patients ayant pris part aux essais cliniques sur COPAXONE® ont subi des analyses de laboratoire. Les variations des paramètres de laboratoire (hématologie, biochimie sanguine et analyse des urines) qui étaient significatives sur le plan clinique étaient comparables entre les patients du groupe COPAXONE® et ceux du groupe placebo, dans le cadre des essais cliniques à l'insu. Aucun patient ayant reçu COPAXONE® ne s'est retiré d'un essai en raison d'une anomalie des résultats des épreuves de laboratoire.

Autres effets indésirables observés durant tous les essais cliniques

COPAXONE® a été administré à environ 900 personnes dans l'ensemble des essais cliniques, dont seulement certains étaient comparatifs (avec placebo). Au cours de ces essais, tous les effets indésirables ont été regroupés en un plus petit nombre de catégories normalisées faisant appel à la terminologie du dictionnaire COSTART II. Tous les effets signalés qui sont survenus à au moins deux reprises ainsi que les effets potentiellement graves qui sont survenus une seule fois sont inclus dans cette compilation, à l'exception des effets déjà inscrits au tableau précédent, les effets dont le caractère trop général ne procurait aucune information, les effets sans importance et les autres effets qui se sont manifestés chez au moins 2 % des patients traités et qui étaient présents à une fréquence égale ou plus grande que dans le groupe placebo.

Les effets indésirables ont été de plus classés en fonction des systèmes ou des appareils et énumérés en ordre décroissant de fréquence selon les définitions suivantes : les effets indésirables *fréquents* sont ceux qui sont survenus chez au moins un patient sur 100 (1/100), tandis que les effets indésirables *peu fréquents* sont ceux qui sont survenus dans une proportion de un patient sur 100 (1/100) à un patient sur 1 000 (1/1 000).

Organisme dans son ensemble : *Fréquents :* Œdème au point d'injection, atrophie au point d'injection, abcès et hypersensibilité au point d'injection.
Peu fréquents : Hématome au point d'injection, fibrose au point d'injection, faciès lunaire, cellulite, œdème généralisé, hernie, abcès au point d'injection, maladie du sérum, tentative de suicide, hypertrophie au point d'injection, mélanose au point d'injection, lipome et réaction de photosensibilité.
Appareil cardiovasculaire : *Frequent :* Hypertension. *Peu fréquents :* Hypotension, claquement systolique, souffle systolique, fibrillation auriculaire, bradycardie, apparition d'un quatrième bruit du cœur, hypotension orthostatique et varices.
Appareil digestif : *Peu fréquents :* Sécheresse de la bouche, stomatite, sensation de brûlure sur la langue, cholécystite, colite, ulcère de l'œsophage, œsophagite, cancer gastro-intestinal, hémorragie gingivale, hépatomégalie, augmentation de l'appétit, méléna, ulcération de la bouche, troubles du pancréas, pancréatite, hémorragie rectale, ténesme, coloration anormale de la langue et ulcère duodénal.
Système endocrinien : *Peu fréquents :* Goitre, hyperthyroïdie et hypothyroïdie.
Troubles gastro-intestinaux : *Fréquents :* Défécation impérieuse, candidose orale, hypertrophie des glandes salivaires, carie dentaire et stomatite ulcéreuse.
Systèmes hématopoïétique et lymphatique : *Peu fréquents :* Leucopénie, anémie, cyanose, éosinophilie, hématémèse, lymphœdème, pancytopénie et splénomégalie.
Troubles métaboliques et nutritionnels : *Peu fréquents :* Perte pondérale, intolérance à l'alcool, syndrome de Cushing, goutte, anomalies de la cicatrisation et xanthome.
Appareil musculosquelettique : *Peu fréquents :* Arthrite, atrophie musculaire, douleur osseuse, bursite, douleur rénale, troubles musculaires, myopathie, ostéomyélite, douleur tendineuse et ténosynovite.
Système nerveux : *Fréquents:* Rêves inhabituels, instabilité émotionnelle et stupeur. *Peu fréquents :* Aphasie, ataxie, convulsion, paresthésie péribuccale, dépersonnalisation, hallucinations, hostilité, hypocinésie, coma, troubles de la concentration, paralysie faciale, diminution de la libido, réaction maniaque, troubles de la mémoire, myoclonie, névralgie, réaction paranoïde, paraplégie, dépression psychotique et stupeur transitoire.
Appareil respiratoire : *Fréquent :* Hyperventilation, rhume des foins. *Peu fréquents :* Asthme, pneumonie, épistaxis, hypoventilation et modification de la voix.
Peau et annexes cutanées : *Fréquents :* Eczéma, zona, éruption pustuleuse, atrophie cutanée et verrues. *Peu fréquents :* Sécheresse cutanée, hypertrophie cutanée, dermatite, furonculose, psoriasis, angio-œdème, eczéma de contact, érythème noueux, dermatite fongique, éruption maculopapuleuse, pigmentation, tumeur cutanée bénigne, cancer de la peau, vergetures et éruption vésiculobulleuse.
Organes des sens : *Fréquents :* Atteinte du champ visuel. *Peu fréquents :* Sécheresse oculaire, otite externe, ptose, cataractes, ulcère de la cornée, mydriase, névrite optique, photophobie et agueusie.
Voies urogénitales : *Fréquents :* Aménorrhée, hématurie, impuissance, ménorragie, anomalies des résultats du test de Papanicolaou, pollakiurie et hémorragie vaginale. *Peu fréquents :* Vaginite, douleur au flanc (rein), avortement, engorgement mammaire, hypertrophie mammaire, douleur mammaire, cancer *in situ* du col de l'utérus, mastose sclérokystique, calcul rénal, nycturie, kyste ovarien, priapisme, pyélonéphrite, anomalies de la fonction sexuelle et urétrite.

Effets indésirables rapportés après la commercialisation et qui n'avaient pas déjà été notés lors des essais cliniques

L'expérience de postcommercialisation a dégagé un profil d'effets indésirables similaire à celui présenté ci-dessus. Après la mise sur le marché, on a signalé des effets indésirables, autres que celles indiquées ci-dessus, qui sont survenues pendant le traitement par COPAXONE® (acétate de glatiramère pour injection). Ces réactions, qui peuvent avoir ou non un lien de causalité avec le médicament, comprennent :
Organisme dans son ensemble : Septicémie, syndrome lupoïde, hydrocéphalie, distension de l'abdomen, hypersensibilité au point d'injection, réaction allergique, réaction anaphylactoïde, infection bactérienne, fièvre et infection.
Appareil cardiovasculaire : Thrombose, maladie vasculaire périphérique, épanchement péricardique, infarctus du myocarde, thrombophlébite extensive, occlusion coronarienne, insuffisance cardiaque congestive, cardiomyopathie, cardiomégalie, arrythmie, angine de poitrine et tachycardie.
Appareil digestif : Œdème de la langue, hémorragie gastrique d'origine ulcéreuse, altération de la fonction hépatique, atteinte hépatique, hépatite, éructation, cirrhose du foie, calculs biliaires, diarrhée et troubles gastro-intestinaux.
Systèmes hématopoïétique et lymphatique : Thrombocytopénie, réaction de type lymphome et leucémie aiguë.
Troubles métaboliques et nutritionnels : Hypercholestérolémie.
Appareil musculosquelettique : Polyarthrite rhumatoïde et spasme généralisé.
Système nerveux : Myélite, méningite, néoplasme du SNC, accident vasculaire cérébral, œdème cérébral, rêves inhabituels, aphasie, convulsion, névralgie, anxiété, pied tombant, nervosité, trouble de l'élocution et vertige.
Appareil respiratoire : Embolie pulmonaire, épanchement pleural, cancer du poumon, rhume des foins et laryngisme.
Peau et annexes cutanées : Herpès, prurit, éruption cutanée et urticaire.
Organes des sens : Glaucome, cécité et atteinte du champ visuel.
Voies urogénitales : Néoplasme des voies urogénitales, anomalie urinaire, cancer des ovaires, néphrose, insuffisance rénale, cancer du sein, cancer de la vessie et pollakiurie.

SURDOSAGE : SYMPTÔMES ET TRAITEMENT

Des surdosages de COPAXONE® ont été signalés chez trois patients. Un patient s'est injecté quatre doses (soit un total de 80 mg) de COPAXONE® à la fois. Aucune séquelle n'a été notée. Deux autres patients, un homme de 28 ans et une femme de 37 ans, ont reçu, par erreur, trois injections de 20 mg of COPAXONE® à des intervalles de une demi-heure. Aucun patient n'a manifesté de variation de sa pression artérielle, de sa fréquence cardiaque ni de sa température. Le suivi téléphonique effectué plusieurs heures plus tard n'a pas révélé d'effets indésirables dans un cas comme dans l'autre.

POSOLOGIE ET MODE D'ADMINISTRATION

La prescription de COPAXONE® doit être réservée aux médecins (ou après une consultation avec un médecin) qui connaissent à fond le diagnostic et la prise en charge de la sclérose en plaques.
La dose recommandée de COPAXONE® (acétate de glatiramère pour injection ou acétate de glatiramère injectable) dans le traitement de la SEP rémittente est de une injection quotidienne de 20 mg par voie sous-cutanée.
Directives d'administration : Pour reconstituer le lyophilisat de COPAXONE® avant l'injection, utiliser une

seringue et un adaptateur de flacon stériles afin de prélever 1,1 mL du diluant fourni (eau stérile pour injection) et de l'injecter dans le flacon de COPAXONE®. Agiter très délicatement, par un mouvement de rotation, le flacon de COPAXONE® et le laisser reposer à la température ambiante jusqu'à dissolution complète du lyophilisat. Inspecter visuellement le produit reconstitué et le jeter ou le retourner au pharmacien avant l'utilisation s'il renferme des particules. Administrer dans les huit heures suivant la reconstitution. Prélever 1,0 mL de la solution à l'aide d'une seringue stérile. Retirer l'adaptateur de flacon, connecter une aiguille de calibre 27 et injecter la solution par voie sous-cutanée. Les points d'auto-administration comprennent les bras, l'abdomen, les fesses et les cuisses. Un flacon ne convient qu'à une seule utilisation; toute portion inutilisée doit être jetée (voir **INFORMATION À L'INTENTION DU PATIENT, Produit reconstitué**).
Pour obtenir les directives concernant la préparation et l'injection de COPAXONE® au moyen de la seringue préremplie, voir **INFORMATION À L'INTENTION DU PATIENT, Seringue préremplie.**

RENSEIGNEMENTS PHARMACEUTIQUES

Substance médicamenteuse :

Nom propre : Acétate de glatiramère
Dénomination Chimique : L'acétate de glatiramère est le sel acétate de polypeptides synthétiques.
Description : L'acétate de glatiramère est préparé par réaction chimique des dérivés activés de quatre acides aminés : *l'acide L-glutamique (L-Glu), la L-alanine (L-Ala), la L-tyrosine (L-Tyr) et la L-lysine (L-lys) dans une* proportion spécifique. La fraction molaire de chaue résidu d'acide aminé s'échelonne comme suit : L-Glu, de 0,129 à 0,153 ; L-Ala, de 0,392 à 0,462 ; L-Tyr, de 0,086 à 0,100 et L-Lys, de 0,300 à 0,374.
Formule Developpée : Poly[L-Glu$^{13\text{-}15}$, L-Ala$^{39\text{-}46}$, L-Tyr$^{8\text{-}9}$, L-Lys$^{30\text{-}37}$]•nCH$_3$CO$_2$H (n=15-24)
Poids moléculaire : Le poids moléculaire moyen du polypeptide se situe entre 4 700 et 11 000 daltons, au moins 68% du matériel se situant entre 2 500 et 22 500 daltons.
Description Physique : Lyophilisat de couleur blanche à légèrement jaunâtre.
Solubilité : Légèrement soluble dans l'eau, insoluble dans l'acétone.
ph : Le pH d'une solution à 0,5 % p/V d'acétate de glatiramère dans de l'eau se situe entre 5,5 et 8,0.

Composition : COPAXONE® (acétate de glatiramère pour injection) est un lyophilisat stérile destiné à l'injection sous-cutanée après reconstitution avec de l'eau stérile pour injection. Un flacon de lyophilisat renferme 20 mg d'acétate de glatiramère et un surtitrage de 2 mg pour tenir compte des pertes possibles pendant la reconstitution et le prélèvement ainsi que 40 mg de mannitol. Un flacon d'eau stérile pour injection renferme 1,1 mL d'eau stérile pour injection et un surtitrage de 0,35 mL pour tenir compte des pertes possibles pendant la reconstitution et le prélèvement.
COPAXONE® (acétate de glatiramère injectable) est présenté en seringue préremplie à usage unique renfermant 20 mg/1,0 mL de solution stérile équivalant à la solution reconstituée de COPAXONE® (c.-à-d., 20 mg/mL d'acétate de glatiramère et 40 mg de mannitol dans de l'eau stérile pour injection).
Stabilité et conditions d'entreposage : Les flacons de lyophilisat de COPAXONE® doivent être réfrigérés (entre 2 et 8° C). COPAXONE® peut également être conservé à la température ambiante (entre 15 et 30° C) pendant un maximum de 14 jours. Les flacons de diluant (eau stérile pour injection) doivent être conservés à la température ambiante.
Les seringues préremplies de COPAXONE® doivent être réfrigérées dès leur réception (entre 2 et 8° C). NE PAS CONGELER.
S'il n'est pas possible de conserver les seringues préremplies de COPAXONE® au réfrigérateur, elles peuvent être conservées à la température ambiante (entre 15 et 30° C) pendant un maximum d'une semaine. Ne pas conserver les seringues préremplies de COPAXONE® à la température ambiante pendant plus de sept jours. Remarque : ce médicament est sensible à la lumière, le protéger de la lumière lorsqu'on ne fait pas d'injection. Une seringue préremplie ne doit servir qu'une seule fois.
Reconstitution du lyophilisat : Pour reconstituer le lyophilisat de COPAXONE®, avant l'injection, utiliser une seringue et un adaptateur de flacon stériles afin de prélever le diluant fourni (eau stérile pour injection) et de *l'injecter dans le flacon de COPAXONE®. Agiter très délicatement, par un mouvement de rotation, le flacon* de COPAXONE® et le laisser reposer à la température ambiante jusqu'à dissolution complète du lyophilisat. Inspecter visuellement le produit reconstitué et le jeter ou le retourner au pharmacien avant l'utilisation s'il renferme des particules. Une fois le produit complètement dissous, prélever 1,0 mL de la solution à l'aide d'une seringue stérile. Retirer l'adaptateur de flacon, connecter une aiguille de calibre 27 et injecter la solution par voie sous-cutanée. Un flacon ne convient qu'à une seule utilisation ; toute portion inutilisée doit être jetée. La solution reconstituée ne doit pas être conservée plus de huit heures à la température ambiante.
Produits parentéraux : COPAXONE® ne doit être reconstitué qu'avec le diluant fourni (eau stérile pour injection).

Format du flacon	Volume de diluant à ajouter	Volume à injecter	Concentration nominale par mL
2 mL	1,1 mL	1,0 mL	20 mg

PRÉSENTATION

COPAXONE® (acétate de glatiramère pour injection) est offert sous la forme d'une dose de 20 mg de lyophilisat stérile d'acétate de glatiramère avec du mannitol, le produit étant conditionné dans des flacons unidoses de 2 mL de couleur ambre. Un deuxième flacon renfermant 1,1 mL de diluant (eau stérile pour injection) et un surtitrage de 0,35 mL accompagne chaque flacon de médicament et est inclus dans la trousse *d'auto-administration. COPAXONE® (acétate de glatiramère pour injection) est offert en emballages de* 32 flacons de couleur ambre renfermant le lyophilisat stérile destiné à l'injection sous-cutanée. Le diluant (eau stérile pour injection) accompagnant COPAXONE® est offert en emballages de 32 flacons transparents qui sont inclus dans la trousse d'auto-administration.

COPAXONE® (acétate de glatiramère injectable) est présenté en seringues préremplies à usage unique renfermant 20 mg/1,0 mL de solution stérile équivalant à la solution reconstituée de COPAXONE®. COPAXONE® *(acétate de glatiramère injectable) est offert en emballages de 30 seringues en verre préremplies à usage unique* (20 mg/1,0 mL), accompagnées de 33 tampons d'alcool.
Monographie fournie sur demande.

Bibliographie :

1. Monographie de COPAXONE® (acétate de glatiramère), Teva Neuroscience.

TEVA NEUROSCIENCE

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CCPP

Voir pages A-22, A-23

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Pr REQUIP® ropinirole

Ropinirole (as ropinirole hydrochloride)

TABLETS: 0.25 mg, 1.0 mg, 2.0 mg, 5.0 mg

THERAPEUTIC CLASSIFICATION: AntiParkinsonian Agent / Dopamine Agonist

INDICATIONS AND CLINICAL USE: REQUIP® (ropinirole hydrochloride) is indicated in the treatment of the signs and symptoms of idiopathic Parkinson's disease. REQUIP® can be used both as early therapy, without concomitant levodopa and as an adjunct to levodopa. Three year and five year active-comparator controlled clinical trials have been conducted.

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

WARNINGS: Sudden Onset of Sleep – Patients receiving treatment with REQUIP® (ropinirole hydrochloride), and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including operating a motor vehicle, which has sometimes resulted in accidents. Although some of the patients reported somnolence while on REQUIP®, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs. If drowsiness or sudden onset of sleep should occur, patients should immediately contact their physician. Until further information is available on the management of this unpredictable and serious adverse event, patients should be warned not to drive or engage in other activities where impaired alertness could put themselves and others at risk of serious injury or death (e.g., operating machines). Episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products. Presently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness. There is insufficient information to determine whether this event is associated with REQUIP®, all dopaminergic agents or Parkinson's disease itself. **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 – *Early Therapy*:** In placebo- controlled trials, REQUIP® (ropinirole hydrochloride) caused hallucination in 5.1% of patients during early therapy (1.4% in the placebo group). Hallucination was of sufficient severity that it led to discontinuation in 1.3% of patients. The incidence of hallucination was dose-dependent. In a 5-year study comparing REQUIP® with levodopa in early Parkinson's patients, the overall incidence of hallucinations was 17.3% (31/179) for patients treated with REQUIP® and 5.6% (5/89) for levodopa patients. Hallucinations led to discontinuation of the study treatment in 5.0% of REQUIP® and 2.2% of levodopa patients. In a 3-year study comparing REQUIP® with another dopamine agonist, the overall incidence of hallucinations was 9.5% (16/168) for patients treated with REQUIP® and 9.0% (15/167) for patients receiving active comparator. Hallucinations led to discontinuation of the study treatment in 2.4% of REQUIP® patients and 3.0% of comparator patients. Concomitant Selegiline: In a 5-year study, REQUIP® patients receiving concomitant selegiline reported a higher incidence of hallucinations (23.5%) than did those without (12.2%); this subpopulation effect was not seen in the L-dopa arm (hallucinations with concomitant selegiline = 2.0% vs hallucinations without selegiline = 8.0%). ***Adjunct Therapy***: Hallucinations were experienced by 10.1% of patients receiving REQUIP® and levodopa, compared to 4.2% receiving placebo and levodopa. Hallucinations were of sufficient severity that it led to discontinuation in 1.9% of patients. The incidence of hallucinations was dose dependent.

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. **Orthostatic Symptoms** - Orthostatic symptoms of dizziness or lightheadedness as well as somnolence may occur during REQUIP® therapy. **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. In patients, already receiving estrogen replacement therapy, REQUIP® may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or introduced during treatment with REQUIP®, adjustment of the REQUIP® dosage may be required. **Pediatric Use** – Safety and effectiveness in the pediatric population have not been established. **Renal and Hepatic Impairment** – No dosage adjustment is needed in patients with mild to moderate renal impairment (creatinine clearance of 30 to 50 mL/min). Because the use of REQUIP® in patients with severe renal impairment or hepatic impairment has not been studied, administration of REQUIP® to such patients is not recommended. **Drug Interactions** – ***Psychotropic Drugs:*** Neuroleptics and other centrally active dopamine antagonists may diminish the effectiveness of REQUIP®. Therefore, concomitant use of these products is not recommended. Based on population pharmacokinetic assessment, no interaction was seen between REQUIP® and tricyclic antidepressants or benzodiazepines. ***Anti-Parkinson Drugs:*** Based on population pharmacokinetic assessment, there were no interactions between REQUIP® and drugs commonly used to treat Parkinson's disease, i.e., selegiline, amantadine, and anticholinergics. ***Levodopa:*** The potential pharmacokinetic interaction of levodopa/ carbidopa (100 mg/10 mg b.i.d.) and REQUIP® (2 mg t.i.d.) was assessed in levodopa naive (de novo) male and female patients with Parkinson's disease (n=30, mean age 64 years). The rate and extent of availability of REQUIP® at steady state were essentially the same with or without levodopa. Similarly, the rate and extent of availability of levodopa, as well as its elimination half-life, were essentially the same in the presence and absence of REQUIP®. ***Inhibitors of CYP1A2: Ciprofloxacin:*** The effect of ciprofloxacin (500 mg b.i.d.) on the pharmacokinetics of REQUIP® (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 55 years). The extent of systemic availability of REQUIP® was significantly increased when coadministered with ciprofloxacin (AUC increased by 1.84 fold). Thus, in patients already receiving CYP1A2 inhibitors such as ciprofloxacin, REQUIP® therapy may be instituted in the recommended manner and the dose titrated according to clinical response. However, if therapy with a drug known to be an inhibitor of CYP1A2 is stopped or introduced during treatment with REQUIP®, adjustment of the REQUIP® dosage will be required. ***Substrates of CYP1A2: Theophylline:*** The effect of oral theophylline (300 mg b.i.d.) on the pharmacokinetics of REQUIP® (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 59 years). There was no marked change in the rate or extent of availability of REQUIP® when coadministered with theophylline. Similarly, coadministration of REQUIP® with intravenous theophylline (5 mg/kg) did not result in any marked change in the pharmacokinetics of theophylline. It is therefore unlikely that substrates of CYP1A2 would significantly alter the pharmacokinetics of REQUIP®, and vice-versa. ***Digoxin:*** The effect of REQUIP® (2 mg t.i.d.) on the pharmacokinetics of digoxin (0.125–0.25 mg o.d.) was studied in male and female patients with Parkinson's disease (n=10, mean age 72 years). Coadministration at steady state with REQUIP® resulted in a 10% decrease in digoxin AUC although mean trough digoxin plasma concentrations were unaltered. However, the effect of higher recommended doses of REQUIP® on the pharmacokinetics of digoxin is not known. ***Alcohol:*** No information is available on the potential for interaction between REQUIP® and alcohol. As with other centrally active medications, patients should be cautioned against taking REQUIP® with alcohol. **Psycho-Motor Performance** – (see WARNINGS - Sudden Onset of Sleep).

ADVERSE REACTIONS: Adverse Reactions Associated with Discontinuation of Treatment – Of 1599 patients who received REQUIP® (ropinirole hydrochloride) during the premarketing clinical trials, 17.1% in early-therapy studies and 17.3% in adjunct-therapy studies discontinued treatment due to adverse reactions. The events resulting in discontinuation of REQUIP® in 1% or more of patients were as follows: ***Early therapy:*** nausea (6.4%), dizziness (3.8%), aggravated Parkinson's disease (1.3%), hallucination (1.3%), headache (1.3%), somnolence (1.3%) and vomiting (1.3%). ***Adjunct therapy:*** dizziness (2.9%), dyskinesia (2.4%), confusion (2.4%), vomiting (2.4%), hallucination (1.9%), nausea (1.9%), anxiety (1.9%), and increased sweating (1.4%). Patients over 75 years of age (n=130) showed slightly higher incidences of withdrawal due to hallucination, confusion and dizziness than patients less than 75 years of age. **Most Frequent Adverse Events** – Adverse events occurring with an incidence of greater than, or equal to, 10% were as follows: ***Early therapy:*** nausea, dizziness, somnolence, headache, peripheral edema, vomiting, syncope, fatigue and viral infection. ***Adjunct therapy:*** dyskinesia, nausea, dizziness, somnolence and headache. Dopamine agonists, with an ergoline chemical structure have been associated with adverse experiences such as retroperitoneal fibrosis, erythromelalgia and pulmonary reactions. REQUIP® has a novel, non-ergoline chemical structure and no reports of such events have been observed in clinical trials. **Incidence of Adverse Events in Placebo Controlled Trials** – The incidence of postural hypotension, an event commonly associated with initiation of dopamine agonist therapy, was not notably different from placebo in clinical trials. However, decreases in systolic blood pressure to < 90 mmHg have been observed in 13% (<65 years), 16% (65 – 75 years) and 7.6% (>75 years) of patients treated with REQUIP®. **Table 2** lists adverse events that occurred at an incidence of 1% or more among REQUIP®-treated patients who participated in placebo-controlled trials for up to one year. Patients were dosed in a range of 0.75 mg to 24 mg/day. Reported adverse events were classified using a standard World Health Organization (WHO)-based dictionary terminology. The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies can not be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse events incidence rate in the population studied.

TABLE 2
Adverse events with incidence ≥1% from all placebo-controlled early and adjunct therapy studies

	Early Therapy		Adjunct Therapy	
	REQUIP® N = 157 % occurrence	Placebo N = 147 % occurrence	REQUIP® N = 208 % occurrence	Placebo N = 120 % occurrence
Autonomic Nervous System				
Sweating Increased	6.4	4.1	7.2	1.7
Mouth Dry	5.1	3.4	5.3	0.8
Flushing	3.2	0.7	1.4	0.8
Body as a Whole General				
Peripheral Edema	13.4	4.1	3.9	2.5
Fatigue	10.8	4.1	–	–
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
Tooth Ache	–	–	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

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	Early Therapy		Adjunct Therapy	
	REQUIP® N = 157 % occurrence	Placebo N = 147 % occurrence	REQUIP® N = 208 % occurrence	Placebo N = 120 % occurrence
Heart Rate and Rhythm				
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
Xeropthalmia	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%.

Post-Marketing Experience - Patients treated with REQUIP® have rarely reported suddenly falling asleep while engaged in activities of daily living, including operation of motor vehicles which has sometimes resulted in accidents (see WARNINGS).

DOSAGE AND ADMINISTRATION: *REQUIP® (ropinirole hydrochloride) should* be taken three times daily. While administration of REQUIP® with meals may improve gastrointestinal tolerance, REQUIP® may be taken with or without food. The recommended starting dosage is 0.25 mg three times daily. Based on individual patient response, dosage should then be titrated by weekly increments of 0.25 mg per dose as described in the table below. After week 4, daily dosage may be increased by 0.5 to 1.0 mg per dose on a weekly basis until an optimal therapeutic response is established. Smaller dose increments are recommended for patients who may be at risk for orthostatic symptoms.

	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*

In clinical trials, initial benefits were observed with 3 mg/day and higher doses. Doses greater than 24 mg/day have not been included in clinical trials. In a 5-year, double-blind study of early therapy in Parkinson's disease patients, the average daily dose of REQUIP® (based on the observed data set) was 10.1 mg at 6 months (median dose = 9.0 mg), 14.4 mg at 3 years (median dose = 15.0 mg), and 16.6 mg at 5 years (median dose = 18.0 mg), regardless of levodopa supplementation. When REQUIP® is administered as adjunct therapy to levodopa, the dose of levodopa may be decreased gradually as tolerated once a therapeutic effect with REQUIP® has been observed. REQUIP® should be discontinued gradually over a 7-day period. The frequency of administration should be reduced from three times daily to twice daily for 4 days. For the remaining 3 days, the frequency should be reduced to once daily prior to complete withdrawal of REQUIP®. **Renal and Hepatic Impairment:** In patients with mild to moderate renal impairment, REQUIP® may be titrated in the recommended manner according to clinical response. Patients with severe *renal impairment or on hemodialysis have not been studied and administration* of REQUIP® to such patients is not recommended. Patients with hepatic impairment have not been studied and administration of REQUIP® to such patients is not recommended. **Estrogen Replacement Therapy:** In patients already receiving estrogen replacement therapy, REQUIP® may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or started during treatment with REQUIP®, adjustment of the REQUIP® dosage may be required. **AVAILABILITY OF DOSAGE FORM:** REQUIP® is supplied as a pentagonal film-coated Tiltab® tablet with beveled edges containing ropinirole (as ropinirole hydrochloride) as follows: 0.25 mg – white imprinted with SB and 4890; 1.0 mg – green imprinted with SB and 4892; 2.0 mg – pale pink imprinted with SB and 4893; 5.0 mg – blue tablets imprinted with SB and 4894. REQUIP® is available in bottles in the pack size of 100 tablets. Full Product Monograph available to practitioners upon request.

GlaxoSmithKline Inc.
7333 Mississauga Road North
Mississauga, Ontario
L5N 6L4

Date of preparation: June 18, 2001
Date of revisions: July 31, 2002

1. Rascol O *et al.* A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Eng J Med* 2000;342(20):1484–1491. 2. Product Monograph of ReQuip® (ropinirole hydrochloride), GlaxoSmithKline, July 31, 2002.

GlaxoSmithKline Member R&D PAAB

Hepatic Impairment

The pharmacokinetics of almotriptan have not been assessed in this population. The maximum decrease expected in the clearance of almotriptan due to hepatic impairment is 60%. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS).

Renal Impairment

In patients with severe renal impairment, the clearance of almotriptan was decreased. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24 hour period, and a starting dose of 6.25 mg should be used (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS).

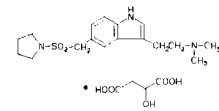
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: almotriptan malate

Chemical Name: 1-[[3-[2-(Dimethylamino)ethyl] 1H indol 5 yl] methyl]-sulfonyl]-pyrrolidine-hydroxybutanedioate

Structural Formula:



Molecular Formula: $C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$

Molecular Weight: 469.56

Physical Form: Almotriptan is a white to slightly yellow crystalline powder.

Solubility: Freely soluble in water and in methanol, but practically insoluble in ethanol and methylene chloride.

pKa: 8.77 at 22 ± 2°C

Melting Point: 167 - 173°C

pH: 1% solution in purified water has pH 4.1

Partition Coefficient: A partition coefficient of 0.008 between octanol and water was determined, when measured at the normal pH value (5.4-6.3) for purified water.

Composition

Active Ingredient: almotriptan malate equivalent to 6.25 or 12.5 mg of almotriptan.

Inactive Ingredients: mannitol, cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, titanium oxide, hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol, iron oxide (6.25 mg only), FD&C Blue No. 2 (12.5 mg only), and carnauba wax.

Stability and Storage Recommendations

AXERT tablets should be stored between 15 30°C.

AVAILABILITY OF DOSAGE FORMS

AXERT (almotriptan malate) tablets are available through prescription only.

AXERT 6.25 mg tablet contains 6.25 mg of almotriptan and is a white, circular, biconvex tablet, printed in red with the code "2080". Available in unit dose (aluminum blister pack) of 6 tablets.

AXERT 12.5 mg tablet contains 12.5 mg of almotriptan and is a white, circular, biconvex tablet, printed in blue with a stylized "A". Available in unit dose (aluminum blister pack) of 6 tablets.

AXERT is a Schedule F drug.

Product Monograph available to healthcare professionals upon request.

JANSSEN-ORTHO

JANSSEN-ORTHO Inc.
Toronto, Ontario M3C 1L9

Date of Issuance: October 2003
AXP1041006A

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See page A-13

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

PRESCRIBING INFORMATION

THERAPEUTIC CLASSIFICATION

Immunomodulator

INDICATIONS AND CLINICAL USE

Relapsing Forms of Multiple Sclerosis:

AVONEX® (Interferon beta-1a) is indicated for the treatment of relapsing forms of multiple sclerosis (MS) 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.

Single Demyelinating Event:

AVONEX® is also indicated for the treatment of people who have experienced a single demyelinating event, accompanied by abnormal Magnetic Resonance Imaging (MRI) scans with lesions typical of MS, to delay the onset of clinically definite multiple sclerosis (as determined by a second demyelinating event), and to decrease the number and volume of active brain lesions and overall disease burden (as identified by MRI scans). Before initiating treatment with AVONEX, alternate diagnoses should first be excluded.

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® should be used under the supervision of a physician. The first injection should be performed under the supervision of an appropriately qualified health care professional (see **DOSAGE AND ADMINISTRATION**).

Depression and Suicide

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 the AVONEX®-treated patients in the placebo controlled study of relapsing MS patients. In the study of patients with a single demyelinating event AVONEX®-treated patients were more likely to experience depression than placebo-treated patients ($p = 0.05$). Suicidal tendency occurred in one subject treated with placebo, and there were no reports of suicide attempts. 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.

Anaphylaxis

Anaphylaxis has been reported as a rare complication of AVONEX® use. Other allergic reactions have included dyspnea, orolingual edema, skin rash and urticaria (see **ADVERSE EVENTS**).

Decreased Peripheral Blood Counts

Decreased peripheral blood counts in all cell lines, including very rare pancytopenia and thrombocytopenia have been reported from post-marketing experience (see **ADVERSE EVENTS**). Some cases of thrombocytopenia have had nadirs below 10,000/μL. Some cases reoccur with re-challenge. Patients should be monitored for signs of these disorders (see **PRECAUTIONS**: Laboratory Tests).

Pregnancy and Lactation

AVONEX® should not be administered in case of pregnancy and lactation. There are no adequate and well-controlled studies of AVONEX® in pregnant women. Patients should be advised of the abortifacient potential of AVONEX®. Fertile women receiving AVONEX® should be advised to take adequate contraceptive measures. It is not known if interferons alter the efficacy of oral contraceptives (see **PRECAUTIONS**: Information to Patients).

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®.

PRECAUTIONS

General

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

Seizures

Caution should be exercised when administering AVONEX® (Interferon beta-1a) to patients with pre-existing seizure disorder. In the two placebo-controlled studies of MS, 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.

Cardiac Disease

Patients with cardiac disease, such as angina, congestive heart failure, or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation and continued treatment with AVONEX®. While AVONEX® does not have any known direct-acting cardiac toxicity, during the post-marketing period infrequent cases of congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure have been reported in patients without known predisposition to these events or other known etiologies. In rare cases, these events have been temporally related to the administration of AVONEX® and have recurred upon re-challenge in patients with known predisposition.

Autoimmune Disorders

As with other interferon treatment, autoimmune disorders of multiple target organs have been reported post marketing including idiopathic thrombocytopenia, hyper and hypothyroidism, and rare cases of autoimmune hepatitis have also been reported. Patients should be monitored for signs of these disorders (see **PRECAUTIONS**: Laboratory Tests) and appropriate treatment implemented when observed.

Hepatic Injury

AVONEX®, like other interferon beta products, has the potential for causing severe liver injury (see **ADVERSE EVENTS**). Hepatic injury including elevated serum hepatic enzyme levels and hepatitis, some of which have been severe, has been reported post-marketing. In some patients a recurrence of elevated serum levels of hepatic enzymes have occurred upon AVONEX® re-challenge. In some cases, these events have occurred in the presence of other drugs that have been associated with hepatic injury. The potential of additive effects from multiple drugs or other hepatotoxic agents (e.g., alcohol) has not been determined. Patients should be monitored for signs of hepatic injury (see **PRECAUTIONS**: Laboratory Tests) and caution exercised when AVONEX® is used concomitantly with other drugs associated with hepatic injury.

Laboratory Tests

Laboratory abnormalities are associated with the use of interferons. During the placebo-controlled trials in multiple sclerosis, liver function tests were performed at least every 6 months. Liver function tests including serum ALT are recommended during AVONEX® therapy and should be performed at baseline, monthly at months 1 through 6, and every 6 months thereafter. AVONEX® should be initiated with caution in patients with a history of significant liver disease, clinical evidence of active liver disease, alcohol abuse, increased serum ALT (>2.5 times ULN), and in patients receiving concomitant medications associated with hepatic injury. These patients may require more frequent monitoring of serum hepatic enzymes. Discontinuation or interruption of AVONEX® should be considered if ALT rises above 5 times the ULN. Treatment with AVONEX® should be stopped if jaundice or other clinical symptoms of liver dysfunction appear. In addition to those laboratory tests normally required for monitoring patients with MS, and in addition to liver enzyme monitoring (see **PRECAUTIONS**: Hepatic Injury) complete blood cell counts and white blood cell differential, platelet counts, and blood chemistries, including thyroid function tests, are recommended during AVONEX® therapy (see **WARNINGS**: Decreased Peripheral Blood Counts and **ADVERSE EVENTS**). These tests should be performed at baseline, months 1, 3, 6, and every 6 months thereafter. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Immunogenicity

Serum neutralizing antibodies were reported to develop in only 2% to 6% of AVONEX®-treated patients. Although the exact clinical significance of antibodies has not been fully established, there are multiple literature reports indicating that the occurrence of neutralizing antibodies with beta interferon treatment impacts clinical efficacy, MRI measures and the induction of biological markers.

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.

Carcinogenesis and Mutagenesis

Carcinogenesis: No carcinogenicity data for Interferon beta-1a are available in animals or humans.

Mutagenesis: Interferon beta-1a was not mutagenic when tested in the Ames bacterial test and in an in vitro cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation. These assays are designed to detect agents that interact directly with and cause damage to cellular DNA. Interferon beta-1a is a glycosylated protein that does not directly bind to DNA.

Impairment of Fertility

No studies were conducted to evaluate the effects of interferon beta on fertility in normal women or women with MS. It is not known whether AVONEX® can affect human reproductive capacity. Menstrual irregularities were observed in monkeys administered interferon beta at a dose 100 times the recommended weekly human dose (based upon a body surface area comparison). Anovulation and decreased serum progesterone levels were also noted transiently in some animals. These effects were reversible after discontinuation of drug.

Treatment of monkeys with interferon beta at 2 times the recommended weekly human dose (based upon a body surface area comparison) had no effects on cycle duration or ovulation.

The accuracy of extrapolating animal doses to human doses is not known. In the placebo-controlled study, 6% of patients receiving placebo and 5% of patients receiving AVONEX® experienced menstrual disorder. If menstrual irregularities occur in humans, it is not known how long they will persist following treatment.

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**).

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

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

Patients should be informed about the risk of decreased blood counts including white blood cells and platelet counts and of the requirement for periodic laboratory testing (see **WARNINGS**). Patients should be advised to report immediately any clinical symptoms associated with blood count abnormalities and laboratory testing should be performed according to standard medical practice (see **WARNINGS**). Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Patients should be informed of the potential risk of liver injury with AVONEX® therapy, and of the requirement for frequent laboratory testing (see **PRECAUTIONS**). Patients should be informed of the symptoms suggesting liver dysfunction, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, and jaundice, and advised to consult with their physician immediately should such symptoms arise.

Patients should be instructed to report any symptoms of thyroid dysfunction (hypo or hyperthyroidism) and thyroid function tests should be performed according to standard medical practice (see **PRECAUTIONS**).

Female patients should be advised about the abortifacient potential of AVONEX® and instructed to take adequate contraceptive measures (see **PRECAUTIONS**).

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. 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. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of injection site reactions. 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

Relapsing Multiple Sclerosis

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 with relapsing multiple sclerosis randomized to AVONEX® were treated for up to 2 years.

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 1 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.

Table 1

Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study of Relapsing MS

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%

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Table 1 (continued)

Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study of Relapsing MS

Adverse Event	Placebo (N = 143)	AVONEX® (N = 158)
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%

Table 1 (continued)

Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study of Relapsing MS

Adverse Event	Placebo (N = 143)	AVONEX® (N = 158)
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 ($p \leq 0.05$).

Post-Marketing Experience

Anaphylaxis and other allergic reactions have been reported in patients using AVONEX® (see **WARNINGS**: Anaphylaxis). Decreased peripheral blood counts have been reported in patients using AVONEX® (see **WARNINGS**: Decreased Peripheral Blood Counts). Seizures, cardiovascular adverse events, and autoimmune disorders also have been reported in association with the use of AVONEX® (see **PRECAUTIONS**).

Single Demyelinating Event

The adverse events observed in the placebo-controlled study of patients with a single demyelinating event were similar to those observed in the placebo-controlled study of relapsing MS patients. Patients in this trial (N = 193) initiated AVONEX® treatment while on oral prednisone, which was used to treat the initial demyelinating event. The most common adverse events associated with AVONEX® ($p \leq 0.05$) during the first 6 months of treatment were flu-like syndrome (AVONEX®: 39%, placebo: 22%), fever (AVONEX®: 17%, placebo: 6%), and chills (AVONEX®: 17%, placebo: 3%). A higher proportion of patients treated with AVONEX® (20%) experienced depression, as compared with placebo (13%) ($p = 0.05$) (see **WARNINGS**).

DOSAGE AND ADMINISTRATION

The recommended dosage of AVONEX® (Interferon beta-1a) 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.

Before initiating a patient on AVONEX® therapy, please note the following **CONTRAINDICATIONS**.

- AVONEX® is contraindicated in patients with a known hypersensitivity to natural or recombinant interferon beta, albumin (human), or any other component of the formulation. Anaphylaxis has been observed with the use of AVONEX®.

Please also review the **WARNINGS** and **PRECAUTIONS** sections and ensure appropriate monitoring of patients with depression, hepatic dysfunction, a history of seizures, cardiac disease, thyroid dysfunction, myelosuppression, and female patients of child-bearing potential.

Patients should be advised of the side-effects of AVONEX™ and instructed on the use of aseptic technique when administering AVONEX™. The AVONEX™ Patient Leaflet should be carefully reviewed with all patients, and patients should be educated on self-care and advised to keep the Leaflet for continued reference during AVONEX® therapy.

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 10mL (10cc) diluent vial, two alcohol wipes, one 3cc syringe, one Micro Pin™, one needle, one adhesive bandage, one gauze pad).

Product Monograph available upon request.

REFERENCES

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4. Rudick RA, Simonian NA, Alam JA. Incidence and significance of neutralizing antibodies to interferon beta-1a in multiple sclerosis. *Neurology* 1998;50:1266-1272.
5. AVONEX® Product Monograph, 2003.

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See pages A-14, A-15

Continued from page A-58

DOSAGE AND ADMINISTRATION

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

Adults

The dosage of REMINYL shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day given in a b.i.d. regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL might provide additional benefit for some patients.

The recommended starting dose of REMINYL is 4 mg twice a day (8 mg/day). After a minimum of 4 weeks of treatment, if this dose is well tolerated, the dose should be increased to 8 mg twice a day (16 mg/day). A further increase to 12 mg twice a day (24 mg/day) after a minimum of 4 weeks at the previous dose may be considered following appropriate assessment of clinical benefit and tolerability.

REMINYL should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be warned that if therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

The abrupt withdrawal of REMINYL in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of REMINYL are lost, however, when the drug is discontinued.

Concomitant Treatment

In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered.

Special Populations

Dose escalation for elderly patients (>85 years old) with low body weight (especially females) or serious comorbid diseases should be undertaken with particular caution.

Hepatic Impairment

Galantamine plasma levels may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), dosing could begin with 4 mg once daily for at least 1 week. Then the dosage should be increased to 4 mg twice a day for at least 4 weeks. In these patients, daily doses should not exceed 8 mg twice a day (16 mg/day). Since no data are available on the use of REMINYL in patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL is not recommended for this population (see PRECAUTIONS).

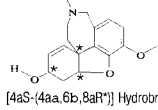
Renal Impairment

For patients with renal impairment (creatinine clearance of 9 to 60 mL/min), dose escalation should proceed cautiously and the maintenance dose should generally not exceed 16 mg/day. Since no data are available on the use of REMINYL in patients with a creatinine clearance less than 9 mL/min, REMINYL is not recommended for this population (see PRECAUTIONS).

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

PHARMACEUTICAL INFORMATION

Drug Substance

Trade Name:	REMINYL
Common Name:	galantamine hydrobromide
Chemical Name:	(4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide
Structural Formula:	
	[4aS-(4aa,6b,8aR*)] Hydrobromide (1:1)
Molecular Formula:	$C_{17}H_{21}NO_3 \cdot HBr$
Molecular Weight:	368.27
Ionization Constant:	pKa=8.2 (azepine moiety)
Partition Coefficient:	log P=1.09, between n-octanol and an aqueous buffer solution at pH=12.0
Melting Point:	257.3°C
Description:	Galantamine hydrobromide is a white to almost white powder. It is freely soluble in water (pH=5.2), 0.1 N hydrochloric acid (pH=1.0) and 0.1 N sodium hydroxide (pH=8.3).

Composition

REMINYL (galantamine hydrobromide) tablets are available in three strengths containing 4, 8, 12 mg of galantamine per tablet, as galantamine hydrobromide. The inactive ingredients are lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, propylene glycol, talc, and titanium dioxide. The 4 mg tablet also contains yellow ferric oxide. The 8 mg tablet also contains red ferric oxide. The 12 mg tablet also contains red ferric oxide and FD & C yellow #6 (also known as orange yellow S aluminum lake).

Stability and Storage Recommendations

REMINYL tablets should be stored between 15°C–30°C.

AVAILABILITY OF DOSAGE FORMS

REMINYL (galantamine hydrobromide), expressed as galantamine base, is available as film-coated tablets in the following strengths:

4 mg tablets which are off-white, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G4" on the other side;
8 mg tablets which are pink, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G8" on the other side;
12 mg tablets which are orange-brown, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G12" on the other side.
REMINYL is available in bottles of 60 tablets and in blisters of 56 tablets per carton.

Product Monograph available to healthcare professionals upon request.

JANSSEN-ORTHO

19 Green Belt Drive, Toronto, Ontario M3C 1L9

Date of Issuance: September 2003
RMPI031032A

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See page A-21

World Focus on Stroke

5th WORLD STROKE CONGRESS

VANCOUVER, B.C., CANADA, JUNE 23 – 26, 2004

The Scientific Program will include the following:
Plenary Sessions, Course, Breakfast Sessions, Workshops, Platform Sessions

Congress Chairs:
V. Hachinski, Canada
J.W. Norris, Canada

President International Stroke Society:
J.F. Toole, USA

Chairman Canadian Stroke Consortium:
P.A. Teal, Canada

Sponsored by: International Stroke Society

Hosted by: Canadian Stroke Consortium

Co-hosts:

National Stroke Association

Canadian Stroke Network

Deadline for abstracts: January 15, 2004

ORGANIZERS AND SECRETARIAT
Kenes International
17 Rue du Cendrier, B.P. 1726, CH-1211 Geneva 1, Switzerland
e-mail: stroke2004@kenes.com

You can also visit us on the web!! http://www.kenes.com/stroke2004

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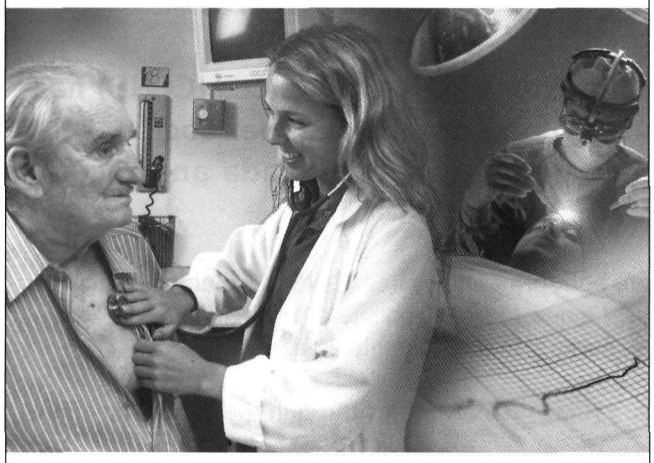
GRAND RIVER HOSPITAL



Located in the heart of South-Western Ontario, Grand River Hospital is designated as the district stroke centre, and is home to the region's hospital based MRI and the area's largest emergency department. Our 2,300 staff, 500 physicians and 800 volunteers provide quality health care for Waterloo Region, a community rich in opportunity, diversity and healthy lifestyle choices.

To meet our growing needs we have openings for:

Full Time Neurologists

Our community based neurology deparment has opportunities available for full time neurologists to become involved in clinical practice, the District Stroke program and clinical research. Particular needs for the community exist in the areas of neuromuscular diseases, MS, epilepsy and stroke. A multidisciplinary outpatient neurology clinic with emphasis on movement disorders, stroke and MS is about to be launched with full hospital support. Candidates are expected to be involved in this clinic and to share neurology and stroke call. Currently, clinical research projects in stroke, MS and headache are available for interested individuals. Please send your resume and a summary of your areas of interest to: ***Dr. D. J. Stewart, Medical Director of Neurological Sciences, Grand River Hospital.***

GRAND RIVER HOSPITAL

835 King Street West, Kitchener, ON N2G 1G3
Fax: 519.579.9226 • Email: dstewart2549@rogers.com

www.grandriverhospital.on.ca

Palliser Health Region

NEUROLOGIST

The Palliser Health Region invites applications for a Neurologist position.

Activities would be concentrated at Medicine Hat Regional Hospital, a 213 acute care bed regional referral centre, in a community of 51,000 located in southeastern Alberta, and a referral area with a population of 105,000.

Candidate should possess a recognized Fellowship and be eligible for licensure by The College of Physicians and Surgeons of Alberta. Attractive relocation package with site paid visits for approved candidates. Remuneration is fee for service.

Inquiries and c.v. can be directed to :

Dr. V.L. Di Ninno, B.Sc., Ph.D., M.D., C.C.F.P.
Vice President – Medical Services
PALLISER HEALTH REGION
666 – 5 Street S.W.
Medicine Hat, Alberta, T1A 4H6
Tel: 403-529-8024; Fax: 403-529-8998
e-mail: chiefofstaffpalliserhealth.ca
www.palliserhealth.ca

Caritas St. Elizabeth's Medical Center of Boston
736 Cambridge Street, Boston, MA 02135

Post-doctoral position in the newly established neuroscience center

Caritas St. Elizabeth's Medical Center, affiliated with Tufts University School of Medicine, department of neurology invites applications from post-doctorate candidates in the life sciences to meet the demand in the growing neuroscience center with a special focus on neurodegenerative disease research. Opportunities are available in the lab of **Henry Querfurth, M.D., Ph.D.**, an established neuroscience laboratory investigating the cell and molecular biology of Alzheimer's disease, amyloid angiopathy, inclusion body myositis and related neurodegenerative conditions. ***Postdoctoral fellow applicants:*** Experience in basic cell culture, microscopy, subcloning, Western and nucleic acid separation procedures required. Work will include preparation and use of viral vectors for gene delivery and metabolic labeling studies. Working knowledge of PC or Macintosh platforms expected; familiarity with sub-cellular fractionation, chromatography and transgenic models a plus. Applicants are asked to submit a curriculum vitae, a brief description of research accomplishments and three letters of reference directly to either: **Henry Querfurth, M.D., Ph.D.**, Chief, Neurology Research at hquerfur@opal.tufts.edu, or to **Caritas St. Elizabeth's Medical Center, 736 Cambridge Street, CBR4, Boston, MA 02135**. Candidates must be available for interview. Caritas St. Elizabeth's offers competitive salary, benefits and an outstanding collaborative research environment.

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Department of Medicine and Centre for Neuroscience Studies

A Tier 1 Canada Research Chair (tenure-track position) In Clinical Neurosciences

The Department of Medicine and Centre for Neuroscience Studies at Queen's University in Kingston, Ontario, Canada is seeking a senior investigator/scholar in the clinical neurosciences to fill a Tier I Canada Research Chair in Clinical Neuroscience. The successful candidate must be an MD with certification in the specialty of Neurology and must have an internationally recognized research program in neuroscience that ideally links to other research strengths, which include stroke, neuroimaging, motor control and movement disorders, pain, neurodegenerative disorders, regeneration, cognitive/behavioural neuroscience, and infectious disease. It is expected that the successful candidate will provide leadership in one or more fields of clinical neuroscience research. Successful candidates must be eligible for licensure in Ontario.

Queen's is ranked among the top "doctorate-level" universities in Canada; successfully merging the collegiality of a medium-sized university with an academic rigour that has enabled members of the Faculty of Health Sciences to achieve world-class distinction.

Kingston is one of Canada's most beautiful and historic cities - bordered by the calm, blue waters of Lake Ontario and the St. Lawrence River. Housing prices compare favourably with the rest of Canada, with no part of the City of Kingston more than a twenty-minute drive to Queen's. Kingston's 147,500 residents enjoy a calendar full of festivals and a variety of cultural and recreational activities appealing to people of all ages. Located only two and a half hours from the major Canadian centres of Toronto and Montreal, two hours from Canada's capital of Ottawa, and just a 20-minute drive from the American border, Kingston is easily accessible.

Queen's University is committed to employment equity and welcomes applications from all qualified candidates, including women, aboriginal people, people with disabilities and visible minorities.

Please submit a letter of application, curriculum vitae, the names and addresses of three referees, copies of recent publications and a one page statement of current research interests and future plans to Dr. J.L. McCans, Professor and Head, Department of Medicine, Rm. #3033 Etherington Hall, Queen's University, Kingston, Ontario, Canada K7L 3N6. Fax: (613)533-6695; e-mail: koenn@post.queensu.ca. Review of applications will commence on May 01, 2004 and will continue until the position is filled.

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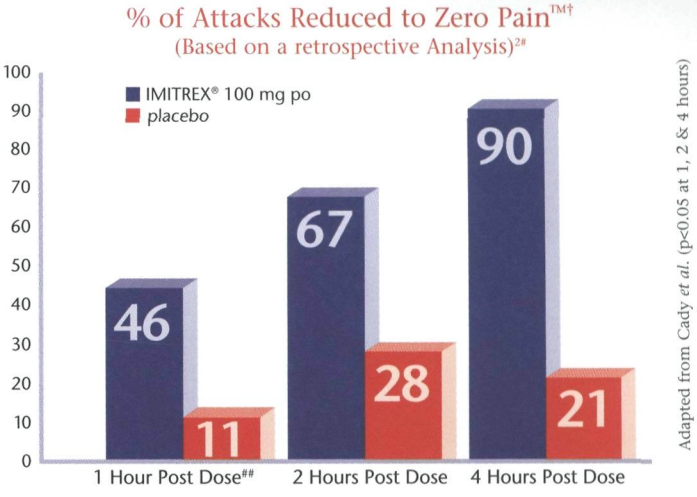
OUR GOAL: ZERO PAIN™† IN MIGRAINE

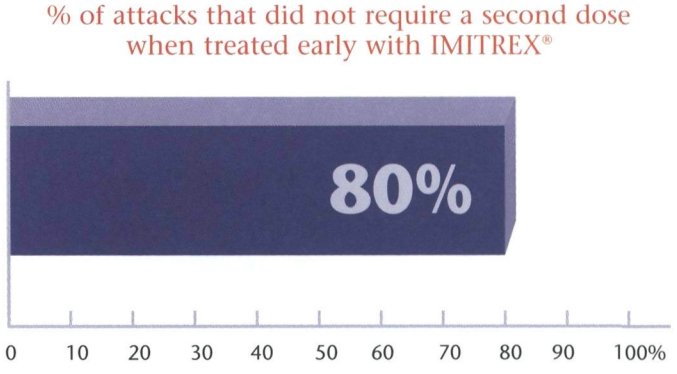
- IMITREX® is effective at any stage of migraine pain[†Δ]
- IMITREX® at the first sign of pain reduced most attacks to ZERO[2‡]
- Nearly 1 out of 2 attacks reduced to ZERO PAIN™ at 1 hour
- 2 out of 3 attacks reduced to ZERO PAIN™ at 2 hours
- 9 out of 10 attacks reduced to ZERO PAIN™ at 4 hours



##2 and 4 hour post dose time points were the primary endpoints.

SUCCESS WITH JUST ONE DOSE[2]

- When IMITREX® was taken at first sign of pain‡, 80% of migraine attacks did not require a second dose[2]
- Reduced need for a second dose = Potential cost savings (acquisition cost only)



IMITREX® (sumatriptan succinate/sumatriptan) is a selective 5-HT_1 receptor agonist indicated for the acute treatment of migraine attacks with or without aura.[1] IMITREX® is not indicated for prophylactic therapy of migraine, or for the management of hemiplegic, basilar or ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache.[1]

IMITREX® is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX®. IMITREX® is also contraindicated in patients with uncontrolled or severe hypertension.

The most common adverse events with IMITREX® 100 mg tablets included: nausea (11.0% vs. 5.8% placebo), malaise/fatigue (9.5% vs. 5.1% placebo), sensations (body regions unspecified) (9.0% vs. 4.5% placebo).

† Refers to 0 (zero) on a 4 point pain scale where 0=no pain, 1=mild pain, 2=moderate pain and 3=severe pain.[2]
Δ IMITREX® should not be used prophylactically. Administration during migraine aura prior to other symptoms occurring may not prevent the development of a headache.[1]
‡ Early intervention = treatment initiated at first sign of pain - when pain was mild, before progression to moderate-severe pain.
# Based on a retrospective analysis, 92 patients treated 118 headaches at first sign of pain, where the original prospective study did not pre-define this end-point. Further investigation using prospective analysis is required to prove clinical significance.

IMITREX®
SUMATRIPTAN SUCCINATE
SUMATRIPTAN

A faster way back.™*

GlaxoSmithKline

* Onset of action: 10-15 min. subcutaneous, 15 min. nasal spray, 30 min. tablet.

For brief prescribing information see pages A-42, A-43

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For brief prescribing information see page A-35

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