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Once-a-day

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Aricept*

donepezil HCl 5 & 10 mg tablets

PHARMACOLOGIC CLASSIFICATION Cholinesterase Inhibitor **ACTION AND CLINICAL PHARMACOLOGY ARICEPT** (donepezil hydrochloride) is a piperidine-based, reversible inhibitor of the enzyme acetylcholinesterase. A consistent pathological change in Alzheimer's disease is the degeneration of cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. The resulting hypofunction of these pathways is thought to account for some of the clinical manifestations of dementia. Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine (ACh) through reversible inhibition of its hydrolysis by acetylcholinesterase (AchE). If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that donepezil alters the course of the underlying dementing process. **INDICATIONS AND CLINICAL USE ARICEPT** (donepezil hydrochloride) is indicated for the symptomatic treatment of patients with mild-to-moderate dementia of the Alzheimer's type. **ARICEPT** tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. **CONTRAINDICATIONS ARICEPT** (donepezil hydrochloride) is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS *Anaesthesia:* ARICEPT** (donepezil hydrochloride), as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia. ***Neurological Conditions:* Seizures:** Some cases of seizures have been reported with the use of **ARICEPT** in clinical trials and from spontaneous Adverse Reaction reporting. Cholinomimetics can cause a reduction of seizure threshold, increasing the risk of seizures. However, seizure activity may also be a manifestation of Alzheimer's disease. The risk/benefit of **ARICEPT** treatment for patients with a history of seizure disorder must therefore be carefully evaluated. **ARICEPT** has not been studied in patients with moderately severe or severe Alzheimer's disease, non-Alzheimer dementias or individuals with Parkinsonian features. The efficacy and safety of **ARICEPT** in these patient populations is unknown. ***Pulmonary Conditions:*** Because of their cholinomimetic action, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **ARICEPT** has not been studied in patients under treatment for these conditions and should therefore be used with particular caution in such patients. ***Cardiovascular:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, most patients with serious cardiovascular conditions were excluded. Patients such as those with controlled hypertension (DBP<95 mmHg), right bundle branch blockage, and pacemakers were included. Therefore, caution should be taken in treating patients with active coronary artery disease and congestive heart failure. Syncopal episodes have been reported in association with the use of **ARICEPT**. It is recommended that **ARICEPT** should not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes. ***Gastrointestinal:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs) including high doses of acetylsalicylic acid (ASA), should be monitored for symptoms of active or occult gastrointestinal bleeding. Clinical studies of **ARICEPT** have shown no increase, relative to placebo in the incidence of either peptic ulcer disease or gastrointestinal bleeding. (See **ADVERSE REACTIONS** Section) **ARICEPT**, as a predictable consequence of its pharmacological properties, has been shown to produce, in controlled clinical trials in patients with Alzheimer's disease, diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg dose than with the 5 mg dose. In most cases, these effects have usually been mild and transient, sometimes lasting one -to- three weeks and have resolved during continued use of **ARICEPT**. (See **ADVERSE REACTIONS** Section) Treatment with the 5 mg/day dose for 4-6 weeks prior to increasing the dose to 10 mg/day is associated with a lower incidence of gastrointestinal intolerance. ***Genitourinary:*** Although not observed in clinical trials of **ARICEPT**, cholinomimetics may cause bladder outflow obstruction. **PRECAUTIONS Concomitant Use with other Drugs: *Use with Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. ***Use with Cholinomimetics and other Cholinesterase Inhibitors:*** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. ***Use with other Psychoactive Drugs:*** Few patients in controlled clinical trials received neuroleptics, antidepressants or anticonvulsants; there is thus limited information concerning the interaction of **ARICEPT** with these drugs. ***Use in Patients ≥65 Years Old:*** In controlled clinical studies with 5 and 10 mg of **ARICEPT**, 536 patients were between the ages of 65 to 84, and 37 patients were aged 85 years or older. In Alzheimer's disease patients, nausea, diarrhea, vomiting, insomnia, fatigue and anorexia increased with dose and age and the incidence appeared to be greater in female patients. Since cholinesterase inhibitors as well as Alzheimer's disease can be associated with significant weight loss, caution is advised regarding the use of **ARICEPT** in low body weight elderly patients, especially in those ≥ 85 years old. ***Use in Elderly Patients with Comorbid Disease:*** There is limited safety information for **ARICEPT** in patients with mild-to-moderate Alzheimer's disease and significant comorbidity. The use of **ARICEPT** in Alzheimer's disease patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Caution is advised regarding the use of **ARICEPT** doses above 5 mg in this patient population. ***Renally and Hepatically Impaired:*** There is limited information regarding the pharmacokinetics of **ARICEPT** in renally and hepatically impaired Alzheimer's disease patients. Close monitoring for adverse effects in Alzheimer's disease patients with renal or hepatic disease being treated with **ARICEPT** is therefore recommended. **Drug-Drug Interactions:** Pharmacokinetic studies, limited to short-term, single-dose studies in young subjects evaluated the potential of **ARICEPT** for interaction with theophylline, cimetidine, warfarin and digoxin administration. No significant effects on the pharmacokinetics of these drugs were observed. Similar studies in elderly patients were not done. ***Drugs Highly Bound to Plasma Proteins:*** Drug displacement studies have been performed *in vitro* between donepezil, a highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil at concentrations of 0.3 - 10 μg/mL did not affect the binding of furosemide (5 μg/mL), digoxin (2 ng/mL) and warfarin (3 μg/mL) to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin. ***Effect of ARICEPT on the Metabolism of Other Drugs:*** *In vitro* studies show a low rate of donepezil binding to CYP 3A4 and CYP 2D6 isoenzymes (mean Ki about 50 - 130 μM), which, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interferences. In a pharmacokinetic study involving 18 healthy volunteers, the administration of **ARICEPT** at a dose of 5mg/day for 7 days had no clinically significant effect on the pharmacokinetics of ketoconazole. No other clinical trials have been conducted to investigate the effect of **ARICEPT** on the clearance of drugs metabolized by CYP 3A4 (e.g., cisapride, terfenadine) or by CYP 2D6 (e.g., imipramine). It is not known whether **ARICEPT** has any potential for enzyme induction. ***Effect of Other Drugs on the Metabolism of ARICEPT:*** Ketoconazole and quinidine, inhibitors of CYP 450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. In a pharmacokinetic study, 18 healthy volunteers received 5 mg/day **ARICEPT** together with 200 mg/day ketoconazole for 7 days. In these volunteers, mean donepezil plasma concentrations were increased by about 30-36%. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin and phenobarbital) could increase the rate of elimination of **ARICEPT**. Pharmacokinetic studies demonstrated that the metabolism of **ARICEPT** is not significantly affected by concurrent administration of digoxin or cimetidine. ***Use in Pregnancy and Nursing Mothers:*** The safety of **ARICEPT** during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or in nursing mothers unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus or the infant. Teratology studies conducted in pregnant rats at doses of up to 16 mg/kg/day and in pregnant rabbits at doses of up to 10 mg/kg/day did not disclose any evidence for a teratogenic potential of **ARICEPT**. ***Pediatric Use:*** There are no adequate and well-controlled trials to document the safety and efficacy of **ARICEPT** in any illness occurring in children. Therefore, **ARICEPT** is not recommended for use in children. **ADVERSE REACTIONS** A total of 747 patients with mild-to-moderate Alzheimer's disease were treated in controlled clinical studies with **ARICEPT** (donepezil hydrochloride). Of these patients, 613 (82%) completed the studies. The mean duration of treatment for all **ARICEPT** groups was 132 days (range 1-356 days). ***Adverse Events Leading to Discontinuation:*** The rates of discontinuation from controlled clinical trials of **ARICEPT** due to adverse events for the **ARICEPT** 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. *The rate of discontinuation of patients who* received the 10 mg/day dose after only a 1-week initial treatment with 5 mg/day **ARICEPT** was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group

Dose Group	Placebo	5 mg/day ARICEPT	10 mg/day ARICEPT
Number of Patients Randomized	355	350	315
Events/% Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT: The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by **ARICEPT**'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued **ARICEPT** treatment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the duration of treatment with an initial 5 mg daily dose prior to increasing the dose to 10 mg/day. An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients received a 5 mg/day dose for 6 weeks prior to initiating treatment with 10 mg/day. The rates of common adverse events were lower than those seen in controlled clinical trial patients who received 10 mg/day after only a one-week initial treatment period with a 5 mg daily dose, and were comparable to the rates noted in patients treated only with 5 mg/day. See Table 2 for a comparison of the most common adverse events following one- and six-week initial treatment periods with 5 mg/day **ARICEPT**.

Table 2. Comparison of Rates of Adverse Events in Patients Treated with 10 mg/day after 1 and 6 Weeks of Initial Treatment with 5 mg/day

	No Initial Treatment		One-Week Initial Treatment with 5 mg/day	Six-Week Initial Treatment with 5 mg/day
Adverse Event	**Placebo (n = 315)**	**5 mg/day (n = 311)**	**10 mg/day (n = 315)**	**10 mg/day (n = 269)**
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle Cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Adverse Events Reported in Controlled Trials: The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment-emergent signs and symptoms (TESS) that were reported in at least 2% of patients from placebo-controlled clinical trials who received **ARICEPT** and for which the rate of occurrence was greater for **ARICEPT** than placebo-assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

Table 3. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT and at a Higher Frequency than Placebo-Treated Patients

Body System/ Adverse Events	Placebo n = 355	ARICEPT n = 747	Body System/ Adverse Events	Placebo n = 355	ARICEPT n = 747
Percent of Patients with any Adverse Event	72	74	**Metabolic and Nutritional**		
Body as a Whole			Weight Decrease	1	3
Headache	9	10	**Musculoskeletal System**		
Pain, various locations	8	9	Muscle Cramps	2	6
Accident	6	7	Arthritis	1	2
Fatigue	3	5	**Nervous System**		
Cardiovascular System			Insomnia	6	9
Syncope	1	2	Dizziness	6	8
Digestive System			Depression	<1	3
Nausea	6	11	Abnormal Dreams	0	3
Diarrhea	5	10	Somnolence	<1	2
Vomiting	3	5	**Urogenital**		
Anorexia	2	4	Frequent Urination	1	2
Hemic and Lymphatic Systems					
Ecchymosis	3	4			

Other Adverse Events Observed During Clinical Trials: During the pre-marketing phase, **ARICEPT** has been administered to over 1700 individuals for various lengths of time during clinical trials worldwide. Approximately 1,200 patients have been treated for at least 3 months, and more than 1,000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 115 patients treated for over 1 year. The range of patient exposure is from 1 to 1,214 days. Treatment-emergent signs and symptoms that occurred during three placebo-controlled clinical trials and two open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the studies were integrated and the events were grouped into a smaller number of standardized categones using a modified *COSTART* dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving **ARICEPT**. All adverse events occurring at least twice are included. Adverse events already listed in Tables 2 and 3 are not repeated here (i.e., events occurring at an incidence >2%). Also excluded are *COSTART* terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed as occurring in ≥1% and <2% of patients (i.e., in 1/100 to 2/100 patients: *frequent*) or in < 1% of patients (i.e., in 1/100 to 1/1,000 patients: *infrequent*). These adverse events are not necessarily related to **ARICEPT** treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. **Adverse Events Occurring in ≥1% and <2% or <1% of Patients Receiving ARICEPT: *Body as a Whole:*** (≥1% and <2%) influenza, chest pain, toothache; (<1%) fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, head pressure, listlessness. ***Cardiovascular System:*** (≥1% and <2%) hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; (<1%) angina pectoris, postural hypotension, myocardial infarction, premature ventricular contraction, arrhythmia, AV Block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thromboses. ***Digestive System:*** (≥1% and <2%) faecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; (<1%) eructation, gingivitis, increased appetite, flatulence, penodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, haemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. ***Endocrine System:*** (<1%) diabetes mellitus, goiter. ***Hemic & Lymphatic System:*** (<1%) anaemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. ***Metabolic and Nutritional Disorders:*** (≥1% and <2%) dehydration; (<1%) gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. ***Musculoskeletal System:*** (≥1% and <2%) bone fracture; (<1%) muscle weakness, muscle fasciculation. ***Nervous System:*** (≥1% and <2%) delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, libido increased, restlessness, abnormal crying, nervousness, aphasia; (<1%) cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing, seizures. ***Respiratory System:*** (≥1% and <2%) dyspnea, sore throat, bronchitis; (<1%) epistaxis, postnasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. ***Skin and Appendages:*** (≥1% and <2%) abrasion, pruritus, diaphoresis, urticaria; (<1%) dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. ***Special Senses:*** (≥1% and <2%) cataract, eye irritation, blurred vision; (<1%) dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. ***Urogenital System:*** (≥1% and <2%) urinary incontinence, nocturia; (<1%) dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. ***Long-Term Safety:*** Patients were exposed to **ARICEPT** in two open-label extension studies (n=885) of over two years. In one of the studies, 763 patients who previously completed one of two placebo-controlled studies of 15 or 30 weeks duration continued to receive **ARICEPT** and were evaluated for safety and neuropsychological evaluations for up to 152 weeks; the safety profile of **ARICEPT** in this extension study remained consistent with that observed in placebo-controlled trials. Following one and two years of treatment, 76% (n=580) and 49% (n=374) of these patients, respectively, were still receiving therapy (cumulative weeks 48 and 108). ***Postmarketing Reports:*** Voluntary reports of adverse events temporally associated with **ARICEPT** that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash. **DOSAGE AND ADMINISTRATION *ARICEPT*** (donepezil hydrochloride) tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. The recommended initial dose of **ARICEPT** is 5 mg taken once daily. Therapy with the 5 mg dose should be maintained for 4-6 weeks before considering a dose increase, in order to avoid or decrease the incidence of the most common adverse reactions to the drug (see **ADVERSE REACTIONS** Section) and to allow plasma levels to reach steady state. For those patients who do not respond adequately to the 5 mg daily dose after 4 -to- 6 weeks of treatment, the 10 mg daily dose may then be considered. The maximum recommended dose is 10 mg taken once daily. Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects. Adverse events are more common in individuals of low body weight, in patients ≥ 85 years old and in females. It is recommended that **ARICEPT** be used with caution in elderly women of low body weight and that the dose should not exceed 5 mg/day. **ARICEPT** should be taken once daily in the evening, before retiring. For patients experiencing insomnia, **ARICEPT** may be taken in the morning. It may be taken with or without food. In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision. **AVAILABILITY OF DOSAGE FORMS ARICEPT** is supplied as film-coated tablets containing 5 mg (white tablets) or 10 mg (yellow tablets) of donepezil hydrochloride. The name **ARICEPT** and the strength are embossed on each tablet. **ARICEPT** is available in high density polyethylene (HDPE) bottles of 30 tablets and in blister strips boxed as 28 tablets (combination of 2 strips of 14 tablets).

Product Monograph available upon request.

Pfizer NEUROSCIENCE

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Pfizer Canada Inc., licensee

Member R&D PAAB

See OBC

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

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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	35.8	32.8	41.3
Depression	27.8	20.6	23.9
Fever	**15.5**	**24.9**	**27.7**
Back pain	21.4	19.6	23.4
Myalgia	19.8	24.9	25.0
Nausea	23.0	24.9	24.5
Insomnia	21.4	19.6	23.4
Diarrhoea	18.7	17.5	19.0
Laboratory Test Abnormalities			
Lymphopenia	11.2	20.1	28.8
Leukopenia	3.7	12.7	22.3
Granulocytopenia	3.7	11.6	15.2
AST increase	3.7	10.1	17.4
ALT increase	4.3	19.6	27.2

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

The adverse events experienced during the study are listed below, by WHOART System Organ Class. The most common amongst the injection site reactions was in the form of mild erythema. The majority of the other injection site reactions were also mild in the 2 Rebif® groups. Necrosis was reported in 8 patients treated with Rebif®. Two of these patients were in the 66 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 exacerbation rate in the neutralizing antibody-positive groups compared to the neutralizing antibody-negative groups. There is no clear indication that the development of serum 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
SUMATRIPTAN

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.

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See IBC

PrCOPAXONE®
(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*		
	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

* 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*		
	Glatiramer acetate n=125	Placebo n=126	p-Value
Mean No. of Relapses/2 years†	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‡	98/125 (78%)	95/126 (75%)	0.48
Mean Change in EDSS	-0.05	+0.21	0.023

* The primary efficacy measure for **Trial II** was the number of relapses during treatment. Analyses were based on the intent-to-treat population.

† Baseline adjusted mean.

‡ 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$^{1-15}$, L-Ala$^{39-46}$, L-Tyr$^{8-10}$, L-Lys$^{30-37}$]•nCH$_3$CO$_2$H (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.

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Montreal, Quebec H3A 3L4

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See page A-3

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 topiramate in monotherapy at this time.

CONTRAINDICATIONS

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

WARNINGS

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

Central Nervous System Effects

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

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

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

PRECAUTIONS

Effects Related to Carbonic Anhydrase Inhibition

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

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

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

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

Nutritional Supplementation

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

Weight Loss in Pediatrics

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

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with impaired renal function (CL_r < 70 mL/min/1.73m²) or with end-stage renal disease receiving hemodialysis treatments may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function. As with all patients, the titration schedule should be guided by clinical outcome (i.e. seizure control, avoidance of side effects) with the knowledge that patients with known renal impairment may require a longer time to reach steady-state at each dose. (See **DOSAGE AND ADMINISTRATION.**)

Decreased Hepatic Function

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

Information for Patients

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

Effects on Ability to Drive and Use Machines

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

Drug Interactions

Antiepileptic Drugs

Effects of TOPAMAX on Other Antiepileptic Drugs: Potential interactions between topiramate 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 topiramate on steady-state pharmacokinetics of phenytoin may be related to the frequency of phenytoin dosing. A slight increase in steady-state phenytoin plasma concentrations was observed, primarily in patients receiving phenytoin in two divided doses. The slight increase may be due to the saturable nature of phenytoin pharmacokinetics and inhibition of phenytoin metabolism ($CYP2C_{min}$).

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 TOPAMAX. 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 TOPAMAX, and therefore, does not warrant dosage adjustment of TOPAMAX.

The effect of these interactions on plasma concentrations are summarized in Table 1:

Table 1
Drug Interactions with TOPAMAX Therapy

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

* Is not administered but is an active metabolite of carbamazepine
↔ No effect on plasma concentration (< 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 topiramate and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. It is recommended that TOPAMAX topiramate not be used concomitantly with alcohol or other CNS depressant drugs.

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

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

Laboratory Tests

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

Use in Pregnancy and Lactation

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

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

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

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

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

Pediatric Use

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

Geriatric Use

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

Race and Gender Effects

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

ADVERSE REACTIONS

Adults

The most commonly observed adverse events associated with the adjunctive use of TOPAMAX topiramate at dosages of 200 to 400 mg/day in controlled trials in adults that were seen at greater frequency in topiramate-treated patients and did not appear to be dose related within this dosage range were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, nystagmus, and paresthesia (see Table 2).

The most common dose-related adverse events at dosages of 200 to 1,000 mg/day were: nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, and mood problems (see Table 3).

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

	TOPAMAX Dosage (mg/day)		
Body System/ Adverse Event	Placebo (n=216)	200-400 (n=113)	600-1,000 (n=414)
Body as a Whole			
Asthenia	1.4	8.0	3.1
Back Pain	4.2	6.2	2.9
Chest Pain	2.8	4.4	2.4
Influenza-Like Symptoms	3.2	3.5	3.6
Leg Pain	2.3	3.5	3.6
Hot Flushes	1.9	2.7	0.7
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

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

Table 3

Dose-Related Adverse Events From Placebo-Controlled, Add-On Trials in ADULTS

Adverse Event	TOPAMAX Dosage (mg/day)			
	Placebo (n=216)	200 (n=45)	400 (n=68)	600 – 1,000 (n=414)
Fatigue	13.4	11.1	11.8	29.7
Nervousness	7.4	13.3	17.6	19.3
Difficulty with Concentration/Attention	1.4	6.7	8.8	14.5
Confusion	4.2	8.9	10.3	13.8
Depression	5.6	8.9	7.4	13.0
Anorexia	3.7	4.4	5.9	12.3
Language problems	0.5	2.2	8.8	10.1
Anxiety	6.0	2.2	2.9	10.4
Mood problems	1.9	0.0	5.9	9.2

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

Pediatrics

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

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

Table 4

Incidence (%) of Treatment-Emergent Adverse Events in Worldwide Pediatric Clinical Trials Experience (2-16 years of Age)[a,b]

(Events that Occurred in ≥2% of Topiramate-Treated Patients and Occurred More Frequently in Topiramate-Treated Than Placebo-Treated Patients)

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

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

[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

[c] Not Otherwise Specified

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

In adult and pediatric patients, nephrolithiasis was reported rarely. Isolated cases of thromboembolic events have also been reported; a causal association with the drug has not been established.

When the safety experience of patients receiving TOPAMAX topiramate as adjunctive therapy in both double-blind and open-label trials (1,446 adults and 303 children) was analyzed, a similar pattern of adverse events emerged.

Post-Marketing Adverse Reactions

The most frequently reported adverse events in spontaneous post-marketing reports on topiramate include:

Psychiatric: somnolence or sedation, hallucination(s), depression, anorexia, aggressive reaction, psychosis, thinking abnormal, paranoid reaction, insomnia, emotional lability, suicide attempt, delusion

Central and Peripheral Nervous System: confusion, convulsions aggravated, paresthesia, agitation, speech disorder, ataxia, dizziness, convulsions, amnesia, headache, hyperkinesia

Metabolic and Nutritional: weight decrease

Autonomic Nervous System: vomiting

Vision: vision abnormal

Gastrointestinal: nausea, diarrhea, abdominal pain, constipation

Body as a Whole - General Disorders: fatigue

Urinary System: renal calculus

Skin and Appendages: rash

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

General TOPAMAX Tablets or Sprinkle Capsules can be taken without regard to meals. Tablets should not be broken. TOPAMAX Sprinkle Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use. The sprinkle formulation is provided for those patients who cannot swallow tablets, e.g. pediatric and the elderly.

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

The recommended total daily maintenance dose is 200 mg-400 mg/day in two divided doses. Doses above 400 mg/day have not been shown to improve responses and have been associated with a greater incidence of adverse events. The maximum recommended dose is 800 mg/day. Daily doses above 1,600 mg have not been studied.

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

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

Geriatrics

See **PRECAUTIONS** section.

Patients with Renal Impairment

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

Patients Undergoing Hemodialysis

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

Patients with Hepatic Disease

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

AVAILABILITY OF DOSAGE FORMS

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

25 mg: white, round, coated tablets containing 25 mg topiramate.
100 mg: yellow, round, coated tablets containing 100 mg topiramate.
200 mg: salmon-coloured, round, coated tablets containing 200 mg topiramate.

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 tablets with desiccant.
Bottles of 60 capsules without desiccant.

TOPAMAX is a Schedule F Drug.

Product Monograph available to physicians and pharmacists upon request.

JANSSEN-ORTHO Inc. Janssen-Ortho Inc., Toronto, Ontario M3C 1L9

Date of Issuance: April 2000
TXPI001013A

See pages A-4, A-5

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 ®BETASERON® (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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See pages A-6, A-7, A-18, A-19

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 [pl6.2]) 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†	—	500 to 1000 mg once daily

† 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.

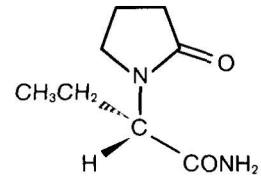
PHARMACEUTICAL INFORMATION

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.

Keppra® is distributed by Lundbeck Canada Inc.,
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See pages A-22, A-23

08841856 (Rev. July 2003)

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 antidiotypic antibodies provided by human immune globulin.[7-10]

Allogeneic Bone Marrow Transplantation

The mechanism of action of Immune Globulin Intravenous (Human), 10% in protecting immune-compromised patients with Allogeneic Bone Marrow Transplantation (BMT) from serious bacterial infections is similar to the anti-infective mechanism of action in PID.[11] The *immunomodulatory 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.[8,9,12-14]

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.[13-22]

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.[23-25]

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 post-transplant 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.[11,26]

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.[27-29]

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/mm³) at entry.[30] The benefit of Immune Globulin Intravenous (Human) is still present for children who cannot be treated with trimethoprim-sulfamethoxazole and are receiving zidovudine.[31]

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.[32,33] 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).[34,35] 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.[36] 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.[37,38]

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.[40-42] 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.[43] 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.* 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.[44,45]

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.[46-48]

Similar adverse reactions as for **PID** are expected for the 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).[49] 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. 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.

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™ 10% 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).[49] 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. 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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See page A-9

ONCE-A-WEEK

AVONEX®

(Interferon beta-1a)

IM Injection

PRESCRIBING INFORMATION

THERAPEUTIC CLASSIFICATION

Immunomodulator

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General

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

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

Laboratory Tests

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

Drug Interactions

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

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

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

Use in Pregnancy

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

Although no teratogenic effects were seen in these studies, it is not known if teratogenic effects would be observed in humans. There are no adequate and well-controlled studies with interferons in pregnant women.

Nursing Mothers

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

Pediatric Use

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

Information to Patients

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

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

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

ADVERSE EVENTS

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

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.*

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

Table 1
Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study

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

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

DOSAGE AND ADMINISTRATION

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

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

AVAILABILITY OF DOSAGE FORMS

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

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

Product Monograph Available upon request.

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CANADA

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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
Xerophthalmia	1.9	0.0	1.4	0.8
Cataract	–	–	1.4	0.8
Lacrimation Abnormal	–	–	1.4	0.0
White Cell and Reticuloendothelial System				
Eosinophilia	–	–	1.4	0.0

a: Incidence of adverse event <1%.

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

REQUIP® is a registered trademark, used under license by GlaxoSmithKline Inc.
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.

ADVERTISERS INDEX

See page A-21

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CLINICIAN-SCIENTISTS

Department of Neurology and Neurosurgery

McGill University

McGill

The Department of Neurology and Neurosurgery is seeking Clinician-Scientists and invites applications from outstanding applicants at the fellowship, assistant, associate, and full professor levels.

Successful candidates will have outstanding clinical and academic skills and commitment to an academic career.

With an overarching focus on transformative neuroscience at the interface, primary responsibilities will be the management of patients with nervous system disorders and conduct of peer-funded research. It is anticipated that this cohort will achieve status as leaders of transformative neurosciences in the post-genomic era.

Sited on four hospital sites within the McGill associated hospitals complex, the Department of Neurology and Neurosurgery plays a pivotal role in academic and clinical neurosciences in McGill University, in Montreal, and in Canada, and is a major reason that the neurosciences is a core program of the University. With its affiliated research institute, Montreal Neurological Institute, and its research centres - the Centre for Research in Neuroscience of the McGill University Health Centre, and the Bloomfield Centre for Research in Ageing of the Lady Davis Institute, the Department offers unprecedented opportunities for clinician-scientists to fluorish in an environment that embodies the dream of the founder of the MNI, Dr. Wilder Penfield.

Currently the Department of Neurology and Neurosurgery has approximately 150 members, two-thirds of whom are full time scientists. The Department is also the academic home of the Graduate Program in Neurological Sciences, the largest program of its kind in North America, with associate members from a large number of Departments in McGill, a novel graduate curriculum, and a graduate student enrolment of approximately 150.

Also integrated into the Department, McGill offers numerous strong programs in the areas of ageing, pain, oncology, genetics, development, epidemiology and biostatistics, neuropsychology, biomedical engineering, imaging, and immunology, and a rich infrastructure supported by Genome Canada, Genome Quebec, and the Canada Foundation for Innovation.

Applicants will also find in Quebec a significant support network provided by the province for training and academic salary and network infrastructure support.

McGill has adopted a policy that all of its Canada Research Chair allocations from the federal government will be used for external recruitment.

While the Department has specific needs in the areas of cognitive neurology, functional neuroscience, neurodegenerative disease, pain, neurooncology, epilepsy, neuromuscular disease, multiple sclerosis, neurogenetics, trauma, and mind and brain development, all applicants of high academic calibre will be given the consideration that is due to excellence.

McGill University is located in Montreal, one of the world's truly cosmopolitan cities. The city celebrates its broad cultural diversity, and is of a size that engenders a distinct European flavour.

Applicants are invited to submit a letter of expression of interest and an updated curriculum vitae to;

Dr. Richard Riopelle,
Chair, Department of Neurology and Neurosurgery,
c/o Montreal Neurological Institute, 3801 University Street, Room 144,
Montreal, QC, Canada, H3A 2B4
(rriopelle@mni.mcgill.ca).

While application is open to all eligible candidates, in accordance with Canadian Immigration requirements, this advertisement is directed primarily to Canadian citizens and permanent residents of Canada. McGill is committed to equity in employment.

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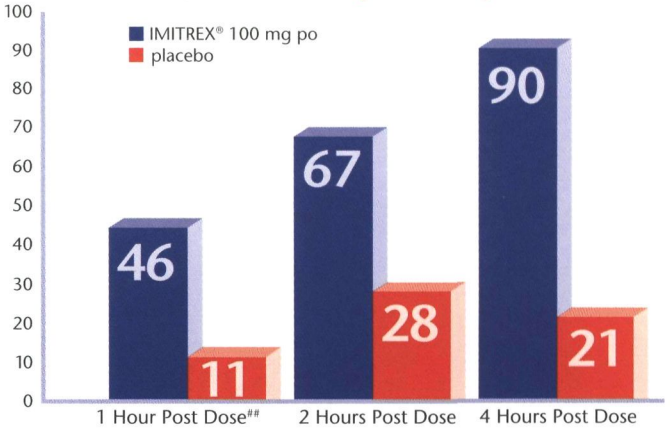
OUR GOAL: ZERO PAIN™† IN MIGRAINE

- IMITREX® is effective at any stage of migraine pain[1Δ]
- 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

% of Attacks Reduced to Zero Pain™†
(Based on a retrospective Analysis)[2#]



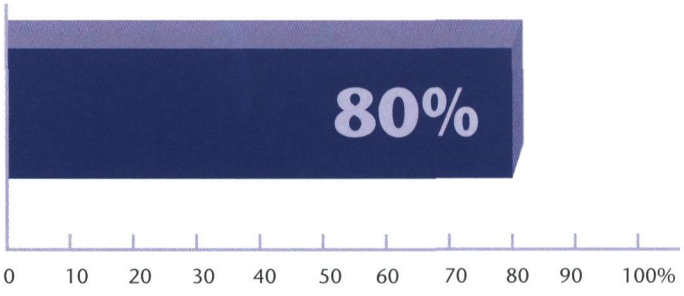
Adapted from Cady *et al.* (p<0.05 at 1, 2 & 4 hours)

##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)

% of attacks that did not require a second dose when treated early with IMITREX®



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.

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For brief prescribing information see pages A-28, A-29

ARICEPT 5 years OF EXCELLENT EFFICACY

For living with Alzheimer's disease.

Aricept® is indicated for the symptomatic treatment of mild-to-moderate dementia of the Alzheimer's type, and does not change the underlying course of the disease. With appropriate dose escalation, 5 mg/d, 10 mg/d and placebo were shown to have comparable adverse events, the most common being diarrhea, nausea, insomnia, fatigue, vomiting, muscle cramps and anorexia. These are usually mild and transient, resolving with continued treatment without need for dose modification.

Make Aricept* your standard of care.

Pfizer NEUROSCIENCE

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Product Monograph available on request.

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Once-a-day Aricept*

donepezil HCl 5 & 10 mg tablets

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