ropinirole

REQUIP®

Rethinking Parkinson's.

ropinirole (as ropinirole hydrochloride)

Tablets: 0.25 mg, 1.0 mg, 2.0 mg, 5.0 mg

THERAPEUTIC CLASSIFICATION

AntiParkinsonian Agent / Dopamine Agonist

INDICATIONS AND CLINICAL USE

REQUIP (ropinirole hydrochloride) is indicated in the treatment of the signs and symptoms of idiopathic Parkinson's disease. REQUIP can be used both as early therapy, without concomitant levodopa and as an adjunct to levodopa.

CONTRAINDICATIONS

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

WARNINGS

Orthostatic Symptoms – Dopamine agonists appear to impair the systemic regulation of blood pressure with resulting orthostatic symptoms of dizziness or lightheadedness, with or without documented hypotension. These symptoms appear to occur especially during dose escalation. Therefore, patients treated with dopamine agonists should be carefully monitored for signs and symptoms of orthostatic hypotension, especially during dose escalation and should be informed of this risk. **Hallucinations –** In controlled trials, REQUIP (ropinirole hydrochloride) caused hallucination in 5.1% of patients during early therapy (1.4% in the placebo group) and in 10.1% of patients receiving REQUIP and levodopa (4.2% receiving placebo and levodopa). Hallucination was of sufficient severity that it led to discontinuation in 1.3% and 1.9% of patients during early and adjunct therapy, respectively. The incidence of hallucination was dose-dependent both in early and adjunct therapy studies.

PRECAUTIONS

Cardiovascular – Since REQUIP (ropinirole hydrochloride) has not been studied in patients with a history or evidence of significant cardiovascular disease including myocardial infarction, unstable angina, cardiac decompensation, cardiac arrhythmias, vaso-occlusive disease (including cerebral) or cardiomyopathy, it should be used with caution in such patients. There is limited experience with REQUIP in patients treated with antihypertensive and antiarrhythmic agents. Consequently, in such patients, the dose of REQUIP should be titrated with caution. **Neuroleptic Malignant Syndrome –** A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy. A single spontaneous report of a symptom complex resembling the neuroleptic malignant syndrome has been observed in a 66 year old diabetic male patient with Parkinson's disease, who developed fever, muscle stiffness, and drowsiness 8 days after beginning REQUIP treatment. The patient also experienced acute bronchitis, which did not respond to antibiotic treatment. REQUIP was discontinued three days before the patient died. The reporting physician considered these events to be possibly related to REQUIP treatment. A single spontaneous report of severe muscle pain has been reported in a 66 year old male patient around his thigh. The reporting physician considered the event to be probably related to REQUIP treatment. **Retinal Pathology in Rats –** In a two year carcinogenicity study in albino Sprague-Dawley rats, retinal atrophy was observed at incidences of 0%, 1.4%, 1.4% and 10% of male rats and 0%, 4.4%, 2.9% and 12.9% of female rats dosed at 0, 1.5, 15 and 50 mg/kg/day respectively. The incidence was significantly higher in both male and female animals dosed at 50 mg/kg/day. The 50 mg/kg/day dose represents a 2.8 fold greater exposure (AUC) and a 13.1 fold greater exposure (C_{max}) to ropinirole in rats than the exposure would be in humans at the maximum recommended dose of 24 mg/day. The relevance of this finding to humans is not known. **Pregnancy –** The use of REQUIP during pregnancy is not recommended. REQUIP given to pregnant rats during organogenesis (gestation days 8 through 15) resulted in decreased fetal body weight at 60 mg/kg/day (approximately 3 - 4 times the AUC at the maximal human dose of 8 mg t.i.d), increased fetal death at 90 mg/kg/day (approximately 5 times the AUC at the maximal human dose of 8 mg t.i.d) and digital malformations at 150 mg/kg/day (approximately 8-9 times the AUC at the maximal human dose of 8 mg t.i.d). These effects occurred at maternally toxic doses. There was no indication of an effect on development of the conceptus at a maternally toxic dose of 20 mg/kg/day in the rabbit. In a perinatal-postnatal study in rats, 10 mg/kg/day of REQUIP (approximately 0.5 - 0.6 times the AUC at the maximal human dose of 8 mg t.i.d) impaired growth and development of nursing offspring and altered neurological development of female offspring. **Nursing Mothers –** Since REQUIP suppresses lactation, it should not be administered to mothers who wish to breast-feed infants. Studies in rats have shown that REQUIP and/or its metabolites cross the placenta and are excreted in breast milk. Consequently, the human fetus and/or neonate may be exposed to dopamine agonist activity. **Use in Women receiving Estrogen Replacement Therapy –** In female patients on long-term treatment with conjugated estrogens, oral clearance was reduced and elimination half-life prolonged compared to patients not receiving estrogens (see Pharmacokinetics). In patients, already receiving estrogen replacement therapy, REQUIP may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or introduced during treatment with REQUIP, adjustment of the REQUIP dosage may be required. **Pediatric Use –** Safety and effectiveness in the pediatric population have not been established. **Renal and Hepatic Impairment –** No dosage adjustment is needed in patients with mild to moderate renal impairment (creatinine clearance of 30 to 50 mL/min). Because the use of REQUIP in patients with severe renal impairment or hepatic impairment has not been studied, administration of REQUIP to such patients is not recommended. **Drug Interactions –** *Psychotropic Drugs:* Neuroleptics and other centrally active dopamine antagonists may diminish the effectiveness of REQUIP. Therefore, concomitant use of these products is not recommended. Based on population pharmacokinetic assessment, no interaction was seen between REQUIP and tricyclic antidepressants or benzodiazepines. *Anti-Parkinson Drugs:* Based on population pharmacokinetic assessment, there were no interactions between REQUIP and drugs commonly used to treat Parkinson's disease, i.e., selegiline, amantadine, and anticholinergics. *Levodopa:* The potential pharmacokinetic interaction of levodopa/carbidopa (100 mg/10 mg b.i.d.) and REQUIP (2 mg t.i.d.) was assessed in levodopa naive (*de novo*) male and female patients with Parkinson's disease (n=30, mean age 64 years). The rate and extent of availability of REQUIP at steady state were essentially the same with or without levodopa. Similarly, the rate and extent of availability of levodopa, as well as its elimination half-life, were essentially the same in the presence and absence of REQUIP. *Inhibitors of CYP1A2: Ciprofloxacin:* The effect of ciprofloxacin (500 mg b.i.d.) on the pharmacokinetics of REQUIP (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 55 years). The extent of systemic availability of REQUIP was significantly increased when coadministered with ciprofloxacin (AUC increased by 1.84 fold). Thus, in patients already receiving CYP1A2 inhibitors such as ciprofloxacin, REQUIP therapy may be instituted in the recommended manner and the dose titrated according to clinical response. However, if therapy with a drug known to be an inhibitor of CYP1A2 is stopped or introduced during treatment with REQUIP, adjustment of the REQUIP dosage will be required. *Substrates of CYP1A2: Theophylline:* The effect of oral theophylline (300 mg b.i.d.) on the pharmacokinetics of REQUIP (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 59 years). There was no marked change in the rate or extent of availability of REQUIP when coadministered with theophylline. Similarly, coadministration of REQUIP with intravenous theophylline (5 mg/kg) did not result in any marked change in the pharmacokinetics of theophylline. It is therefore unlikely that substrates of CYP1A2 would significantly alter the pharmacokinetics of REQUIP, and vice-versa. *Digoxin:* The effect of REQUIP (2 mg t.i.d.) on the pharmacokinetics of digoxin (0.125-0.25 mg o.d.) was studied in male and female patients with Parkinson's disease (n=10, mean age 72 years). Coadministration at steady state with REQUIP resulted in a 10% decrease in digoxin AUC although mean trough digoxin plasma concentrations were unaltered. However, the effect of higher recommended doses of REQUIP on the pharmacokinetics of digoxin is not known. *Alcohol:* No information is available on the potential for interaction between REQUIP and alcohol. As with other centrally active medications, patients should be cautioned against taking REQUIP with alcohol. **Psycho-Motor Performance –** As orthostatic symptoms of dizziness or lightheadedness as well as somnolence may occur during REQUIP therapy patients should be cautioned not to drive a motor vehicle or operate potentially hazardous machinery until they are reasonably certain that REQUIP therapy does not affect their ability to engage in such activities.

ADVERSE REACTIONS

Adverse Reactions Associated with Discontinuation of Treatment – Of 1599 patients who received REQUIP (ropinirole hydrochloride) during the premarketing clinical trials, 17.1% in early-therapy studies and 17.3% in adjunct-therapy studies discontinued treatment due to adverse reactions. The events resulting in discontinuation of REQUIP in 1% or more of patients were as follows: *Early therapy:* nausea (6.4%), dizziness (3.8%), aggravated Parkinson's disease (1.3%), hallucination (1.3%), headache (1.3%), somnolence (1.3%) and vomiting (1.3%). *Adjunct therapy:* dizziness (2.9%), dyskinesia (2.4%), confusion (2.4%), vomiting (2.4%), hallucination (1.9%), nausea (1.9%), anxiety (1.9%), and increased sweating (1.4%). Patients over 75 years of age (n=130) showed slightly higher incidences of withdrawal due to hallucination, confusion and dizziness than patients less than 75 years of age. **Most Frequent Adverse Events –** Adverse events occurring with an incidence of greater than, or equal to, 10% were as follows: *Early therapy:* nausea, dizziness, somnolence, headache, peripheral edema, vomiting, syncope, fatigue and viral infection. *Adjunct therapy:* dyskinesia, nausea, dizziness, somnolence and headache. Dopamine agonists, with an ergoline chemical structure have been associated with adverse experiences such as retroperitoneal fibrosis, erythromelalgia and pulmonary reactions. REQUIP has a novel, non-ergoline chemical structure and no reports of such events have been observed in clinical trials. **Incidence of Adverse Events in Placebo Controlled Trials –** The incidence of postural hypotension, an event commonly associated with initiation of dopamine agonist therapy, was not notably different from placebo in clinical trials. However, decreases in systolic blood pressure to < 90 mmHg have been observed in 13% (<65 years), 16% (65-75 years) and 7.6% (>75 years) of patients treated with REQUIP. Table 1 lists adverse events that occurred at an incidence of 2% or more among REQUIP-treated patients who participated in placebo-controlled trials for up to one year. Patients were dosed in a range of 0.75 mg to 24 mg/day. Reported adverse events were classified using a standard World Health Organization (WHO)-based dictionary terminology. The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies can not be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse events incidence rate in the population studied. The Adverse Reactions section has been condensed. See full Product Monograph for the complete information.

DOSAGE AND ADMINISTRATION

REQUIP (ropinirole hydrochloride) should be taken three times daily. While administration of REQUIP with meals may improve gastrointestinal tolerance, REQUIP may be taken with or without food. The recommended starting dosage is 0.25 mg three times daily. Based on individual patient response, dosage should then be titrated by weekly increments of 0.25 mg per dose as described in the table below. After week 4, daily dosage may be increased by 0.5 to 1.0 mg per dose on a weekly basis up to 24 mg per day. Doses greater than 24 mg/day have not been tested in clinical trials. Smaller dose increments are recommended for patients who may be at risk for orthostatic symptoms. In clinical trials, initial benefits were observed with 3 mg/day and higher doses.

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

TABLE 1

Adverse events with incidence ≥2% from all placebo-controlled early and adjunct therapy studies

	Early Therapy		Adjunct Therapy	
	REQUIP N = 157 % occurrence	Placebo N = 147 % occurrence	REQUIP N = 208 % occurrence	Placebo N = 120 % occurrence
Autonomic Nervous System				
Sweating Increased	6.4	4.1	7.2	1.7
Mouth Dry	5.1	3.4	5.3	0.8
Flushing	3.2	0.7	1.4	0.8
Body as a Whole General				
Peripheral Edema	13.4	4.1	3.9	2.5
Fatigue	10.8	4.1	*	–
Injury	–	–	10.6	9.2
Pain	7.6	4.1	5.3	3.3
Asthenia	6.4	1.4	–	–
Drug Level Increased	4.5	2.7	6.7	3.3
Chest Pain	3.8	2.0	–	–
Malaise	3.2	0.7	1.4	0.8
Cardiovascular General				
Syncope	11.5	1.4	2.9	1.7
Hypotension Postural	6.4	4.8	–	–
Hypertension	4.5	3.4	3.4	3.3
Hypotension	1.9	0.0	2.4	0.8
Central and Peripheral Nervous System				
Dizziness	40.1	21.8	26.0	15.8
Dyskinesia	–	–	33.7	12.5
Headache	17.2	17.0	16.8	11.7
Ataxia (Falls)	–	–	9.6	6.7
Tremor	–	–	6.3	2.5
Paresthesia	–	–	5.3	2.5
Hyperesthesia	3.8	2.0	–	–
Dystonia	–	–	4.3	4.2
Hypokinesia	–	–	5.3	4.2
Paresis	–	–	2.9	0.0
Gastrointestinal System				
Nausea	59.9	21.8	29.8	18.3
Vomiting	12.1	6.8	7.2	4.2
Dyspepsia	9.6	4.8	–	–
Constipation	8.3	7.5	5.8	3.3
Abdominal Pain	6.4	2.7	8.7	7.5
Diarrhea	–	–	4.8	2.5
Anorexia	3.8	1.4	–	–
Flatulence	2.5	1.4	1.9	0.8
Saliva Increased	–	–	2.4	0.8
Dysphagia	1.3	0.0	2.4	0.8
Heart Rate and Rhythm				
Palpitation	3.2	2.0	2.9	2.5
Metabolic and Nutritional				
Alkaline Phosphate Increased	2.5	1.4	1.0	0.0
Weight Decrease	–	–	2.4	0.8
Musculoskeletal System				
Arthralgia	–	–	6.7	5.0
Arthritis	–	–	2.9	0.8
Psychiatric				
Somnolence	40.1	6.1	20.2	8.3
Anxiety	–	–	6.3	3.3
Confusion	5.1	1.4	8.7	1.7
Hallucination	5.1	1.4	10.1	4.2
Nervousness	–	–	4.8	2.5
Yawning	3.2	0.0	–	–
Amnesia	2.5	1.4	4.8	0.8
Dreaming Abnormal	–	–	2.9	1.7
Red Blood Cell				
Anemia	–	–	2.4	0.0
Reproductive Male				
Impotence	2.5	1.4	–	–
Resistance Mechanism				
Upper Respiratory Tract Infection	–	–	8.7	8.3
Infection Viral	10.8	3.4	7.2	6.7
Respiratory System				
Pharyngitis	6.4	4.1	–	–
Rhinitis	3.8	2.7	–	–
Sinusitis	3.8	2.7	–	–
Dyspnea	3.2	0.0	2.9	1.7
Bronchitis	2.5	1.4	–	–
Urinary System				
Urinary Tract Infection	5.1	4.1	6.3	2.5
Vascular Extracardiac				
Peripheral Ischemia	2.5	0.0	–	–
Vision				
Vision Abnormal	5.7	3.4	–	–
Eye Abnormality	3.2	1.4	–	–

*: Incidence of adverse event <1%.

When REQUIP is administered as adjunct therapy to levodopa, the dose of levodopa may be decreased gradually as tolerated once a therapeutic effect with REQUIP has been observed. REQUIP should be discontinued gradually over a 7-day period. The frequency of administration should be reduced from three times daily to twice daily for 4 days. For the remaining 3 days, the frequency should be reduced to once daily prior to complete withdrawal of REQUIP. *Renal and Hepatic Impairment:* In patients with mild to moderate renal impairment, REQUIP may be titrated in the recommended manner according to clinical response. Patients with severe renal impairment or on hemodialysis have not been studied and administration of REQUIP to such patients is not recommended. Patients with hepatic impairment have not been studied and administration of REQUIP to such patients is not recommended. *Estrogen Replacement Therapy:* In patients already receiving estrogen replacement therapy, REQUIP may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or started during treatment with REQUIP, adjustment of the REQUIP dosage may be required.

AVAILABILITY OF DOSAGE FORM

REQUIP is supplied as a pentagonal film-coated Tiltab® tablet with beveled edges containing ropinirole (as ropinirole hydrochloride) as follows: 0.25 mg – white imprinted with SB and 4890; 1.0 mg – green imprinted with SB and 4892; 2.0 mg – pale pink imprinted with SB and 4893; 5.0 mg – blue tablets imprinted with SB and 4894. REQUIP is available in bottles in the pack size of 100 tablets. It is also available in 0.25 mg as a single unit blister pack of 21 tablets.

Full Product Monograph available to practitioners upon request.

REFERENCES:

1. Rascol O, *et al.* Ropinirole in the Treatment of Early Parkinson's Disease: A 6-Month Interim Report of a 5-Year Levodopa-controlled Study. *Mov Disord* 1998;13:39-45.

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

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interferon beta-1a

Rebif®

11 µg (3MIU), 44 µg (12MIU) lyophilized powder for injection
22 µg (6MIU)/0.5mL, 44 µg (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-ß NIH standard that is obtained from human fibroblasts (BILS 11), which has been calibrated against the NIH natural hIFN-ß 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-γ 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 µg (6MIU) Rebif®, or 44 µg (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 µg 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 µg weekly Rebif® reduced the number of hospitalizations for multiple sclerosis.

Effect on exacerbation

Efficacy parameters	Treatment Groups			p-value	
	Placebo	Rebif® 66 µg/wk	Rebif® 132 µg/wk	Rebif® 66 µg/wk vs placebo	Rebif® 132 µg/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 µg/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 µg/wk	Rebif® 132 µg/wk	Rebif® 66 µg/wk vs placebo	Rebif® 132 µg/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 µg/wk	Rebif® 132 µg/wk	Rebif® 66 µg/wk vs placebo	Rebif® 132 µg/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 µg 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 µg weekly dose significantly prolonged time to confirmed progression whereas the 66 µg 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 µg weekly dose significantly reduced the number of T2 active lesions in this population. The efficacy results in this cohort of patients with established disability confirms that the 132 µg 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 µg/week	Rebif® 132 µg/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 µg weekly	41%	35	not reached	226
Rebif® 132 µg 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 µg weekly vs placebo	p=0.4465
	132 µg weekly vs placebo	p=0.0481

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

	Placebo	Rebif® 66µg/week	Rebif® 132 µg/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 µg weekly	0.9	1.7	Rebif® 66 µg vs placebo: p=0.0612
Rebif® 132 µg weekly	0.5	0.9	Rebif® 132 µg 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 µg (3MIU) (n=35) or 33 µg (9MIU) (n=33) of Rebif®, self-administered subcutaneously three times per week. The total dose was therefore 33 or 99 µg 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 T2-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 µg weekly 99 µg weekly	0.914 0.788	0.429 0.242	53% 69%	p=0.007 p=0.003
# exacerbation-free patients	33 µg weekly 99 µg weekly	15/35 17/33	23/35 26/33		p=0.059 p=0.02
# of monthly lesions / patient	33 µg weekly 99 µg weekly	3.47 2.42	1.77 0.86	49% 64%	p<0.001 p<0.001
Volume of lesions / patient	33 µg weekly 99 µg 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 µg weekly 99 µg weekly	5.67 3.93	1.97 1.18	65% 70%	p<0.001 p<0.001
Total mean # of T2 enlarged lesions	33 µg weekly 99 µg 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 T2 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 µg (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 µg of Rebif®/lesion, or placebo, 3 times per week for 3 weeks	Rebif® at a dose of 3.67 µg/ lesion is efficacious, as evidenced by the induction of complete disappearance of lesions and the reduction in the area of lesions. The 0.12 µg dose of Rebif® did not show advantages over placebo treatment.
2	100/72%	6	3.67 µg 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 µg 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 µg 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 T1-Gd enhanced and T2 (burden of disease) MRI evaluations. Evidence of efficacy beyond 2 years is not known since the primary evidence of efficacy derives from 2-year trials.

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

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

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

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

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

PRECAUTIONS

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

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

Serum neutralising antibodies against Rebif® (interferon beta-1a) may develop.

The precise incidence and clinical significance of antibodies is as yet uncertain (see Adverse Reactions). Hypersensitivity reactions, both local and systemic, have developed during therapy with Rebif®.

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

Pregnancy and Lactation: Rebif® should not be administered in case of pregnancy and lactation. There are no studies of interferon beta-1a in pregnant women. At high doses in monkeys, abortifacient effects were observed with other interferons. Fertile

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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 health care 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/necroses 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 µg / weekly	Rebif® 132 µg / 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 µg weekly and six in the 132 µg 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 µg weekly (n=189)	Rebif® 132 µg 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 µg weekly groups (p≤0.05)
(b) Significant difference between placebo and Rebif® 132 µg weekly groups (p≤0.05)
(c) Significant difference between Rebif® 66 µg and Rebif® 132 µg 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 µg weekly	Rebif® 132 µg 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-ß 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-ß 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 µg (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 µg (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 µg (3 MIU)	0.5 mL	0.5 mL	22 µg (6 MIU)
44 µg (12 MIU)	0.5 mL	0.5 mL	88 µg (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 µg and 44 µg of Rebif® respectively. The pre-filled syringes are ready for subcutaneous use only.

CONDYLOMA ACUMINATUM: The recommended posology is 3.67 µg (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 3.67 µg 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 µg (3 MIU)	0.3 mL	0.3mL	37 µg (10 MIU)
44 µg (12 MIU)	1.2 mL	1.2 mL	37 µg (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 µg (3 MIU)	9 mg	5 mg	0.2 mg
44 µg (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 µg (6 MIU)	2 mg	27.3 mg	q.s. to 0.5 mL
44 µg (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. 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 µg (3MIU), and 44 µg (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 µg (6MIU)/0.5 mL and 44 µg (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.

Reference: 1. Rebif® Product Monograph, 2000. Serono Canada Inc.

Product Monograph available to Healthcare Professionals on request.

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See IFC

Interféron bêta-1a

Rebif®

11 µg (3 MUI); 44 µg (12 MUI) de poudre lyophilisée pour injection
22 µg (6 MUI)/0,5 mL; 44 µg (12 MUI)/0,5 mL de formulation liquide pour injection

CLASSIFICATION THÉRAPEUTIQUE

Immunomodulateur

MODES D'ACTION ET PHARMACOLOGIE CLINIQUE

Description: Rebif® (interféron bêta-1a) est un produit de glycoprotéine stérile purifiée, fabriqué selon des techniques d'ADN recombinant et formulé pour être injecté. Le principe actif de Rebif est produit par des cellules ovariennes de hamster chinois ayant fait l'objet d'une recombinaison génétique. L'interféron (IFN) bêta-1a est une glycoprotéine très purifiée qui comprend 166 acides aminés et dont le poids moléculaire approximatif est de 22 500 daltons. Il compte un fragment de glucide à liaison-N fixé à l'Asn-80, semblable à l'interféron bêta humain naturel. L'activité spécifique de Rebif est d'environ 0,27 million d'unités internationales (MUI)/µg d'interféron bêta-1a. On obtient la mesure unitaire en comparant l'activité antivirale du produit à un étalon NIH interne naturel d'IFN-ß-h obtenu de fibroblastes humains (BILS 11) qui ont été étalonnés par comparaison à l'étalon d'IFN-ß-h naturel NIH (GB 23-902-531). Généralités: Les interférons forment une famille de protéines naturelles dont la masse moléculaire varie de 15 000 à 21 000 daltons. Trois grandes classes d'interférons ont été identifiées: alpha, bêta et gamma. Les activités biologiques respectives de l'interféron bêta, l'interféron alpha et l'interféron gamma se chevauchent, mais demeurent distinctes.

L'interféron bêta-1a agit par l'intermédiaire de divers mécanismes :

- Immunomodulation par induction de composantes de membranes cellulaires du complexe majeur d'histocompatibilité (CMH), c.-à-d., antigènes de CMH de classe I, accroissement en activité de cellules tueuses naturelles et inhibition de l'expression d'antigènes du CMH de classe II déclenchée par l'IFN-γ, ainsi qu'une réduction soutenue du niveau du facteur de nécrose des tumeurs.
- Effet antiviral par induction de protéines comme la synthétase-2'-5'-oligoadénylate et la p78.
- Effet antiprolifératif par activité cytostatique directe et indirecte par la stimulation de la réponse immunitaire antitumorale.

Le mécanisme d'action de Rebif® dans la sclérose en plaques rémittente est toujours à l'étude.

Sclérose en plaques (SEP) rémittente

On a mené deux études essentielles, incluant au total 628 patients, afin d'évaluer l'innocuité et l'efficacité de Rebif® administré par voie sous-cutanée trois fois par semaine à des patients atteints de sclérose en plaques rémittente. Les résultats indiquent que Rebif® est apte à modifier l'évolution naturelle de la sclérose en plaques rémittente. L'efficacité du médicament a été démontrée en fonction de trois aspects principaux de cette maladie, soit l'état d'invalidité (patients cotés de 0 à 5 sur l'échelle EDSS), les poussées évolutives et le *fardeau imposé par la maladie* et son activité observée par IRM (*imagerie par résonance magnétique*).

ÉTUDE PRISMS

Dans l'étude de plus grande envergure, 560 patients en tout ayant reçu un diagnostic de sclérose en plaques rémittente, cliniquement ou biologiquement avérée, cotée de 0 à 5 sur l'échelle EDSS et dont les antécédents de la maladie remontaient au moins à un an avant leur entrée dans l'étude, furent recrutés et répartis au hasard en trois groupes recevant respectivement un placebo, 22 µg (6 MUI) de Rebif® ou 44 µg (12 MUI) de Rebif® dans un rapport de 1:1:1. Environ 90 % des patients ont poursuivi leur traitement pendant la durée entière de cette étude de deux ans et fort peu de patients se sont retirés de l'étude en raison de réactions indésirables.

Les principaux critères d'inclusion à l'étude étaient les suivants:

- antécédents d'au moins 2 poussées aiguës pendant les 2 années précédant le recrutement dans l'étude
- aucun traitement général antérieur par interférons
- aucune corticothérapie ni traitement par ACTH dans les 2 mois précédant le recrutement dans l'étude
- aucune poussée évolutive dans les 8 semaines précédant le recrutement dans l'étude.

Les patients étaient évalués à intervalles de 3 mois, durant les poussées et de concert avec des examens par IRM. Chaque patient a fait l'objet d'examens IRM initiaux de la densité des protons crâniens/pondérés en T2 (PD/T2), puis à tous les six mois durant l'étude. Un sous-groupe de patients a fait l'objet d'examens IRM PD/T2 et pondérés en T1 (T1) avec marquage des lésions au gadolinium (Gd) un mois avant le début du traitement, au début du traitement, puis mensuellement jusqu'à concurrence des 9 premiers mois de traitement. Parmi ces sujets, un autre sous-groupe de 39 patients a continué de se prêter aux examens IRM mensuels du début à la fin de la période de traitement de 24 mois.

Cette étude a démontré que Rebif® à la dose hebdomadaire totale de 66 ou de 132 µg, a procuré une amélioration significative des trois aspects principaux de la maladie, soit la fréquence des poussées évolutives, l'activité pathologique et le fardeau imposé par la maladie tel que mesuré par les examens d'IRM et la progression de l'état d'invalidité. De plus, l'étude a démontré l'efficacité de Rebif® à ralentir la progression de l'incapacité chez les patients ayant une cote de 4,0 ou plus sur l'échelle EDSS. En outre, le médicament a donné lieu à une diminution des besoins en corticostéroïdes pour traiter la sclérose en plaques et, à raison de 132 µg par semaine, Rebif® a réduit le nombre de séjours à l'hôpital attribuables à la sclérose en plaques.

Effet sur les poussées évolutives

Paramètres d'efficacité	Groupe de traitement			Valeur de p	
	Placebo	Rebif® 66 µg/sem	Rebif® 132 µg/sem	Rebif® 66 µg/sem vs placebo	Rebif® 132 µg/sem vs placebo
Nbre moyen de poussées sur les 2 ans de l'étude	2,56	1,82	1,73	0,0002	<0,0001
Pourcentage de patients n'ayant eu aucune poussée en 2 ans	14,6%	25,6%	32,0%	0,0140	<0,0001
Nbre médian de mois avant la première poussée	4,5	7,6	9,6	0,0008	<0,0001
Nbre médian de mois avant la deuxième poussé	15,0	23,4	>24*	0,0020	<0,0001
Nbre moyen de poussées modérées et graves durant la période de 2 ans	0,99	0,71	0,62	0,0025	0,0003

*Le nombre médian de mois avant la deuxième poussée n'a pas été atteint dans le groupe qui recevait la dose de 132 µg.

Les résultats après un an de traitement étaient également significatifs

Effet sur le temps de la progression initiale de l'état d'invalidité

Paramètres d'efficacité	Groupe de traitement			p-value	
	Placebo	Rebif® 66 µg/sem	Rebif® 132 µg/sem	Rebif® 66 µg/sem vs placebo	Rebif® 132 µg/sem vs placebo
Nbre de mois écoulés avant l'apparition confirmée d'une progression de l'état d'invalidité - premier quartile	11,8	18,2	21,0	0,0398	0,0136
Modification médiane de la cote EDSS après 2 ans	0,5	0	0	0,0263	0,0519

Effet sur la pathologie de la sclérose en plaques tel que visualisé par IRM

Paramètres d'efficacité	Groupe de traitement			Valeur de p	
	Placebo	Rebif® 66 µg/sem	Rebif® 132 µg/sem	Rebif® 66 µg/sem vs placebo	Rebif® 132 µg/sem vs placebo
% médian de modification du fardeau imposé par la maladie (FIM)	+10,9	-1,2	-3,8	<0,0001	<0,0001
Activité observée par IRM					
Tous les patients					
Nbre de lésions actives (par période de 6 mois)	2,25	0,75	0,5	<0,0001	<0,0001
% d'activité observée par IRM	75%	50%	25%	<0,0001	<0,0001
Patients subissant des examens IRM mensuels (9 mois)					
Nbre de lésions actives (par mois)	0.88	0.17	0,11	<0,0001	<0,0001
% d'activité observée par IRM	44%	12,5%	11%	<0,0001	<0,0001
Patients ayant subi des examens IRM mensuels du début à la fin de l'étude (2 ans)					
Nbre de lésions actives	0,9	0,1	0,02	0,0905	0,0105
% d'activité observée par IRM	52%	10%	2%	0,0920	0,0117

Besoin de corticothérapie: La proportion de patients ayant nécessité une corticothérapie pour le traitement de la sclérose en plaques (indications autres que la SEP exclues) était plus élevé dans le groupe placebo (plus de 50%) que dans l'un ou l'autre des 2 groupes Rebif® (à peu près 40 % dans chaque groupe).

Hospitalisations dues à la sclérose en plaques: Le nombre moyen des hospitalisations imputables à la sclérose en plaques observées dans les groupes de traitement recevant Rebif® à raison de 66 ou de 132µg/semaine a été réduit de 21% et de 48% respectivement, par rapport aux hospitalisations dans le groupe placebo.

Cohorte de patients aux valeurs initiales élevées sur l'échelle EDSS (valeurs EDSS initiales > 3,5)

On a effectué d'autres analyses dans le but d'étudier l'efficacité de Rebif® auprès de populations manifestant des prédicteurs de résultats adverses et potentiellement exposées à un plus haut risque de progression de l'invalidité. Le principal prédicteur examiné était une valeur EDSS initiale >3,5. Les patients de cette cohorte accusent un degré plus marqué d'invalidité et sont davantage vulnérables à la progression de leur maladie que ceux dont la valeur EDSS est moins élevée. Des études de l'historique naturelle montrent que les patients dont la valeur EDSS se situe dans l'intervalle de 4,0 à 5,0 demeurent moins longtemps à ce niveau de valeurs EDSS qu'à l'un des niveaux moindres d'invalidité.

Le traitement aux deux posologies de Rebif® a eu pour effet de réduire significativement le nombre moyen de poussées évolutives par patient comparativement au placebo. La progression de la maladie chez ce groupe de patients est particulièrement préoccupante, étant donnée l'apparition potentielle de difficultés de déambulation. L'administration du médicament à la posologie hebdomadaire de 132 µg a permis de prolonger significativement la période écoulée avant qu'on ne puisse confirmer la survenue d'un nouvel épisode de progression de la maladie, alors que la dose hebdomadaire de 66 µg n'a pas eu cet effet. Les deux doses de Rebif® ont influé significativement sur le pourcentage de variation d'après les valeurs initiales de fardeau imposé par la maladie observé lors des examens IRM chez la cohorte aux valeurs EDSS élevées, tandis que la dose hebdomadaire de 132 µg a procuré une diminution significative du nombre de lésions T2 actives dans cette population. Dans cette cohorte de patients dont l'invalidité a été établie, les résultats en terme d'efficacité confirment que la dose hebdomadaire de 132 µg exerce un effet marqué sur la progression de l'invalidité et sur la pathologie sous-jacente de la maladie.

Effet sur les poussées évolutives (cohorte aux valeurs EDSS élevées)

Paramètres d'efficacité	Placebo	Rebif® 66 µg/sem	Rebif® 132 µg/sem
Nbre moyen de poussées évolutives	3,07	1,83	1,22
Nbre et% de patients n'ayant manifesté aucune poussée évolutive	2 (7%)	7 (20%)	10 (32%)
Valeur de p* (Rebif® vs placebo)		p = 0,0121	p = 0,0002

*Modèle log-linéaire

Progression de l'invalidité d'un point sur l'échelle EDSS (cohorte aux valeurs EDSS élevées)

Groupe de traitement	% de progresseurs*	Délai d'apparition de la progression		
		Nbre de patients	Médiane (jours)	T1 (jours)
Placebo	56%	28	638	218
Rebif® 66 µg/sem	41%	35	non atteinte	226
Rebif® 132 µg/sem	27%	31	non atteinte	638

*exclu les patients chez lesquels la maladie n'accusait aucune progression lorsqu'on les a perdus de vue durant le suivi

Progression de l'invalidité: comparaisons statistiques

Test	Comparaison des groupes	Valeur de p
Test logarithmique	66 µg/sem vs placebo	p = 0,4465
	132 µg/sem vs placebo	p = 0,0481

Pourcentage de variation du fardeau imposé par la maladie observé par IRM (Cohorte aux valeurs EDSS élevées)

	Placebo	Rebif® 66µg/sem	Rebif® 132 µg/sem
Fardeau de la maladie – % médian de variation	5,3	-2,3	-6,9
Fardeau de la maladie – % moyen de variation	12,2	13,6	0,7
Valeur de p* (Rebif® vs placebo)		p = 0,0146	p = 0,0287

*Analyse de la variance – rangs

Nombre de lésions T2 actives (cohorte aux valeurs EDSS élevées)

	Nombre de lésions T2 actives		
Groupe de traitement	Médiane	Moyenne	Valeur de p*
Placebo	1,9	2,6	
Rebif® 66 µg/sem	0,9	1,7	Rebif® 66 µg vs placebo: p = 0,0612
Rebif® 132 µg/sem	0,5	0,9	Rebif® 132 µg vs placebo: p = 0,0042

*Analyse de la variance – rangs

ÉTUDE SELON LE MODÈLE CROISÉ

L'autre étude a été réalisée selon le modèle ouvert et croisé où les examens IRM étaient effectués à l'insu. Les 68 patients recrutés, âgés de 15 à 45 ans, étaient atteints de SEP rémittente cliniquement ou biologiquement avérée depuis 10 ans au maximum. Les principaux critères d'inclusion à l'étude étaient les suivants :

- minimum de 2 récidives pendant les 2 dernières années
- cote EDSS entre 1 et 5
- aucune corticothérapie ni traitement de plasmaphérèse ni administration de gammaglobulines dans les 3 mois précédant l'étude.
- aucun traitement immunomodulateur ou immunodépresseur durant les 6 mois précédant l'étude
- absence d'Ag HBs et d'anticorps anti-VIH

Une fois recrutés, les patients sont demeurés sous observation clinique pendant 6 mois et ont fait l'objet d'évaluations de leur état neurologique et d'autres paramètres, et d'une surveillance vigilante des poussées. Ensuite, les patients ont été répartis au hasard dans l'un des deux groupes de traitement pour recevoir soit 11 µg (3 MUI) (n=35) ou 33 µg (9 MUI) (n=33) de Rebif®, auto-administré par voie sous-cutanée trois fois par semaine. La dose hebdomadaire totale se chiffrait donc à 33 ou 99µg.

Comparaison des six mois d'observation aux six mois de traitement

Le traitement avec Rebif®, aux deux posologies administrées dans le cadre de cette étude, a procuré une réduction, significative au point de vue statistique, de l'activité de la SEP dans le cerveau observée par IRM, ainsi que du taux de récidives cliniques par rapport aux périodes d'observation correspondantes. Ce modèle d'amélioration était également reflété par des mesures additionnelles réalisées par IRM. Dans les examens pondérés en T2 effectués deux fois par année, on a mis en évidence une réduction du nombre moyen de nouvelles lésions et du nombre moyen de lésions croissantes.

	Dosage	Période d'observation	Période de Traitement	% de Réduction	valeur de p
Nbre de poussées évolutives/patient	33 µg/sem 99 µg/sem	0,914 0,788	0,429 0,242	53% 69%	p=0,007 p=0,003
Nbre de patients n'ayant eu aucune poussée évolutive	33 µg/sem 99 µg/sem	15/35 17/33	23/35 26/33		p=0,059 p=0,02
Nbre de lésions/ *mois/patient*	33 µg/sem *99 µg/sem*	3,47 *2,42*	1,77 *0,86*	49% *64%*	p<0,001 *p<0,001*
Volume des lésions/patient	33 µg/sem 99 µg/sem	557 mm^3 379 mm^3	220 mm^3 100 mm^3	61% 73%	p<0,001 p<0,001
Nbre moyen total de nouvelles lésions observées par T2	33 µg/sem 99 µg/sem	5,67 3,93	1,97 1,18	65% 70%	p<0,001 p<0,001
Nbre moyen total de lésions élargies observées par T2	33 µg/sem 99 µg/sem	2,26 1,81	0,97 0,45	57% 75%	p=0,001 p=0,004

Résultats de l'étude de deux ans : À la fin de cette étude, 62 patients ont poursuivi le traitement pendant une période supplémentaire de 18 mois. Chacun de ces patients a continué de recevoir la dose qui lui avait été attribuée au hasard. La validation des résultats de la période de traitement de 2 ans se poursuit toujours, mais les résultats obtenus de la continuité du traitement aux deux concentrations a permis d'établir que Rebif® maintient son effet proportionnel à la dose administrée quant à la réduction du taux de récidive et du volume de lésions détectées au cerveau par le biais d'examens IRM pondérés en T2, comparativement à la période d'observation, ce qui corrobore les résultats de l'étude de plus longue durée avec contrôle par placebo.

Condylome acuminé : Les résultats de quatre études, chacune menée en double insu et contrôlées contre placebo, incluant 349 patients (agés de 17 - 62 ans), révèlent que Rebif® est efficace dans le traitement du condylome acuminé, chez les hommes aussi bien que chez les femmes, lorsqu'il est injecté par voie intralésionelle à la dose de 3,67 µg (1 MUI)/lésion 3 fois par semaine pendant 3 semaines. L'induction de la disparition complète des lésions ainsi que la réduction de la taille des lésions ont fait foi de l'efficacité du traitement. La majorité des patients traités dans le cadre de ces études présentaient des verrues récidivantes qui avaient résisté aux autres traitements. Le nombre de lésions traitées par patient était entre 3 et 8, comme illustré dans le tableau ci-joint.

Étude	Nbre de patients/% déjà traité	Nbre de lésions traitées	Traitement	Résultats
1	25 / 80%	3	0,12 ou 3,67 µg de Rebif® /lésion, ou un placebo, 3 fois/sem durant 3 semaines	Rebif®, administré à la dose de 3,67 µg/lésion, s'est avéré efficace, comme l'ont corroboré l'induction de la disparition complète des lésions ainsi que la réduction de l'étendue des lésions. La dose de 0,12 µg de Rebif® n'a pas semblé offrir un avantage supérieur par rapport au placebo.
2	100 / 72%	6	3,67 µg de Rebif® /lésion, ou un placebo, 3 fois/sem durant 3 semaines	Il y a eu une augmentation importante des taux de réponses majeures au mois 3 chez les patients qui ont reçu Rebif® vs le placebo (p<0,0001). Le taux de réponses complètes au mois 3 était significativement favorable chez les patients qui ont reçu Rebif® (p ≤ 0,0162).
3	100 / 52%	8	3,67 µg de Rebif® /lésion, ou un placebo, 3 fois/sem durant 3 semaines	Les résultats du centre israélien pour la semaine 6, avec l'appui de ceux du jour 19, sont indicatifs de l'efficacité de Rebif® En raison de l'organisation de l'étude et de la non-conformité au protocole au centre allemand, ces indications de l'efficacité n'étaient pas soutenues par les résultats obtenus des analyses dans lesquelles on a regroupé les patients des deux centres.
4	124 /72 %	6	3,67 µg de Rebif® /lésion, ou un placebo, 3 fois/sem durant 3 semaines	Cette étude a démontré que Rebif® s'est avéré efficace chez la proportion de patients qui présentaient une réponse complète ou partielle au jour 19 et à la semaine 6. En raison de l'organisation de l'étude, on n'a pu démontrer l'effet thérapeutique de Rebif® au mois 3.

INDICATIONS ET USAGE CLINIQUE

Sclérose en plaques: Rebif® (interféron bêta-1a) est indiqué pour le traitement de la sclérose en plaques rémittente chez des patients dont la cote EDSS se situe entre 0 et 5,0, afin de réduire le nombre et la gravité des poussées évolutives cliniques, de ralentir la progression *des états d'invalidité physiques, et de réduire les besoins de corticothérapie et le nombre de* séjours à l'hôpital pour le traitement de la sclérose en plaques. Son efficacité a été confirmée au moyen d'évaluations IRM en T1 marquées au Gd et d'évaluations IRM en T2 (fardeau imposé par la maladie). On ne dispose pas de preuves d'efficacité sur des périodes de plus de 2 ans puisque les confirmations primaires d'efficacité proviennent d'études de 2 ans.

Condylome acuminé: Rebif® convient préférablement au patient qui présente moins de neuf lésions et chez qui plusieurs traitements antérieurs ont déjà échoué. Dans le cas des patients atteints de neuf lésions ou plus, si le premier traitement avec Rebif® est une réussite, les lésions qui restent pourraient faire l'objet d'un deuxième traitement avec Rebif® . On devrait aussi envisager Rebif® pour traiter le condylome acuminé chez les patients pour qui les effets secondaires d'autres traitements, comme la production de cicatrices, sont inquiétants. Tandis que les patients traités avec Rebif® n'ont pas tous présenté une réponse complète, ceux chez qui l'étendue des lésions a diminué et qui ont eu tout au moins une réponse partielle peuvent aussi avoir bénéficié du traitement, car la diminution des lésions pourrait favoriser la prise en charge subséquente de la maladie avec d'autres traitements, comme on l'a rapporté dans le cas de l'IFN-alpha.

CONTRE-INDICATIONS

Rebif® (interféron bêta-1a) est contre-indiqué chez les patients ayant une hypersensibilité connue à l'interféron bêta naturel ou recombinant, à l'albumine (humaine) ou à n'importe quel autre composant de la formulation.

MISES EN GARDE

Rebif® (interféron bêta-1a) devrait être utilisé sous la surveillance d'un médecin.

Sclérose en plaques rémittente

On sait que la population atteinte de sclérose en plaques est plus souvent sujette à la dépression et aux idées suicidaires. L'utilisation de Rebif® n'a pas été associée à une hausse de la fréquence et/ou de la gravité de la dépression, ni à une augmentation des tentatives de suicide ou des suicides. Dans l'étude sur la sclérose en plaques rémittente, on a observé une fréquence de dépression semblable dans le groupe de patients sous placebo et les deux groupes de patients sous Rebif® . Néanmoins, les patients souffrant de dépression devraient être surveillés de près au cas où ils manifesteraient des signes d'aggravation considérable de leur état dépressif ou des idées suicidaires.

La première injection devrait être donnée sous la surveillance d'un professionnel de la santé ayant les qualifications requises.

Condylome

Toutes les injections devraient être données par un professionnel de la santé qualifié.

PRÉCAUTIONS

Généralités

Les patients devraient être renseignés sur les réactions indésirables les plus couramment associées à l'administration de l'interféron bêta, y compris les symptômes de type pseudo-grippal (voir RÉACTIONS INDÉSIRABLES). Ces symptômes ont tendance à être plus prononcés au début du traitement et à diminuer en fréquence et en gravité après quelques mois de traitement.

Les résultats des études cliniques sur la sclérose en plaques dans lesquelles Rebif® a été utilisé, ces études comprenant plus de 500 patients traités avec Rebif®, n'ont indiqué aucune augmentation des risques d'avoir une convulsion lors du traitement avec Rebif®. Cependant, de telles convulsions ont été signalées lors de traitement avec d'autres interférons; ainsi, de la prudence est de rigueur si un patient avec des antécédents de convulsion est considéré pour traitement avec Rebif®. Pour les patients dont les antécédents médicaux n'indiquent pas de convulsion, et qui développent des convulsions pendant le traitement, une étiologie devrait être établie et le traitement avec des anti-convulsants appropriés devrait être instauré avant de commencer le traitement avec Rebif®. L'effet de l'administration de Rebif® chez les patients avec des problèmes de convulsion est inconnu.

Des anticorps neutralisants sériques contre Rebif® (interféron bêta-1a) peuvent se développer. La fréquence exacte et l'importance clinique des anticorps demeurent incertaine (voir RÉACTIONS INDÉSIRABLES).

Des réactions d'hypersensibilité, autant locales que systémiques, se sont développées durant le traitement avec Rebif®.

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Les injections intralésionnelles pouvant s'avérer douloureuses chez certains patients traités pour le condylome, on peut, le cas échéant, avoir recours à une crème anesthésique telle la lidocaïne-prilocaïne.

Grossesse et allaitement

Rebif® ne devrait pas être administré aux femmes enceintes ou aux mères qui allaitent. Il n'y a pas eu d'étude sur l'utilisation de l'interféron bêta-1a chez les femmes enceintes. À des doses élevées chez les singes, on a observé des effets abortifs avec d'autres interférons. Les femmes susceptibles de devenir enceintes qui prennent Rebif® doivent utiliser une méthode efficace de contraception. Les patientes qui planifient une grossesse et celles qui deviennent enceintes devraient être renseignées sur les dangers que les interférons pourraient représenter pour le foetus et elles devraient cesser de prendre Rebif®. On ignore si Rebif® est excrété dans le lait maternel humain. En raison du risque d'effets indésirables graves chez les nourrissons, on doit recommander aux patientes de cesser l'allaitement ou d'interrompre le traitement.

Pédiatrie

Aucune expérience n'a été acquise avec Rebif® chez les enfants âgés de moins de 16 ans qui seraient atteints de sclérose en plaques ou de condylome et, par conséquent, Rebif® ne devrait pas être utilisé chez cette population.

Patients atteints de maladies et d'états particuliers

On devrait faire preuve de prudence et de vigilance lorsqu'on administre Rebif® aux patients atteints d'une grave insuffisance rénale ou hépatique, aux patients qui manifestent une myélodépression grave et aux patients dépressifs.

Interaction médicamenteuse

Les interactions entre Rebif® et d'autres médicaments n'ont pas été évalués chez les humains. On a rapporté que les interférons réduisaient l'activité des enzymes hépatiques dont la synthèse dépend du cytochrome P450 chez les humains et les animaux. On devrait faire preuve de prudence lorsqu'on administre Rebif® en association avec des médicaments à l'index thérapeutique étroit dont la clairance repose largement sur le système hépatique du cytochrome P450, p. ex., les antiépileptiques et certaines classes d'antidépresseurs. L'interaction de Rebif® avec les corticostéroïdes ou l'ACTH n'a pas fait l'objet d'une étude systématique. Les études cliniques indiquent que les patients qui ont la sclérose en plaques peuvent recevoir Rebif® et des corticostéroïdes ou de l'ACTH pendant les récidives. Rebif® ne devrait pas être mélangé à d'autres médicaments dans une même seringue.

Analyses de laboratoire

Sclérose en plaques (SEP) rémittente: Les anomalies observées lors d'analyses de laboratoire sont associées à l'utilisation des interférons. Par conséquent, en plus des analyses de laboratoire habituellement demandées pour surveiller les patients atteints de sclérose en plaques, on recommande également de procéder à la numération globulaire et la formule leucocytaire, la numération plaquettaire et les analyses de la chimie sanguine, y compris les épreuves fonctionnelles hépatiques et de la glande thyroïde, pendant le traitement avec Rebif®. Ces analyses devraient être faites après 1 mois, 3 mois et 6 mois de traitement, et à tous les 6 mois par la suite.

Condylome acuminé : Comme pour ce qui concerne la sclérose en plaques (SEP) rémittente, mais tend à ne pas être aussi sévère dû à la dose et à la durée du traitement.

Renseignements à donner aux patients

Il n'est pas rare d'observer des symptômes pseudo-grippaux (fièvre, céphalée, frissons, douleurs musculaires) au début du traitement avec Rebif®. On peut prendre de l'acétaminophène pour soulager les symptômes pseudo-grippaux. Les patients devraient communiquer avec leur médecin ou leur pharmacien s'ils éprouvent des effets indésirables.

La dépression est susceptible de se produire chez les patients atteints de sclérose en plaques rémittente et pourrait survenir alors que les patients prennent Rebif®. Il faut aviser ces patients de communiquer avec un médecin s'ils se sentent déprimés.

On devrait conseiller aux patients de ne pas interrompre ni modifier leur traitement à moins d'en recevoir la directive de leur médecin.

Instruction de la technique et des méthodes d'auto-injection : les patients qui reçoivent un traitement pour la sclérose en plaques rémittente devraient recevoir des instructions sur l'utilisation d'une technique aseptique lors de l'administration de Rebif®. Il est nécessaire d'instruire les patients sur la reconstitution de Rebif® et l'auto-injection, et de passer attentivement en revue le feuillet d'instructions sur Rebif®. La première injection devrait être faite sous la surveillance d'un professionnel de la santé ayant les qualifications requises. On devrait faire une rotation des points d'injection en changeant de site à chaque injection. On peut faire les injections à l'heure du coucher pour tenter d'amoindrir la perception des effets secondaires. Il faut avertir les patients de ne pas réutiliser les aiguilles et les seringues, et les instruire sur la façon d'éliminer ces instruments en toute sécurité. Un contenant résistant à la ponction servant à la mise au rebut des aiguilles et des seringues utilisées devrait être fourni au patient, avec des instructions sur l'élimination sûre des contenants pleins.

Dans l'étude contrôlée sur la SEP, les patients ont couramment signalé des réactions au point d'injection au moins une fois au cours du traitement. En général, ils n'ont pas eu besoin d'abandonner le traitement, mais il importe d'évaluer soigneusement la nature et la gravité de toutes les réactions signalées. Il faudrait réévaluer périodiquement le patient sur sa compréhension et son utilisation des techniques et méthodes aseptiques d'auto-injection.

RÉACTIONS INDÉSIRABLES

Sclérose en plaques

Comme avec les autres préparations à l'interféron, il n'est pas rare d'observer des symptômes pseudo-grippaux. L'utilisation de l'interféron bêta peut provoquer: syndrome pseudo-grippal, asthénie, pyrexie, frissons, arthralgie, myalgie, céphalées et réactions au point d'injection. On a plus rarement observé : boutons de fièvre, congestion nasale, sensation de tête légère, irritation des muqueuses, troubles hématologiques (leucopénie, lymphocytopénie, granulocytopénie) et altérations des analyses de la fonction hépatique telles que SGOT et SGPT élevés. Ces effets sont habituellement légers et réversibles. La tachyphylaxie par rapport à la plupart des effets secondaires est bien reconnue. La fièvre et les symptômes pseudo-grippaux peuvent être traités avec de l'acétaminophène. Selon la gravité et la persistance des effets secondaires, on peut diminuer la dose ou interrompre temporairement le traitement, à la discrétion du médecin. La plupart des réactions au point d'injection étaient d'intensité légère à modérée. On a rapporté de rares cas d'ulcération cutanée/nécrose au point d'injection lors d'un traitement prolongé. Au tableau ci-dessous figurent les réactions indésirables signalées le plus fréquemment ainsi que les anomalies de laboratoire observées le plus souvent chez les patients sous placebo ou Rebif® (interféron bêta-1a) durant l'étude contrôlée contre placebo sur la sclérose en plaques rémittente (traitement de 2 ans comptant 560 patients). Les fréquences représentent les patients qui ont fait état de la réaction au moins une fois au cours de l'étude, comme pourcentage du nombre total de patients, par volet d'étude.

	Placebo	Rebif® 66 µg / sem	Rebif® 132 µg / sem
EFFETS INDÉSIRABLES			
Réactions au point d'injection (toutes)	**38,5**	**89,9**	**92,4**
Infections des voies respiratoires hautes	**85,6**	**75,1**	**74,5**
Céphalée	62,6	64,6	70,1
Syndrome pseudo-grippal	51,3	56,1	58,7
Fatigue	35,8	32,8	41,3
Dépression	27,8	20,6	23,9
Fièvre	**15,5**	**24,9**	**27,7**
Mal de dos	21,4	19,6	23,4
Myalgie	19,8	24,9	25,0
Nausée	23,0	24,9	24,5
Insomnie	21,4	19,6	23,4
Diarrhée	18,7	17,5	19,0
ANOMALIES LORS DES ÉPREUVES DE LABORATOIRE			
Lymphocytopénie	11,2	20,1	28,8
Leucopénie	3,7	12,7	22,3
Granulocytopénie	3,7	11,6	15,2
Augmentation des ASAT	3,7	10,1	17,4
Augmentation des ALAT	4,3	19,6	27,2

Les différences observées pour les effets en caractères gras étaient significatives au point de vue statistique, comparativement au placebo.

Les effets indésirables éprouvés durant l'étude sont énumérés ci-dessous d'après les classes de système organique établies l'OMS (TRIOMS ou, en anglais, WHOART). Parmi les réactions au point d'injection, la plus courante prenait la forme d'un érythème peu grave. La majorité des autres réactions au point d'injection étaient également peu graves dans les deux groupes recevant Rebif®. On a fait état de nécrose chez 8 patients traités avec Rebif®, dont deux dans le groupe recevant 66µg/semaine et les six autres, dans le groupe recevant 132 µg/semaine. Tous les patients ont terminé la période prévue de traitement, l'un d'entre eux uniquement ayant requis une réduction temporaire de la dose et un autre, l'interruption de son traitement pendant 2 semaines. Ceux qui ont requis un traitement ont reçu une antibiothérapie.

Effets indésirables éprouvés par les patients recrutés dans l'étude sur la sclérose en plaques réalisée en double insu et contrôlée contre placebo.

Système organique	Terme privilégié	Placebo (n=187)	Rebif® 66 µg/sem (n=189)	Rebif® 132 µg/sem (n=184)
Troubles au point d'injection	Inflammation au point d'injection (a)(b)	15,0%	65,6%	65,8%
	Réaction au point d'injection (a)(b)	13,4%	31,2%	34,8%
	Douleur au point d'injection (b)	14,4%	20,1%	22,8%
Troubles à caractère général touchant l'organisme entier	Symptômes de type grippal	51,3%	56,1%	58,7%
	Fatigue	35,8%	32,8%	41,3%
	Fièvre (a)(b)	15,5%	24,9%	27,7%
	Douleur à la jambe	14,4%	10,1%	13,0%
	Frisson solennel (b)(c)	5,3%	6,3%	13,0%
Troubles des SN central et périphérique	Céphalée	62,6%	64,6%	70,1%
	Étourdissement	17,6%	14,3%	16,3%
	Paresthésie	18,7%	19,6%	16,3%
	Hypoesthésie	12,8%	12,2%	7,6%
Troubles de l'appareil respiratoire	Rhinite	59,9%	52,4%	50,5%
	Infection des voies resp. hautes	32,6%	36,0%	29,3%
	Pharyngies (b)	38,5%	34,9%	28,3%
	Toux	21,4%	14,8%	19,0%
	Bronchite	9,6%	10,6%	9,2%
Troubles du système gastro-intestinal	Nausée	23,0%	24,9%	24,5%
	Douleur abdominale	17,1%	22,2%	19,6%
	Diarrhée	18,7%	17,5%	19,0%
	Vomissements	12,3%	12,7%	12,0%
Troubles de l'appareil locomoteur	Mal de dos	19,8%	23,3%	24,5%
	Myalgie	19,8%	24,9%	25,0%
	Arthralgie	17,1%	15,3%	19,0%
	Douleur squelettique	10,2%	14,8%	9,8%
Troubles psychiatriques	Dépression	27,8%	20,6%	23,9%
	Insomnie	21,4%	19,6%	23,4%
Troubles des leucocytes et du système réticulo-endothélial	Lymphocytopénie (a)(b)	11,2%	20,1%	28,8%
	Leucocytopénie (a)(b)(c)	3,7%	12,7%	22,3%
	Granulocytopénie (a)(b)	3,7%	11,6%	15,2%
	Lymphadénopathie	8,0%	11,1%	12,0%
Troubles de la peau et des téguments	Prurit	11,8%	9,0%	12,5%
Troubles du système hépatobiliaire	Augmentation des ASAT (a)(b)	4,3%	19,6%	27,2%
	Augmentation des ALAT (a)(b)(c)	3,7%	10,1%	17,4%
Troubles de l'appareil urinaire	Infection des voies urinaires	18,7%	18,0%	16,8%
Troubles de la vision	Vision anormale	7,0%	7,4%	13,0%
Termes secondaires	Chute	16,0%	16,9%	15,8%

(a) Différence significative entre les groupes placebo et Rebif® 66 µg/semaine (p≤0,05)
(b) Différence significative entre les groupes placebo et Rebif® 132 µg/semaine (p≤0,05)
(c) Différence significative entre les groupe Rebif® 66 µg/semaine et Rebif® 132 µg/semaine (p≤0,05)
(n) Nombre de patients

En plus des effets indésirables énumérés ci-dessus, les effets ci-dessous ont été signalés moins fréquemment dans l'une ou les deux études sur la sclérose en plaques rémittente. Ces effets sont les suivants: asthénie, rétention aqueuse, anorexie, gastro-entérite, pyrosis, affections du paradonte, abcès dentaire ou extraction, stomatite, glossite, somnolence, anxiété, irritabilité, confusion, lymphadénopathie, gain pondéral, fracture osseuse, dyspnée, boutons de fièvre, fissure au coin de la bouche, troubles menstruels, cystite, vaginite.

Immunogénicité : Tous les patients ont été testés pour la présence d'anticorps à l'IFN-bêta avant leur inscription à l'étude et aux mois 6, 12, 18 et 24. Les résultats sur la présence d'anticorps neutralisants sont illustrés ci-dessous.

Pourcentage de patients ayant des anticorps neutralisants

Placebo	Rebif® 66 µg/sem	Rebif® 132 µg/sem
0 %	24 %	12,5 %

En raison d'inquiétudes quant à l'impact éventuel de la formation d'anticorps neutralisants sur l'efficacité, on a analysé le dénombrement des poussées (résultat primaire) en tenant compte de la présence d'anticorps neutralisants chez les patients. Pendant la durée de l'étude de 2 ans, il n'y a pas eu de tendance vers un taux supérieur de poussées dans les groupes qui avaient des anticorps neutralisants, comparativement aux groupes qui n'avaient pas d'anticorps neutralisants. On n'a pas d'indications précises que la constitution d'anticorps neutralisants sériques ait pu influer sur l'innocuité ou l'efficacité chez l'un ou l'autre des groupes qui recevaient Rebif®.

Condyloma acuminé

Effets indésirables les plus fréquents chez les patients traités pour le condylome acuminé

Système organique/ Terme privilégié		Essai 1 n = 25	Essai 2 n = 52	Essai 3 n = 50	Essai 4 n = 65
Troubles à caractère général touchant l'organisme entier	Asthénie	24,0 %	3,8 %	36,0 %	15,4 %
	Fièvre	8,0 %	21,2 %	4,0 %	0,0 %
	Syndrome grippal	4,0 %	7,7 %	24,0 %	26,1 %
	Réaction au point d'injection	8,0 %	11,5 %	-	-
	Inflammation au point d'injection	-	5,8 %	-	-
	Céphalée	28,0 %	42,3 %	20,0 %	36,9 %
	Malaise corporel	-	15,4 %	-	-
	Mal de dos	-	9,6 %	-	10,8 %
	Douleur	-	-	-	9,2 %
	Douleur pelvienne	4,0 %	-	6,0 %	-
	Frissons	-	28,8 %	-	6,2 %
	Malaise	-	1,9 %	16,0 %	1,5 %
	Douleur au point d'injection	4,0 %	36,5 %	66,0 %	13,8 %
	Tuméfaction non inflammatoire	-	7,7 %	-	-
	Fatigue	-	28,8%	-	-
Appareil digestif	Nausée	8,0 %	17,3 %	-	1,5 %
	Vomissements	8,0 %	1,9 %	-	3,0 %
Appareil locomoteur	Myalgie	12,0 %	3,8 %	2,0 %	9,2 %
	Endolorissement musculaire	-	26,9 %	-	-
	Douleur musculaire	-	1,9 %	-	-
Appareil respiratoire	Pharyngites	16,0 %	0,0 %	-	3,0 %

Les autres effets indésirables éprouvés par moins de 5% des patients incluaient les suivants: douleur oculaire, trouble cutané, rhinite, bronchite, toux, diarrhée, douleur abdominale, hypotension orthostatique, palpitation, vasodilatation, trouble rectal, lymphocytose, thrombocytopénie, délire, somnolence, douleur articulaire, raideur articulaire, sensation ébrieuse, paresthésie distale, désorientation, irritabilité, insomnie, léthargie, ecchymose, purpura, sudorification accrue, essoufflement, infection des voies respiratoires hautes, tachycardie, bouffée vasomotrice, douleur urétrale, infection, douleur thoracique, lymphadénopathie, augmentation de l'iode protéique sanguine, arthralgie, étourdissement, nervosité, tremblement, vision anormale, affection vulvo-vaginale, balanite, affection péninenne, affection testiculaire, urétrite, infection des voies urinaires, vaginite, leucocytopénie vaginite, herpès, prurit, éruption maculopapuleuse, néoplasie cutanée, éruption cutanée.

Immunogénicité: On a effectué la détermination de la présence d'anticorps anti-IFN-ß humain dans chacune des 4 études. En tout, quatre patients avaient des anticorps anti-interféron bêta lors de l'examen précédant l'inscription et 6 autres patients avaient reçu au moins un résultat positif quant aux anticorps liants totaux à un certain moment de l'étude. Les anticorps étaient de faible titre et aucun des anticorps ne neutralisait l'activité biologique de l'IFN-ß humain.

SYMPTÔMES ET TRAITEMENT DU SURDOSAGE

Jusqu'à présent, on n'a rapporté aucun cas de surdosage. Cependant, en cas de surdosage, les patients devraient être hospitalisés afin qu'on puisse les garder sous observation et leur administrer le traitement d'appoint approprié.

POSOLOGIE ET ADMINISTRATION

SCLÉROSE EN PLAQUES RÉMITTENTE : La posologie recommandée de Rebif® (interféron bêta-1a) est de 22 µg (6 MUI) administrés trois fois par semaine par injection sous-cutanée. Cette dose est efficace chez la majorité des patients pour ralentir la progression de la maladie. Les patients atteints d'un niveau plus élevé d'état d'invalidité (cote EDSS de 4,0 ou plus) pourraient avoir besoin d'une dose de 44 µg (12 MUI) 3 fois/semaine.

Le traitement devrait débuter sous la supervision d'un médecin rompu au traitement de cette maladie. Lorsqu'on amorce initialement le traitement avec Rebif® , il est recommandé de favoriser la constitution de la tachyphylaxie, pour ainsi réduire les effets indésirables, en administrant 20 % de la dose totale pendant les 2 premières semaines de traitement, 50 % de la dose totale pendant les semaines 3 et 4, et la dose entière à partir de la cinquième semaine.

Actuellement, on n'a pas encore établi quelle devrait être la durée du traitement. On a démontré l'innocuité et l'efficacité de Rebif® pendant un traitement de 2 ans. Par conséquent, on recommande d'évaluer les patients après 2 ans de traitement avec Rebif®. La décision de poursuivre davantage le traitement devrait être prise en fonction de chaque cas individuel par le médecin traitant.

Préparation de la solution : formulation lyophilisée (sclérose en plaques rémittente)

Reconstituer le contenu d'un flacon de Rebif® avec 0,5 mL du diluant stérile inclus (voir le tableau ci-dessous pour le volume de diluant et la concentration résultante). La solution reconstituée doit être administrée immédiatement.

Tableau de reconstitution

Concentration	Volume de diluant à ajouter au flacon	Volume disponible approximatif	Concentration nominale/mL
11 µg (3 MUI)	0,5 mL	0,5 mL	22 µg (6 MUI)
44 µg (12 MUI)	0,5 mL	0,5 mL	88 µg (24 MUI)

Préparation de la solution : formulation liquide

La formulation liquide en seringues préremplies est prête à l'administration. Ces seringues sont graduées afin que le traitement soit plus facile à entreprendre. Les seringues préremplies contiennent 22 µg et 44 µg de Rebif® respectivement. Les seringues préremplies sont prêtes à l'administration par voie sous-cutanée uniquement.

CONDYLOME ACUMINÉ:

La posologie recommandée est de 3,67 µg (1 MUI) par lésion trois fois par semaine pendant 3 semaines. On recommande de l'administrer par voie intralésionnelle ou périlésionnelle. Ne pas utiliser les seringues préremplies pour cette indication.

Préparation de la solution : formulation lyophilisée (condylome acuminé)

Reconstituer le contenu d'un flacon de Rebif® dans un diluant stérile de façon à obtenir une concentration finale de 3,7 µg par 0,1 mL de solution. La solution reconstituée doit être administrée immédiatement.

Tableau de reconstitution

Concentration	Volume de diluant à ajouter au flacon	Volume disponible approximatif	Concentration nominale/mL
11 µg (3 MUI)	0,3 mL	0,3mL	37 µg (10 MUI)
44 µg (12 MUI)	1,2 mL	1,2 mL	37 µg (10 MUI)

COMPOSITION

Formulation lyophilisée : Chaque flacon de 3 mL de poudre stérile lyophilisée contient de l'interféron bêta-1a, de l'albumine (humaine), du mannitol et de l'acétate de sodium, comme indiqué dans le tableau ci-dessous. L'acide acétique et l'hydroxyde de sodium servent à ajuster le pH.

Interféron bêta-1a	Albumine (humaine)	Mannitol	Acétate de sodium
11 µg (3 MUI)	9 mg	5 mg	0,2 mg
44 µg (12 MUI)	9 mg	5 mg	0,2 mg

Rebif® (interféron bêta-1a) est présenté avec une ampoule de 2 mL de diluant renfermant 2 mL d'eau pour injection contenant 0,9% NaCl. Aucun agent de conservation n'est présent.

Formulation liquide : La formulation liquide est fournie dans des seringues contenant 0.5 mL de solution. Chaque seringue contient de l'interféron bêta-1a, de l'albumine (humaine), du mannitol et du tampon d'acétate de sodium 0.01M, comme indiqué dans le tableau ci-dessous. La solution ne contient pas de préservateur.

Interféron bêta-1a	Albumine (humaine)	Mannitol	Tampon acétate de sodium 0,01M
22 µg (6 MUI)	2 mg	27,3 mg	q.s. à 0,5 mL
44 µg (12 MUI)	4 mg	27,3 mg	q.s. à 0,5 mL

STABILITÉ ET RECOMMANDATIONS CONCERNANT LA CONSERVATION

Formulation lyophilisée : Consulter la date de péremption qui figure sur l'étiquette du produit. Conserver Rebif® (interféron bêta-1a) sous forme lyophilisée à une température comprise entre 2 et 8°C.

Formulation liquide : Consulter la date de péremption qui figure sur l'étiquette du produit. Conserver Rebif® sous forme liquide en seringues préremplies à une température comprise entre 2 et 8°C. Ne pas congeler.

SOLUTIONS RECONSTITUÉES

Formulation lyophilisée : Rebif® lyophilisé doit être reconstitué avec de l'eau pour injection contenant 0,9% NaCl (présenté dans des ampoules de verre neutre de 2 mL renfermant 2,0 mL). La solution reconstituée doit être administrée immédiatement. Bien qu'on ne le recommande pas, la solution peut être administrée plus tard, le jour même de la reconstitution, si elle est conservée au réfrigérateur (entre 2 et 8°C). Ne pas congeler. La solution reconstituée pourrait prendre une teinte jaune, caractéristique normale du produit.

Formulation liquide : La formulation liquide en seringues préremplies est prête à l'administration.

PRODUITS PARENTÉRAUX

Voir le tableau de reconstitution sous « Préparation de la solution ».

PRÉSENTATION DES FORMES POSOLOGIQUES

Rebif® (interféron bêta-1a) est offert en deux concentrations (flacons de 11 µg (3 MUI) et de 44 µg (12 MUI)), sous forme de poudre stérile lyophilisée. Il est accompagné d'un diluant (eau pour injection contenant 0,9% NaCl) en ampoules de 2 mL. Chacune des deux concentrations du produit lyophilisé est présentée en boîtes de 1 flacon de médicament et de 1 ampoule de 2 mL de diluant, 3 flacons de médicament et de 3 ampoules de 2 mL de diluant ainsi qu'en boîtes de 12 flacons de médicament et de 12 ampoules de 2 mL de diluant.

Rebif® est également offert sous forme liquide, dans des seringues préremplies prêtes à l'administration. Disponible en deux concentrations : 22 µg (6 MUI)/0,5 mL et 44 µg (12 MUI)/0,5 mL. Les seringues préremplies sont conditionnées en formats unitaires et en emballages de 3 seringues et de 12 seringues. Les seringues préremplies ne servent qu'à l'administration sous-cutanée.

La voie d'administration du médicament pour le traitement de la sclérose en plaques rémittente est la voie sous-cutanée. La voie d'administration du médicament dans le cas du condylome acuminé est la voie intralésionnelle ou périlésionnelle.

Référence :

1. Monographie de Rebif, mai 2000. Serono Canada Inc.

Les monographies sont offertes sur demande aux professionnels de la santé.

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Voir page A-18

IMITREX®
SUMATRIPTAN SUCCINATE
SUMATRIPTAN NASAL SPRAY

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

THERAPEUTIC CLASSIFICATION
Migraine Therapy

PHARMACOLOGIC CLASSIFICATION
5-HT_1 Receptor Agonist

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

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

WARNINGS
IMITREX (sumatriptan succinate/sumatriptan) should only be used where a clear diagnosis of migraine has been established.
Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: IMITREX has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. In rare cases, the symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of IMITREX. IMITREX should not be given to patients who have documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). **It is strongly recommended that IMITREX not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female who is surgically or physiologically postmenopausal, or male who is over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, IMITREX should not be administered (see CONTRAINDICATIONS).**
For patients with risk factors predictive of CAD, who are considered to have a satisfactory cardiovascular evaluation, the first dose of IMITREX should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining electrocardiograms in patients with risk factors during the interval immediately following IMITREX administration on the first occasion of use. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.
Intermittent long term users of IMITREX who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluations over the course of treatment.
If symptoms consistent with angina occur after the use of IMITREX, ECG evaluation should be carried out to look for ischemic changes.
The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to IMITREX.
Cardiac Events and Fatalities Associated with 5-HT_1 Agonists: IMITREX can cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low. The fact that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to IMITREX use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.
Premarketing Experience With IMITREX: Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral IMITREX, two experienced clinical adverse events shortly after receiving oral IMITREX that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.
Among the more than 1900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous IMITREX, there were eight patients who sustained clinical events during or shortly after receiving IMITREX that may have reflected coronary artery vasospasm. Six of these eight patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these eight patients, four had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.
Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of IMITREX nasal spray, one patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.
Postmarketing Experience With IMITREX: Serious cardiovascular events, some resulting in death, have been reported in association with the use of IMITREX Injection or IMITREX Tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by IMITREX or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of IMITREX and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of IMITREX.
Cardiac events that have been observed to have onset within 1 hour of IMITREX administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.
Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among reports from the USA of serious cardiac events occurring within 1 hour of IMITREX administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).
Cerebrovascular Events and Fatalities with 5-HT_1 Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous IMITREX, and some have resulted in fatalities. The relationship of IMITREX to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, IMITREX having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. IMITREX should not be administered if the headache being experienced is atypical for the patient. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). If a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given.
Special Cardiovascular Pharmacology Studies: In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT_1 agonist at a subcutaneous dose of 1.5mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.
In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increase in coronary resistance (~20%), and decrease in hyperemic myocardial blood flow (~10%) were noted. The relevance of these finding to the use of the recommended oral doses of this 5-HT_1 agonist is not known.
Similar studies have not been done with IMITREX. However, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.
Hypersensitivity: Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as IMITREX. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS). Owing to the possibility of cross-reactive hypersensitivity reactions, IMITREX should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists. There have been reports of patients with known hypersensitivity to sulphonamides exhibiting an allergic reaction following administration of IMITREX. Reactions ranged from cutaneous hypersensitivity to anaphylaxis.
Other Vasospasm Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of IMITREX to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.
Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. IMITREX is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS).

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

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

* 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).

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

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

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

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

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

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

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

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

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

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

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

AVAILABILITY OF DOSAGE FORMS

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

Product Monograph available to physicians and pharmacists upon request.
Please contact Glaxo Wellcome Inc., 7333 Mississauga Road N, Mississauga, Ontario, L5N 6L4.
Imitrex® (sumatriptan succinate/sumatriptan nasal spray) is a registered trademark of Glaxo Group Limited, Glaxo Wellcome Inc. licensed use. The appearance, namely colour, shape and size of the IMITREX® Nasal Spray device is a trademark of Glaxo Group Limited, Glaxo Wellcome Inc., licensed use.

References:

1. Worldwide estimates, April 2000. Data on file, Glaxo-Wellcome Inc.
2. Product Monograph of IMITREX® (sumatriptan succinate/sumatriptan); Glaxo Wellcome Inc. March 1999.
3. Tansey MJB, Pilgrim J, Martin PM. Long term experience with sumatriptan in the treatment of migraine. Eur Neurol 1993; 33: 310-315.

GlaxoSmithKline
GlaxoSmithKline Inc.
7333 Mississauga Road, Mississauga, Ontario L5N 6L4

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BRIEF PRESCRIBING INFORMATION
CONSULT FULL PRODUCT MONOGRAPH FOR COMPLETE PRESCRIBING INFORMATION

Pr Topamax

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**.)

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

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

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

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_{CR} < 70 mL/min/1.73m²) or with end-stage renal disease requiring 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.

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

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 ($CYP2C_{mephi}$).

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

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

Table 3

Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Add-On Trials in ADULTS

Adverse Event	Placebo (n=216)	TOPAMAX Dosage (mg/day) 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 (includes vision decreased, vision blurred, visual disturbance, visual impairment, amblyopia); rarely reported: diplopia, glaucoma, myopia, eye pain.

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: September 2001
TXPI011026A

See pages A-6, A-7, A-16, A-17

Brief Prescribing Information

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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, interferon alpha, and interferon gamma have overlapping yet distinct biologic activities. The activities of interferon beta-1b are species-restricted and, therefore, the most pertinent pharmacological information on BETASERON (interferon beta-1b) is derived from studies of human cells in culture and *in vivo*.

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

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 183.7 days per year. Three patients withdrew from the 0.25 mg (8 MIU) BETASERON-treated group for injection site pain.

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

Laboratory abnormalities included:

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

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

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

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

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

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

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

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

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

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*Menstrual disorder**	8%	17%
Metrorrhagia	8%	15%
Cystitis	4%	8%
Breast pain	3%	7%
Menorrhagia	3%	6%
Urinary urgency	2%	4%
Fibrocystic breast	1%	3%
Breast neoplasm	0%	2%

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

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

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

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

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

Lymphopenia (<1500/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 Dextrose USP.

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

AVAILABILITY OF DOSAGE FORMS

BETASERON (interferon beta-1b) is presented 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 Dextrose, USP. BETASERON is supplied in cartons containing 15 vials of medication and 15 vials of diluent (2 mL of Sodium Chloride 0.54% solution, per vial). Store under refrigeration between 2°C and 8°C (36°F and 46°F).

References:

1. Product Monograph of PrBETASERON® (interferon beta-1b), Berlex Canada Inc., June 1999.
2. Data on file, Berlex Canada Inc., 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;45:1277-1285.

Product Monograph available upon request.
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Member PAAB R&D

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See pages A-9, A-13

EXELON*

(rivastigmine)

(Rivastigmine as the Hydrogen Tartrate Salt)
Capsules – 1.5 mg, 3 mg, 4.5 mg, 6 mg
PHARMACOLOGICAL CLASSIFICATION
Cholinesterase Inhibitor
ACTIONS AND CLINICAL PHARMACOLOGY

Pathological changes in Dementia of the Alzheimer type involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. A decrease in the function of these cholinergic pathways has been proposed to account for some of the clinical manifestations of dementia. Rivastigmine, a reversible cholinesterase inhibitor of the carbamate-type, is thought to enhance cholinergic neurotransmission by slowing the degradation of acetylcholine released by cholinergic neurons through the inhibition of acetylcholinesterase. If this proposed mechanism of action is correct, rivastigmine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact.There is no evidence that rivastigmine alters the course of the underlying dementing process.

Clinical Pharmacokinetics

Absorption: Rivastigmine is well absorbed and peak plasma concentrations (C_{max}) are reached in approximately 1 hour. A doubling of the dose within the recommended dose range yields an increase in bioavailability by approximately 3 times the expected increase indicating non-linear pharmacokinetics. The estimated absolute bioavailability for a 3 mg dose in healthy young patients is low (<35%). The elimination half-life ($t_{1/2}$) of rivastigmine is about 1 to 2 hours in both the young and elderly. Plasma clearance is dose dependent and is approximately 1 l/h/kg at 3 mg in healthy young subjects. In healthy elderly male patients, plasma rivastigmine levels are approximately 30% higher than that noted in young subjects (see **CLINICAL PHARMACOKINETICS: Age**). When administered with food to healthy young subjects the absorption (T_{max}) of rivastigmine was delayed by 90 min, and C_{max} was lowered while the $AUC_{0-\infty}$ was increased by approximately 25%.

Distribution: Rivastigmine is approximately 40% bound to plasma proteins over a concentration range of 1-400 ng/mL. Rivastigmine distributes equally between blood and plasma with a blood-to-plasma partition ratio of 0.9 at concentrations which cover the therapeutic range (1-400 ng/mL) The apparent volume of distribution is 5 ± 3 L/kg. Rivastigmine can be detected in the CSF, reaching peak concentrations in 1-4 hours. Mean AUC_{0-12h} ratio of CSF/plasma averaged 40 ± 0.5% following 1-6 mg bid doses.

Metabolism: Rivastigmine is subject to first pass clearance and is rapidly and extensively metabolised, primarily via esterase-, including acetylcholinesterase-, mediated hydrolysis to a decarbamylated phenolic metabolite. *In vitro* preclinical studies suggest that the decarbamylated phenolic metabolite has approximately 10% the activity of the parent compound. The plasma half-life of the decarbamylated phenolic metabolite ranges from 2.5 to 4 hours. Additional metabolites include a sulphate conjugate, a demethylated sulfate conjugate and several unidentified minor metabolites. The pharmacokinetics of rivastigmine in patients with butyrylcholinesterase enzyme deficiency are unknown (see **PRECAUTIONS: Genetic Polymorphism**). Evidence from *in vitro* studies suggest that the major cytochrome P450 isozymes are minimally involved in rivastigmine metabolism (see **PRECAUTIONS: Drug-Drug Interactions**). Rivastigmine inhibits acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activity. In patients with Alzheimer Disease significant dose-dependent inhibition of AChE and BChE activity were noted in cerebrospinal fluid, with comparable maximum mean inhibition (62%). In plasma, significant inhibition of BChE activity is generally observed from 1.5 hours post-dose up to 8 hours post-dose, with a maximum observed inhibition of 51% at 5 mg b.i.d. Rivastigmine may therefore inhibit the butyrylcholinesterase mediated metabolism of other drugs (see **PRECAUTIONS: Drug-Drug Interactions**).

Excretion: Unchanged rivastigmine is not found in the urine; renal excretion is the major route of elimination of the metabolites. Following administration of a single 1 mg or 2.5 mg dose of ^{14}C-labelled rivastigmine, excretion of radioactivity in the urine (expressed as a percent of the administered dose) is over 90% within 24 hours. Approximately 7% of the decarbamylated phenolic metabolite is found in the urine. The sulfate conjugates account for about 40% of the dose. Less than 1% of the administered dose is excreted in the faeces. The accumulation potential of rivastigmine and its decarbamylated phenolic metabolite in patients with Alzheimer Disease has not been systematically studied however, population pharmacokinetic analyses suggest that no accumulation is expected.

Renal: In a single-dose study of 8 subjects with moderate renal impairment (GFR = 10-50 mL/min) mean peak plasma concentrations of rivastigmine were increased by almost 2.5 fold and overall plasma levels (AUC) of the decarbamylated phenolic metabolite were increased by approximately 50% compared to levels in age, weight, and gender matched control subjects. In this same study, patients with severe renal impairment (GFR <10 mL/min, n = 8) showed no difference in rivastigmine blood levels compared to controls. The reason for this discrepancy is unclear. The safety and efficacy of rivastigmine in Alzheimer Disease patients with renal impairment have not been studied (see **PRECAUTIONS: Renal Impairment**).

Hepatic: In a single dose study of 10 subjects with biopsy proven liver impairment (Child-Pugh score of 5-12), plasma concentrations of rivastigmine were increased, while that of the decarbamylated phenolic metabolite were decreased by about 60% compared to an age, weight and gender matched control group. The safety and efficacy of rivastigmine in Alzheimer Disease patients with hepatic impairment have not been studied (see **PRECAUTIONS: Hepatic Impairment**).

Age: In a study in which the effect of age on the pharmacokinetics of rivastigmine was assessed, 24 healthy male elderly (age range: 61-71 years) and 24 healthy young patients (age range: 19-40 years) received 1.0 mg or 2.5 mg single oral doses of rivastigmine under fasted conditions. Plasma concentrations of rivastigmine exhibited a wider range of values and tended to be higher in the elderly as compared to young subjects after the 1 mg dose. This difference was more pronounced with the higher dose (2.5 mg) at which rivastigmine plasma concentrations were 30% greater in the elderly than in young subjects. Plasma levels of the decarbamylated phenolic metabolite were not substantially affected by age.

Gender and Race: No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of rivastigmine. However, retrospective pharmacokinetic analyses suggest that gender and race (Blacks, Oriental, and Caucasians) will not affect the clearance of rivastigmine.

Nicotine Use: Population PK analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% (Smokers: n = 75; Nonsmokers: n = 549).

Clinical Trial Data: Efficacy data for rivastigmine in the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer type (diagnosed by DSM-IV and NINCDS criteria, Mini-Mental State Examination ≥10 and ≤26) were derived from four clinical trials. These studies were randomized, double-blind, and placebo controlled. The mean age of patients was 73 years (range: 41 to 95). Approximately 59% of the patients were women and 41% were men, while the racial distribution was: 87% Caucasian, 4% Black and 9% Other. In these clinical studies, the effectiveness of rivastigmine was evaluated using the following criteria: for primary efficacy two measures were used, (1) the cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-Cog), a widely used and well validated multi-item instrument which samples cognitive domains affected by the disease and (2) the CIBIC-Plus (Clinician Interview Based Impression of Change that required caregiver information). The CIBIC-Plus evaluates four major areas of functioning: general, cognition, behaviour and activities of daily living. As a secondary efficacy measure, the Progressive Deterioration Scale (PDS) was used. The PDS is a caregiver-rated evaluation which yields a compound score derived from a visual analogue scale of 29 items concerning participation in activities of daily living. Results for two of these studies, in which a flexible maintenance-dose regimen was used, are presented here. The data shown below were obtained from the Intent-to-Treat population (ITT analysis, i.e., All patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete the study, their last observation while on treatment was carried forward and used at endpoint).

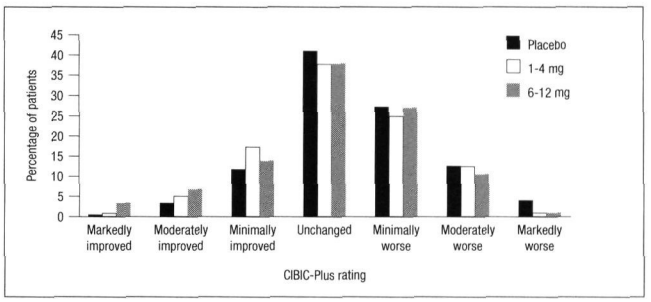
Study I (B352, USA, 26 week trial)

This trial was of 26 weeks duration and was conducted in the USA. The study was subdivided into two phases, a forced titration phase, which could last up to 12 weeks, followed by a 14 week maintenance flexible-dose phase. A total of 699 patients were randomized to a 1-4 mg daily dose (n= 233) or a 6-12 mg daily dose (n = 231) of rivastigmine or placebo (n = 235) to be taken with food in two divided doses. Patients in the active treatment groups must have been able to tolerate the minimum dose in their assigned group (i.e. 0.5 mg bid or 3 mg bid) by titration Week 7 or they were discontinued. The dose escalation rate for the 1-4 mg/day group was: Starting dose 0.5 mg bid with 0.5 mg bid increases every one or two weeks according to tolerability. The dose escalation rate for the 6-12 mg/day group was: Starting dose 1 mg bid increased to 1.5 mg bid after 3 days. Subsequent dose increases were at 0.5 mg bid or 0.75 mg bid every one or two weeks according to patient tolerability. The baseline mean Mini Mental State Exam (MMSE) score of patients was 19.7 and the mean score on the Global Deterioration Scale (GDS) was 4.0.

Effects on ADAS-cog: At baseline, mean ADAS-cog scores (mean ± SE) were for the placebo group: 21.74 ± 0.74 units; for the 1-4 mg/day group: 22.38 ± 0.75 units and for the 6-12 mg/day group: 22.31 ± 0.75 units. At the first measurement of efficacy (Week 12) mean ADAS-cog change scores from placebo (mean ± standard error) were: 0.82 ± 0.52 units for the 1-4 mg/day group and 3.24 ± 0.54 units for the 6-12 mg/day dose groups. Differences from placebo were statistically significantly different only for the 6-12 mg/day group. At Week 18, mean change scores from placebo were significant for both rivastigmine dose groups (1-4 mg/day: 1.67 ± 0.54 units; 6-12 mg/day: 3.83 ± 0.57 units). Both rivastigmine treated groups also showed significant differences from placebo in ADAS-cog mean change scores at Week 26: (1-4 mg/day: 1.66 ± 0.57 units; 6-12 mg/day: 4.32 ± 0.60 units). A greater treatment effect size is noted for the 6-12 mg/day treatment. At the end of the 26-week treatment period, either no evidence of deterioration or an improvement was observed in 27% of the placebo group, 35% (1-4 mg/day) and 51% (6-12 mg/day) in the rivastigmine groups. The difference between the 6-12 mg/day group and the placebo group was statistically significant. A 4-point improvement in ADAS-cog score from baseline was observed in 6% of placebo patients, 12% (1-4 mg/day) and 23% (6-12 mg/day) of rivastigmine treated patients at the end of the 26 week period. Statistical significance from placebo for this categorical measure was noted for both the 1-4 mg/day and 6-12 mg/day group.

Effects on CIBIC-Plus: At Week 26 the mean drug-placebo differences were 0.22 ± 0.11 units for the 1-4 mg/day group and 0.36 ± 0.12 units for the 6-12 mg/day group. Differences from placebo were statistically significant, however, there was no statistically significant difference between the two active treatments. A histogram of the frequency distribution of CIBIC-Plus scores achieved at Week 26 by patients assigned to each of the three treatment groups is shown in Figure 1.

Figure 1: Frequency distribution of CIBIC-Plus scores at week 26



Effects on PDS: The progressive deterioration scale was used as a secondary efficacy measure. At baseline, mean PDS scores (mean ± SE) were for the placebo group: 53.7 ± 1.2 units; for the 1-4 mg/day group: 54.7 ± 1.2 units; for the 6-12 mg/day group: 52.0 ± 1.2 units. At Week 26, the placebo group declined an average of 5.2 ±0.7 units, the 1-4 mg/day group declined 5.3 ± 0.7 units and the 6-12 mg/day group deteriorated minimally (1.0 ± 0.8 units). The difference between the 6-12 mg/day group and the placebo group was statistically significant.

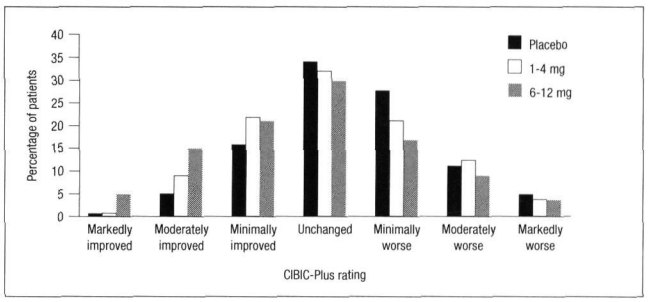
Study II (B303, Multinational, 26 week trial)

This trial of 26 weeks duration was a multinational study (Austria, Canada, France, Germany, Switzerland and USA). A total of 725 patients were randomized into three different treatment arms: Placebo: n = 239; 1-4 mg/day rivastigmine: n = 243; 6-12 mg/day rivastigmine: n = 243. As in Study I, this trial was comprised of two phases, a forced titration phase, which could last up to 12 weeks, followed by a maintenance flexible-dose phase. Patients in the active treatment groups must have been able to tolerate the minimum dose in their assigned group (i.e. 0.5 mg bid or 3 mg bid) by titration Week 7 or they were discontinued. The baseline mean Mini Mental State Exam (MMSE) score was 20 and the mean score on the Global Deterioration Scale (GDS) was 4.0.

Effects on ADAS-cog: At baseline, mean ADAS-cog scores (mean ± SE) were for the placebo group: 23.29 ± 0.75 units; for the 1-4 mg/day group: 23.87 ± 0.76 units and for the 6-12 mg/day group: 23.57 ± 0.77 units. At the first measurement of efficacy (Week 12) the difference in mean ADAS-cog change scores (mean ± standard error) for rivastigmine treated patients compared to placebo treated patients for the intent-to-treat (ITT) population were for the 1-4 mg/day group: 0.19 ± 0.55 units and for the 6-12 mg/day group: 1.71 ± 0.57 units. Only the difference between the 6-12 mg/day group and placebo was significant at this time point. At Weeks 18 and 26 mean ADAS-cog change scores from placebo were for the 1-4 mg/day group: 0.57 ± 0.59 (Week 18); 0.22 ± 0.67 units (Week 26) and for the 6-12 mg/day group: 1.77 ± 0.60 units (Week 18); 2.29 ± 0.69 units (Week 26). As for Week 12, only the difference between the 6-12 mg/day group and placebo was statistically significant. At the end of the 26-week treatment period, either no evidence of deterioration or an improvement was observed in 40% of the placebo group, 45% (1-4 mg/day) and 52% (6-12 mg/day) in the rivastigmine groups. A 4-point improvement in ADAS-cog score from baseline was observed in 18% of patients who received placebo, 16% (1-4 mg/day) and 27% (6-12 mg/day) of rivastigmine treated patients at Week 26. Differences between rivastigmine (6-12 mg/day) and placebo treated groups were significant for both categorical measures.

Effects on CIBIC-Plus: At Week 26 the mean drug-placebo differences were 0.15 ± 0.14 units for the 1-4 mg/day group and 0.44 ± 0.15 units for the 6-12 mg/day group. Differences from placebo were statistically significant only for the 6-12 mg/day dose group. A histogram of the frequency distribution of CIBIC-Plus scores achieved at Week 26 by patients assigned to each of the three treatment groups is shown in Figure 2.

Figure 2: Frequency distribution of CIBIC-Plus scores at week 26



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Effects on PDS: The progressive deterioration scale was used as a secondary efficacy measure. At baseline, mean PDS scores (mean ± SE) were for the placebo group: 54.8 ± 1.3 units; for the 1-4 mg/day group: 53.8 ± 1.3 units; for the 6-12 mg/day group: 55.2 ± 1.2 units. At Week 26, while the placebo group declined an average of 2.2 ± 0.9 units and the 1-4 mg/day group deteriorated by 3.3 ± 0.9 units, the 6-12 mg/day group improved by 0.5 ± 1.0 units, which was a statistically significant difference. The 6-12 mg/day group was statistically significantly superior to placebo as well as the lower dose range.

Data from these controlled clinical trials suggest that rivastigmine doses between 6-12 mg/day are more likely to result in beneficial symptomatic effects.

INDICATIONS AND CLINICAL USE

EXELON (rivastigmine as the hydrogen tartrate salt) is indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer type. EXELON has not been studied in controlled clinical trials for longer than 6 months. EXELON *capsules should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer Disease.*

CONTRAINDICATIONS

EXELON (rivastigmine as the hydrogen tartrate salt) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation.

WARNINGS

Anesthesia: EXELON (rivastigmine as the hydrogen tartrate salt) as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Neurological Conditions: Seizures: In placebo controlled clinical trials with EXELON cases of seizures were reported. Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer Disease. The risk/benefit of EXELON treatment for patients with a history of seizure disorder must therefore be carefully evaluated. EXELON has not been studied in patients with moderately severe or severe Alzheimer Disease, non-Alzheimer dementias or individuals with Parkinsonian features. The efficacy and safety of EXELON in these patient populations is unknown.

Pulmonary Conditions: Like other cholinomimetic drugs, EXELON should be used with care in patients with a history of asthma or obstructive pulmonary disease. No experience is available in treating patients with these conditions.

Cardiovascular Conditions: Because of their pharmacological action, cholinomimetics 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 patients with serious cardiovascular disease were excluded. Caution should therefore be exercised in treating patients with active coronary artery disease or congestive heart failure. Syncopal episodes have been reported in association with the use of EXELON. It is recommended that EXELON 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 Conditions: Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). In controlled clinical studies with EXELON, patients with a past history (last 2 years) of peptic ulceration and chronic diseases of the gastrointestinal tract were excluded. In the trial population who received EXELON there was no significant increase, relative to placebo, in the incidence of peptic ulcer disease. The incidence of GI hemorrhage, in controlled clinical trials was <1% (n = 6/1923) for EXELON and 0% (n =0/868) for placebo. EXELON, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting and diarrhea. These effects appear more frequently at higher doses (see ADVERSE REACTIONS section), with nausea and vomiting being more prevalent in women. Females are more sensitive to the cholinergic adverse effects associated with cholinesterase inhibitors and in general are more likely to experience nausea and vomiting than are males. In most cases these effects were of mild to moderate intensity and transient, and they resolved during continued EXELON treatment or upon treatment discontinuation.

Weight Loss: Cholinesterase inhibitors as well as Alzheimer Disease can be associated with significant weight loss. In controlled clinical trials the use of EXELON was associated with weight loss. Women exposed to doses of EXELON at the higher end of the therapeutic range (6-12 mg/day) were at greater risk for weight loss. Approximately 24% of women on 6-12 mg/day doses of EXELON had weight loss of equal to or greater than 7% of their baseline weight compared to 6% on placebo. For males, 16% (6-12 mg/day) experienced a similar degree of weight loss compared to 4% on placebo. Where weight loss may be of clinical concern, body weight should be monitored.

Genitourinary: Although not reported in clinical trials of EXELON, cholinomimetics may cause bladder spasm.

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:** In controlled clinical trials with EXELON few patients received neuroleptics, antidepressants or anticonvulsants, there is thus limited information concerning the interaction of EXELON with these drugs.

Use in patients > 85 years old: In controlled clinical studies, the number of patients over 85 years old who received EXELON in the therapeutic dose range of 6-12 mg/day was 68. Of these patients, 12 received high doses of EXELON (>9 or ≤12 mg/day). The safety of EXELON in this patient population has not been adequately characterized. In Alzheimer Disease patients in controlled clinical trials, nausea, diarrhea, vomiting, dizziness, anorexia, fatigue, dyspepsia and weakness increased with dose. Dose escalation in patients >85 years old should thus proceed with caution (see **DOSAGE AND ADMINISTRATION: Special Populations**).

Use in elderly patients with serious comorbid disease: There is limited information on the safety of EXELON treatment in patients with mild to moderate Alzheimer Disease and serious comorbidity. The use of EXELON in Alzheimer Disease patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Dose escalation in this patient population should proceed with caution (see **DOSAGE AND ADMINISTRATION: Special Populations**).

Renally and Hepatically Impaired Patients: There is limited information on the pharmacokinetics of EXELON in renally and hepatically impaired patients (see Clinical Pharmacokinetics and Metabolism section). It is therefore recommended that dose escalation with rivastigmine in renally or hepatically impaired patients with Alzheimer Disease be undertaken with caution and under conditions of close monitoring for adverse effects (see **DOSAGE AND ADMINISTRATION: Special Populations**).

Genetic Polymorphism: The effect of genetic polymorphism of butyrylcholinesterase enzyme on rivastigmine metabolism is unknown.

Drug-Drug Interactions

Studies to assess the potential of EXELON for interaction with digoxin, warfarin, diazepam or fluoxetine were limited to short term, single-dose studies in young healthy volunteers. No significant effects on the pharmacokinetics of these drugs or on the metabolism of rivastigmine were observed. Similar studies in elderly patients were not done.

Effect of EXELON on the Metabolism of Other Drugs: Rivastigmine is mainly metabolised through hydrolysis by esterases. No *in vivo* studies have investigated the effects of EXELON on the clearance of drugs metabolised by CYP450. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolised by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19. Rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other drugs (see **ACTIONS AND CLINICAL PHARMACOLOGY: Clinical Pharmacokinetics: Metabolism**).

Effect of Other Drugs on the Metabolism of EXELON: Drugs which induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Formal pharmacokinetic studies to assess the potential for drug interaction with other medications commonly taken by the elderly were not done.

Population-pharmacokinetic analyses of a subset (n = 359; 6-12mg/day) of patients with Alzheimer Disease in controlled clinical trials do not suggest that the administration of EXELON with some commonly prescribed medications is associated with an alteration in the kinetics of rivastigmine, or an increased risk of clinically relevant untoward effects. However, the number of patients who received concomitant medications chronically was as follows: anilides (e.g. acetominophen) (10%), antacids (12%), antianginals (6%), antihistamines (2%), antihypertensives (12%), benzodiazepines (<1%), ß-blockers (7%), calcium channel blockers (12%), digitalis glycosides (5%), non-steroidal anti-inflammatory drugs (13%), oral hypoglycemics (3%), and salicylic acid and derivatives (28%).

Pregnancy

The safety of EXELON in pregnant women has not been established. EXELON should not be used in women of childbearing potential unless, in the opinion of the physician, the potential benefit to the patient justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether EXELON is excreted into human milk, and therefore EXELON should not be used in nursing mothers.

Pediatric Use

The safety and effectiveness of EXELON in any illness occurring in pediatric patients have not been established.

ADVERSE REACTIONS

A total of 1923 patients with mild to moderate Alzheimer Disease were treated in controlled clinical studies with EXELON. Of these patients, 1417 (74%) completed the studies. The mean duration of treatment for all EXELON groups was 154 days (range 1-255 days).

Adverse Events Leading to Discontinuation

Overall, 18% (340/1923) of patients treated with EXELON discontinued from Phase III controlled clinical trials due to adverse events compared to 9% (75/868) in the placebo group. During the titration phases of controlled clinical trials the incidence of discontinuations due to adverse events was 5% for placebo, 5% for EXELON 1-4 mg/day and 21% for EXELON 6-12 mg/day. During the maintenance phases, 3% of patients who received placebo, 3% of patients who received 1-4 mg/day EXELON and 6% of patients who received EXELON 6-12 mg/day withdrew from studies due to adverse events. Female patients treated with EXELON were approximately twice as likely to discontinue study participation due to adverse events than were male patients (Females: 21%; Males: 12%). 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 (≥2% and twice the rate in the placebo group) leading to withdrawal from randomized placebo controlled clinical trials B351, B352, and B303 during titration and maintenance phases*

	Titration phase (weeks 1-12)			Maintenance phase (weeks 13-26)		
	Placebo n=646	1-4 mg/day n=644	6-12 mg/day n=824	Placebo n=588	1-4 mg/day n=587	6-12 mg/day n=601
All events	5%	5%	21%	3%	3%	6%
Nausea	1%	1%	10%	0%	<1%	1%
Vomiting	0%	<1%	5%	0%	<1%	2%
Anorexia	0%	<1%	3%	<1%	<1%	<1%
Dizziness	<1%	<1%	3%	<1%	0%	1%
Abdominal pain	<1%	<1%	2%	<1%	<1%	<1%
Asthenia	0%	0%	2%	0%	0%	<1%
Fatigue	<1%	<1%	2%	0%	0%	<1%

*All patients who received at least one dose of study medication were included in the results for the titration phase. All patients who entered the maintenance phase were represented in the results for the maintenance phase.

Titration and maintenance dosing should remain flexible and be adjusted according to individual needs.

Most Frequent Adverse Clinical Events Seen in Association with the Use of EXELON

The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by EXELON's cholinomimetic effects. These include nausea, vomiting, dizziness, diarrhea, anorexia and abdominal pain. Table 2 presents a comparison of common adverse events (≥5% incidence and twice the placebo rate) by treatment group during titration (Weeks 1-12) and maintenance (Weeks 13-26). The adverse events were generally mild in intensity, more frequent at higher doses, of short duration, and attenuated with continued dosing or discontinuation of drug.

Table 2. Common adverse events (≥5% and twice the rate in the placebo group) in randomized placebo controlled clinical trials B351, B352, and B303 during titration and maintenance phases*

	Titration phase (weeks 1-12)			Maintenance phase (weeks 13-26)		
Adverse event	Placebo n=646	1-4 mg/day n=644	6-12 mg/day n=824	Placebo n=588	1-4 mg/day n=587	6-12 mg/day n=601
Nausea	9%	15%	40%	4%	8%	15%
Vomiting	3%	5%	23%	3%	5%	14%
Dizziness	10%	10%	19%	4%	6%	10%
Diarrhea	9%	8%	16%	4%	5%	9%
Anorexia	2%	5%	13%	1%	2%	4%
Abdominal pain	4%	5%	10%	3%	3%	4%
Fatigue	4%	4%	8%	1%	2%	3%
Asthenia	2%	1%	6%	1%	2%	3%
Somnolence	2%	4%	5%	1%	1%	1%

*All patients who received at least one dose of study medication were included in the results for the titration phase. All patients who entered the maintenance phase were represented in the results for the maintenance phase.

Titration and maintenance dosing should remain flexible and be adjusted according to individual needs.

In an open label study involving 305 patients with Alzheimer Disease the tolerability of a 1.5 mg bid (3 mg/day) starting dose and dose escalation of 1.5 mg bid (3 mg/day) at a minimum interval of every two weeks were assessed. A total of 40 of these patients (13%) discontinued the study due to adverse events. The type and incidence of common adverse events reported did not appear to differ substantially from those noted in placebo-controlled studies.

Adverse Events Reported in Controlled Trials

The events cited reflect experience gained under closely monitored condition 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 that were reported in at least 2% of patients in Phase 3 placebo-controlled trials for which the rate of occurrence was greater for EXELON assigned than placebo assigned patients. There were too few non Caucasian patients enrolled to assess the effect of race on the incidence of adverse events in the Phase III controlled studies. Similarly, there were too few patients aged more than 85 years to systematically assess the effect of advanced age. Female patients were more susceptible to nausea, vomiting, loss of appetite and weight loss.

Table 3. Adverse events reported in controlled clinical trials in at least 2% of patients receiving EXELON and at a higher frequency than placebo-treated patients

Body system/Adverse event	Placebo (n=868)	EXELON (n=1923)
Percent of patients with any adverse event	79	87
Autonomic Nervous System		
Sweating increased	1	3
Body as a Whole		
Fatigue	5	7
Asthenia	2	5
Malaise	2	4
Weight decrease	<1	2
Cardiovascular Disorders, General		
Hypertension	2	3
Central and Peripheral Nervous System		
Dizziness	11	19
Headache	12	15
Somnolence	3	5
Tremor	1	3
Gastrointestinal System		
Nausea	12	37
Vomiting	6	23
Diarrhea	11	16
Anorexia	3	13
Abdominal Pain	6	11
Dyspepsia	4	8
Constipation	4	5
Flatulence	2	4
Eructation	1	2
Psychiatric Disorders		
Insomnia	7	8
Depression	4	5
Anxiety	3	4
Hallucination	3	4
Nervousness	3	4
Aggressive Reaction	2	3
Respiratory System		
Rhinitis	3	4
Dyspnea	1	2
Skin and Appendages		
Pruritus	1	2
Urinary System		
Urinary Incontinence	2	3
Micturition Frequency	1	2
Vision Disorders		
Vision Abnormal	1	2

Other Adverse Events Observed During Clinical Trials

EXELON has been administered to over 5297 individuals during clinical trials worldwide. Of these, 4326 patients have been treated for at least 3 months, 3407 patients have been treated for at least 6 months, 2150 patients have been treated for 1 year, 1250 have been treated for 2 years, and 168 have been treated for over 3 years. With regard to exposure to the highest dose, 1679 patients were exposed to mean daily doses of 10-12 mg, 1659 patients treated for 3 months, 1504 patients treated for 6 months, 885 patients treated for 1 year, 629 patients treated for 2 years, and 86 treated for over 3 years. Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 9 open-label trials in North America, Western Europe, Australia, South Africa and Japan 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 events were grouped into a smaller number of standardized categories using a modified WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5297 patients from these trials who experienced that event while receiving EXELON. All adverse events occurring at least 6 times are included, except for those already listed in Table 3, WHO terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to EXELON treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System:
Frequent: Syncope.
Infrequent: Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole:
Frequent: Accidental trauma, allergy, chest pain, edema, fever, hot flushes, influenza-like symptoms, overdose, rigors.
Infrequent: Allergic reaction, chest pain substernal, edema periorbital, facial edema, feeling cold, halitosis, hypothermia, inflammatory reaction unspecified, pain, pallor, tumor unspecified, unspecified eyelid disorder, weight increase.

Cardiovascular System:
Frequent: Cardiac failure, hypotension, peripheral edema, postural hypotension.
Infrequent: Chest pain, ECG abnormal, edema, generalized edema.

Central and Peripheral Nervous System:
Frequent: Abnormal gait, ataxia, convulsions, extrapyramidal disorder, paresthesia, vertigo.
Infrequent: Abnormal coordination, aphasia, apraxia, coma, dysphonia, hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, hyporeflexia, involuntary muscle contractions, migraine, neuralgia, neuropathy, nystagmus, paresis, peripheral neuropathy, speech disorder.

Collagen Disorders:
Frequent: None.
Infrequent: Rheumatoid arthritis

Endocrine System:
Frequent: None.
Infrequent: Goitre, hypothyroidism.

Gastrointestinal System:
Frequent: Fecal incontinence, gastritis, tooth disorder.
Infrequent: Colitis, colorectal polyp, diverticulitis, duodenal ulcer, dysphagia, esophagitis, gastric ulcer, gastroenteritis, gastroesophageal reflux, GI hemorrhage, gingivitis, glossitis, hematemesis, hernia, hiccup, increased appetite, intestinal obstruction, melena, pancreatitis, peptic ulcer, rectal disorder, rectal hemorrhage, tenesmus, tooth caries, ulcerative stomatitis.

Hearing and Vestibular Disorders:
Frequent: Tinnitus.
Infrequent: Deafness, earache, ear disorder unspecified, vestibular disorder.

Heart Rate and Rhythm Disorders:
Frequent: Bradycardia, fibrillation atrial, palpitation.
Infrequent: Arrhythmia, AV block, bundle branch block, cardiac arrest, extrasystoles, sick sinus syndrome, supraventricular tachycardia, tachycardia.

Liver and Biliary System Disorders:
Frequent: None.
Infrequent: Abnormal hepatic function, cholecystitis, cholelithiasis, increased gamma-glutamyl transferase, increased hepatic enzymes.

Metabolic and Nutritional Disorders:
Frequent: Dehydration, hypokalemia.
Infrequent: Cachexia, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperlipemia, hypoglycemia, hyponatremia, thirst.

Musculoskeletal Disorders:
Frequent: Arthralgia, arthritis, back pain, bone fracture, leg cramps, leg pain, myalgia, pain.
Infrequent: Arthropathy, arthrosis, bone disorder, bone pain, bursitis, cramps, hernia, joint malformation, muscle weakness, osteoporosis, spine malformation, stiffness, tendinitis, tendon disorder, vertebral disc disorder.

Myo-, Endo-, Pericardial and Valve Disorders:
Frequent: Angina pectoris, myocardial infarction.
Infrequent: Coronary artery disorder, heart sounds abnormal, myocardial ischemia.

Neoplasms:
Frequent: Basal cell carcinoma.
Infrequent: Bladder carcinoma, carcinoma, colon carcinoma, malignant breast neoplasm (female), malignant skin neoplasm, unspecified adenocarcinoma, unspecified neoplasm.

Platelet, Bleeding, and Clotting Disorders:
Frequent: Epistaxis.
Infrequent: Hematoma, purpura, thrombocytopenia, unspecified hemorrhage.

Psychiatric Disorders:
Frequent: Agitation, behavioral disturbance, confusion, delusion, paranoid reaction, paroniria.
Infrequent: Abnormal dreaming, amnesia, apathy, decreased libido, delirium, dementia, depersonalization, emotional lability, impaired concentration, increased libido, neurosis, psychosis, sleep disorder, stress reaction, suicidal ideation.

Red Blood Cell Disorders:
Frequent: Anemia.
Infrequent: Anemia B_{12} deficiency, hypochromic anemia.

Reproductive Disorders (Female & Male):
Frequent: Prostatic disorder.
Infrequent: Atrophic vaginitis, breast pain (female), impotence, intermenstrual bleeding, unspecified uterine disorder, vaginal hemorrhage, vaginitis.

Resistance Mechanism Disorders:
Frequent: Infection, pneumonia, upper respiratory tract infection, urinary tract infection, viral infection.
Infrequent: Bacterial infection, cellulitis, cystitis, fungal infection, herpes simplex, herpes zoster, moniliasis, onychomycosis, otitis media, parasitic infection, sepsis.

Respiratory System:
Frequent: Bronchitis, coughing, pharyngitis, sinusitis.
Infrequent: Abnormal chest sounds, apnea, bronchospasm, emphysema, hyperventilation, increased sputum, laryngitis, pleural effusion, pulmonary disorder, pulmonary edema, respiratory disorder, respiratory insufficiency.

Skin and Appendages:
Frequent: Rash, skin disorder, skin ulceration.
Infrequent: Abscess, acne, alopecia, bullous eruption, contact dermatitis, dermatitis, dry skin, eczema, erythematous rash, furunculosis, genital pruritus, hyperkeratosis, maculo-papular rash, nail disorder, otitis externa, psoriaform rash, seborrhea, skin cyst, skin discoloration, skin exfoliation, skin hypertrophy, sunburn, urticaria, verruca.

Special Senses:
Frequent: None.
Infrequent: Loss of taste, perversion of taste.

Urinary System Disorders:
Frequent: Hematuria.
Infrequent: Acute renal failure, albuminuria, dysuria, micturition disorder, micturition urgency, nocturia, polyuria, pyuria, renal calculus, renal cyst, renal function abnormal, unspecified bladder disorder, urethral disorder, urinary retention.

Vascular (extracardiac) Disorders:
Frequent: Cerebrovascular disorder.
Infrequent: Aneurysm, circulatory disorder, hemorrhoids, intracranial hemorrhage, peripheral ischemia, phlebitis, pulmonary embolism, thrombophlebitis deep, thrombosis, varicose vein, vascular disorder.

Vision Disorders:
Frequent: Cataract, conjunctivitis.
Infrequent: Abnormal lacrimation, blepharitis, conjunctival hemorrhage, diplopia, eye abnormality, eye pain, glaucoma.

White Cell and Resistance Disorders:
Frequent: None.
Infrequent: Leukocytosis, lymphadenopathy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterised by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Treatment: EXELON (rivastigmine as the hydrogen tartrate salt) has a short plasma half-life (about 1-2 hours) and a moderate duration of cholinesterase inhibition of 8-12 hours. It is recommended that in cases of asymptomatic overdoses, no further dose of EXELON should be administered for the next 24 hours and that patients be monitored. As in any case of overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for EXELON overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. Due to the short half-life of EXELON, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose. In overdoses accompanied by severe nausea and vomiting, the use of antiemetics should be considered. In a documented case of a 46 mg overdose with EXELON, a 69 year old female patient experienced vomiting, incontinence, hypertension, psychomotor retardation and loss of consciousness. The patient was managed conservatively with only supportive measures and fully recovered within 24 hours. Dose-related signs of toxicity in animals included lacrimation, excessive salivation, vomiting, decreased locomotor activity, ataxia, twitches/flutters, tremors and clonic convulsions.

DOSAGE AND ADMINISTRATION

EXELON (rivastigmine as the hydrogen tartrate salt) *capsules should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer Disease.*

Adults: The usual maintenance dose range for EXELON is 6-12 mg/day. The following dosage escalation recommendations, derived from clinical trial data, are provided as a guide only, as individual tolerance to dose increases will vary. The incidence of cholinergic adverse events associated with EXELON increase with dose and are more prevalent in females (see **ADVERSE REACTIONS** section). The usual starting dose of EXELON is 1.5 mg bid (3 mg/day). If this initial dose is well tolerated, after a minimum of 2 weeks the dose may be increased to 3 mg bid (6 mg/day). Dose increases above 6 mg/day should proceed cautiously.

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ONCE-A-WEEK AVONEX® (Interferon beta-1a)
IM Injection

PRESCRIBING INFORMATION

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

Description

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

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

General

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

Biologic Activities

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

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

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

CLINICAL TRIALS: EFFECTS IN MULTIPLE SCLEROSIS

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

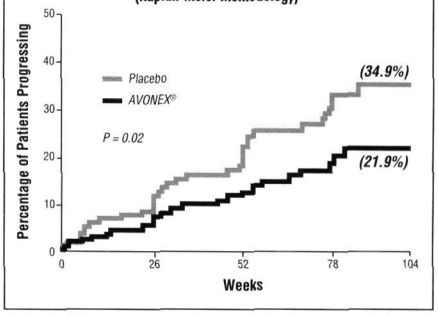
All patients had a definite diagnosis of MS of at least 1 year duration and had at least 2 exacerbations in the 3 years prior to study entry (or 1 per year if the duration of disease was less than 3 years). At entry, study participants were without exacerbation during the prior 2 months and had Kurtzke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

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

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

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

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



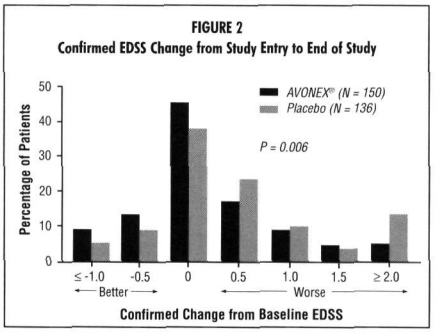
Note: Disability progression represents at least a 1.0 point increase in EDSS score sustained for at least 6 months. The value p=0.02 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given timepoint (e.g., 34.9% vs. 21.9%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

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

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

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

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



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

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

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

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

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

Table 1
MAJOR CLINICAL ENDPOINTS

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

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

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

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

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

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

[5] Analyzed by likelihood ratio test.

[6] Analyzed by Wilcoxon rank-sum test.

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INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General

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

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

Laboratory Tests

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

Drug Interactions

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

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

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

Use in Pregnancy

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

Nursing Mothers

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

Pediatric Use

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

Information to Patients

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

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

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

ADVERSE EVENTS

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

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

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

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

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

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

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

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

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

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

Continued from page A-32

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

Serum Neutralizing Antibodies

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

PHARMACEUTICAL INFORMATION

Composition:

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

Reconstitution:

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

Stability and Storage:

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

AVAILABILITY OF DOSAGE FORMS

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

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

REFERENCES:

1 AVONEX® Product Monograph, April 6, 1998.
2. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol. 1996;39:285-294.
3. Rudick RA, Fisher E, Lee JC, et al. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Neurology 1999;53:1698-1704.
4. Data on file, PRB#8154-1, Biogen, Inc., November 20, 1997.

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BIOGEN®

CANADA

3 Robert Speck Parkway, Suite 300, Mississauga, Ontario L4Z 2G5

Increases to 4.5 mg bid (9 mg/day) and then 6 mg bid (12 mg/day) should also be based on good tolerability of the current dose and should only be considered after a minimum of two weeks treatment at that dose level. The maximum dose should not exceed 6 mg bid (12 mg/day). Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects. If adverse effects (e.g. nausea, vomiting, abdominal pain, loss of appetite) are observed during treatment, the patient should be instructed to stop treatment for a few days and then restart at the same dose level, or lower, as clinically indicated. If side effects persist, the drug should be discontinued.

Special Populations: For elderly patients (>85 years old) with low body weight (especially females) or serious comorbid diseases (see **WARNINGS** and **PRECAUTIONS**), it is recommended to start treatment with less frequent dosing (1.5 mg once a day) and to escalate dosage at a slower rate than for adults.

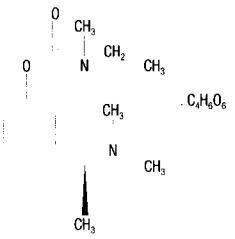
Renally or hepatically impaired: For patients with renal or hepatic impairment (see **PRECAUTIONS**) it is recommended that treatment be started with less frequent dosing (1.5 mg once a day) and that dose escalation be slower than that recommended for adults. EXELON should be taken with food in divided doses in the morning and evening. In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

PHARMACEUTICAL INFORMATION

Trade Name: EXELON

Common Name: (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenylcarbamate hydrogen-(2R,3R)-tartrate, also referred to as (+)(S)-N-Ethyl-3[(1-dimethyl-amino)ethyl] - N-methyl-phenylcarbamate hydrogen tartrate. The optical rotation of the base is (-); the optical rotation of the (+) hydrogen tartrate salt is (+).

Structural Formula:



Molecular Formula: $C_{14}H_{22}N_2O_2$ hydrogen tartrate
Molecular Weight: 400.43
Description: White to off-white, fine crystalline powder
Melting Point: 123.0-127.0°C
Solubilities: Very soluble in water, soluble in ethanol and acetonitrile, slightly soluble in n-octanol and very slightly soluble in ethyl acetate.
pK_a in n-octanol/phosphate buffer solution at pH 7: 8.85
Composition of EXELON: Each hard gelatin capsule contains 1.5, 3.0, 4.5, or 6.0 mg of rivastigmine base. Inactive ingredients are: hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; silicon dioxide; hard gelatin capsules contain: gelatin, titanium dioxide and red and/or yellow iron oxides.
Storage Requirements: Store at room temperature (below 30°C).

AVAILABILITY OF DOSAGE FORM

EXELON (rivastigmine as the hydrogen tartrate salt) is supplied as hard-gelatin capsules containing either 1.5 mg, 3.0 mg, 4.5 mg, or 6.0 mg of rivastigmine base.
The 1.5 mg capsules are yellow. The strength (1.5 mg) and "EXELON" are printed in red on the body of the capsule. Available in bottles of 60.
The 3.0 mg capsules are orange. The strength (3 mg) and "EXELON" are printed in red on the body of the capsule. Available in bottles of 60.
The 4.5 mg capsules are red. The strength (4.5 mg) and "EXELON" are printed in white on the body of the capsule. Available in bottles of 60.
The 6.0 mg capsules are orange and red. The strength (6 mg) and "EXELON" are printed in red on the body of the capsule. Available in bottles of 60.

Product Monograph available on request.

*Registered trademark

EXE-00-06-4980E

NOVARTIS Novartis Pharmaceuticals Canada Inc.
Dorval, Québec H9S 1A9

Member R&D PAAB

See pages A-4, A-5

See page OBC

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Queen's UNIVERSITY

FACULTY POSITIONS: The Department of Medicine, Queen's University invites applications for geographic full-time Neurologist appointments in the Division of Neurology. These individuals will assist the Division in fulfilling the academic and clinical missions of Neurology within the Queen's Health Sciences Centre.

STROKE NEUROLOGIST We are seeking candidates with special interest and training in the field of stroke. The successful candidate will have experience or training in acute stroke care and/or the operation of a stroke program. He/she will have a major responsibility as Medical Director of the Regional Stroke Program at Kingston General Hospital, including leading the clinical research program in stroke. Infrastructure support will be available to facilitate the clinical program and numerous opportunities exist for collaboration with other stroke-related disciplines.

EPILEPSY NEUROLOGIST There is also a position for a Neurologist with special interest and expertise in the field of epilepsy. The candidate will have a primary role in the clinical and research programs in epilepsy. This includes direction of the regional epilepsy clinic and working with regional facilities in the management of patients with epilepsy. The successful

geographic full-time Neurologist appointments in the Division of Neurology. These individuals will assist the Division in fulfilling the academic and clinical missions of Neurology within the Queen's Health Sciences Centre.

OGIST We are seeking candidates with special interest and training in the field of stroke. The ill have experience or training in acute stroke care and/or the operation of a stroke program. He/she will ility as Medical Director of the Regional Stroke Program at Kingston General Hospital, including leading ogram in stroke. Infrastructure support will be available to facilitate the clinical program and numerous collaboration with other stroke-related disciplines.

LOGIST There is also a position for a Neurologist with special interest and expertise in the field of e will have a primary role in the clinical and research programs in epilepsy. This includes direction of the c and working with regional facilities in the management of patients with epilepsy. The successful ls in EEG interpretation. Expertise in intensive EEG monitoring and pre-surgical evaluation of epilepsy

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es are encouraged to apply; however Canadians and permanent residents will be given priority. Queen's d to employment equity and welcomes applications from all qualified candidates, including women, le with disabilities and visible minorities. Successful candidates must be eligible for licensure in Ontario. hould send a curriculum vitae and the names and addresses of three referees to: Dr. D. G. Brunet, Head, Department of Medicine, Rm 3041 Etherington Hall, Queen's University, Kingston, Ontario, : (613) 533-6695, Email: koenn@post.queensu.ca

Queen's UNIVERSITY

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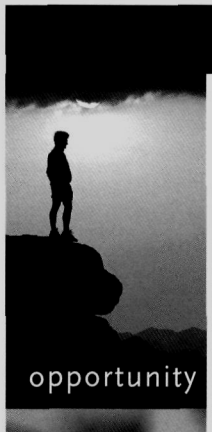

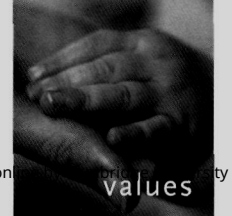

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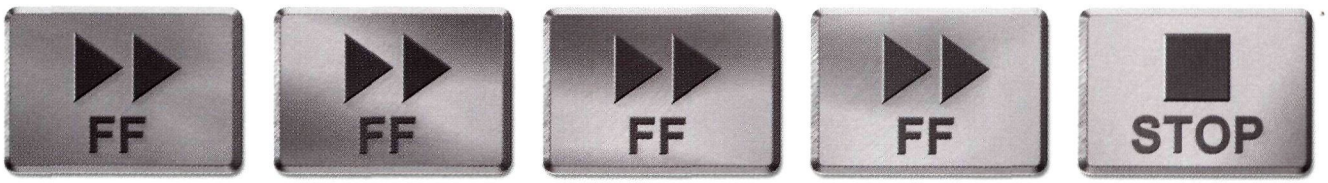

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IMITREX®
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- 340,000,000 migraine attacks treated worldwide[1]
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  * Onset of action: 10–15 min. subcutaneous, 15 min. nasal spray, 30 min. tablet.
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- Established tolerability profile[2]‡
- Flexible formats for fast relief[2]

† Multicentre, multinational open-label study of 288 patients receiving single oral doses of IMITREX® 100 mg. Efficacy was measured as reduction in headache pain from severe or moderate (grade 3 or 2) to mild or no pain (grade 1 or 0).

‡ The most common adverse events with Imitrex 100 mg p.o. were: nausea (11% vs. 5.8% for placebo), malaise/fatigue (9.5% vs. 5.1% for placebo), and sensations (body region unspecified) (9% vs. 4.5% for placebo).

IMITREX® (sumatriptan succinate/sumatriptan) is a selective 5-HT_1 receptor agonist indicated for the acute treatment of migraine attacks with or without aura. 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.

IMITREX® is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular symptoms, 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.

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For brief prescribing information see pages A-24, A-25

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Exelon can make a difference in patients with Alzheimer Disease

The only dual-acting cholinesterase inhibitor†

EXELON can help enhance cholinergic activity in the brain by inhibiting acetylcholinesterase. In addition, EXELON also inhibits butyrylcholinesterase.

Proven efficacy†† in 3 key domains – the ABCs of Alzheimer Disease

Activities of Daily Living were maintained or improved with a mean difference of more than 3 points vs. placebo on the PDS ($p<0.05$).[1,‡]

Behaviour and other parameters of global functioning assessed on the CIBIC-Plus were significantly improved vs. placebo ($p<0.05$).[2,§]

Cognitive function was maintained or enhanced by a mean difference of almost 5 points vs. placebo on the ADAS-Cog ($p<0.001$).[3,¶]

Now, EXELON can help many of your patients with Alzheimer Disease look forward to staying at home a while longer.

EXELON (rivastigmine as the hydrogen tartrate salt) is indicated for the symptomatic treatment of mild to moderate dementia of the Alzheimer type.

The most common side effects associated with EXELON therapy are generally mild and of short duration, occur mainly in the titration phase, and usually subside with continued treatment. During maintenance therapy, the most common side effects at doses of 6-12 mg/day were nausea (15%), vomiting (14%) and dizziness (10%).

EXELON has not been studied in controlled clinical trials for longer than 6 months. There is no evidence that rivastigmine alters the course of the underlying dementing process.

† Comparative clinical significance has not been established
†† Based on EXELON dosages of 6-12 mg/day
‡ Double-blind, randomized, placebo-controlled, international multicentre clinical trial; n=725. PDS=Progressive Deterioration Scale.
§ Pooled results from three prospective, randomized, double-blind, placebo-controlled, international multicentre clinical trials; n=2126. CIBIC-Plus=Clinician Interview-Based Impression of Change Scale.
¶ Prospective, randomized, double-blind, placebo-controlled, clinical trial; n=699. ADAS-Cog= Alzheimer Disease Assessment Scale, Cognitive Subscale.

1. Rösler M, Anand R, Cicin-Sain A, et al. BMJ 1999;318:633-40.
2. Schneider LS, Anand R, Farlow MR. Intl J Ger Psychopharm 1998;Suppl(1):S1-S34.
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4. Exelon Product Monograph, April 13, 2000, Novartis Pharmaceuticals Canada Inc.

Product Monograph available upon request.

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