Interferon beta-1a

Rebif®

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

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTIONS AND CLINICAL PHARMACOLOGY

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

Interferon beta-1a acts through various mechanisms:

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

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

Relapsing-Remitting Multiple Sclerosis

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

PRISMS STUDY

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

The main criteria for inclusion were:

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

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

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

Effect on exacerbation

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

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

The results after one year of treatment were also significant.

Effect on time to first progression in disability

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

Effect on multiple sclerosis pathology as detected by MRI scans

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

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

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

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

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

Effect on exacerbation (High-EDSS cohort)

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

*Log-linear model.

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

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

*Excludes patients lost to follow-up without progression.

Progression in disability: statistical comparisons

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

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

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

*ANOVA on the ranks.

Number of T2 Active Lesions (High-EDSS cohort)

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

*ANOVA on the ranks.

CROSS-OVER STUDY

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

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

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

Six-months observation vs six-months treatment:

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

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

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

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

Study	# patients/ % previously treated	# lesions treated	Treatment	Results
1	25/80%	3	0.12 or 3.67 mcg of Rebif® /lesion, or placebo, 3 times per week for 3 weeks	Rebif® at a dose of 3.67 mcg/ lesion is efficacious, as evidenced by the induction of complete disappearance of lesions and the reduction in the area of lesions. The 0.12 mcg dose of Rebif® did not show advantages over placebo treatment.
2	109/72%	6	3.67 mcg of Rebif® /lesion, or placebo, 3 times per week for 3 weeks	There was a significant increase in Major Response rate at Month 3 in patients who received Rebif® vs placebo (p<0.0001). The Complete Response rate at Month 3 was significantly in favour of patients who received Rebif® (p=0.0162).
3	100/52%	8	3.67 mcg of Rebif® /lesion, or placebo, 3 times per week for 3 weeks	For the Israeli centre, the results from Week 6, supported by those from study Day 19 demonstrate the efficacy of Rebif®. Because of the study design and the non-compliance with the study protocol at the German centre, indications of efficacy were not supported by the results from the analyses where patients from both centres were pooled.
4	124/72%	6	3.67 mcg of Rebif® /lesion, or placebo, 3 times per week for 3 weeks	This study showed that Rebif® was effective with the proportion of patients achieving a complete or Partial Response at Day 19 and Week 6, and a significant reduction in the total area of lesions on Day 19 and Week 6. Because of the study design, the effect of Rebif® at Month 3 was not demonstrated.

INDICATIONS AND CLINICAL USE

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

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

Laboratory Tests

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

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

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

ADVERSE REACTIONS

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

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

	Placebo	Rebif® 66 mcg weekly	Rebif® 132 mcg weekly
Adverse Events			
Injection site disorders (all)	**38.5**	**89.9**	**92.4**
Upper respiratory tract infections	**65.0**	**75.1**	**74.5**
Headache	62.6	64.6	70.1
Flu-like symptoms	51.3	56.1	58.7
Fatigue	35.8	32.8	41.3
Depression	27.8	20.6	23.9
Fever	**15.5**	**24.9**	**27.7**
Back pain	21.4	19.6	23.4
Myalgia	19.8	24.9	25.0
Nausea	23.0	24.9	24.5
Insomnia	21.4	19.6	23.4
Diarrhoea	18.7	17.5	19.0
Laboratory Test Abnormalities			
Lymphopenia	11.2	20.1	28.8
Leukopenia	3.7	12.7	22.3
Granulocytopenia	3.7	11.6	15.2
AST increase	3.7	10.1	17.4
ALT increase	4.3	19.6	27.2

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

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

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

Body System	Preferred term	Placebo (n=187)	Rebif® 66 mcg weekly (n=189)	Rebif® 132 mcg weekly (n=184)
Application Site Disorders	Injection site inflammation (a)(b)	15.0%	65.6%	65.8%
	Injection site reaction (a)(b)	13.4%	31.2%	34.8%
	Injection site pain (b)	14.4%	20.1%	22.8%
Body as a Whole - General Disorders	Influenza-like symptoms	51.3%	56.1%	58.7%
	Fatigue	35.8%	32.8%	41.3%
	Fever (a)(b)	15.5%	24.9%	27.7%
	Leg pain	14.4%	10.1%	13.0%
	Rigors(b)(c)	5.3%	6.3%	13.0%
Centr & Periph Nervous System Disorders	Headache	62.6%	64.6%	70.1%
	Dizziness	17.6%	14.3%	16.3%
	Paraesthesia	18.7%	19.6%	16.3%
	Hypoaesthesia	12.8%	12.2%	7.6%
Respiratory System Disorders	Rhinitis	59.9%	52.4%	50.5%
	Upper Resp Tract Infection	32.6%	36.0%	29.3%
	Pharyngitis (b)	38.5%	34.9%	28.3%
	Coughing	21.4%	14.8%	19.0%
	Bronchitis	9.6%	10.6%	9.2%
Gastro-Intestinal System Disorders	Nausea	23.0%	24.9%	24.5%
	Abdominal pain	17.1%	22.2%	19.6%
	Diarrhoea	18.7%	17.5%	19.0%
	Vomiting	12.3%	12.7%	12.0%
Musculo-Skeletal System Disorders	Back pain	19.8%	23.3%	24.5%
	Myalgia	19.8%	24.9%	25.0%
	Arthralgia	17.1%	15.3%	19.0%
	Skeletal pain	10.2%	14.8%	9.8%
Psychiatric Disorders	Depression	27.8%	20.6%	23.9%
	Insomnia	21.4%	19.6%	23.4%
White Cell & Res Disorders	Lymphopenia (a)(b)	11.2%	20.1%	28.6%
	Leucopenia (a)(b)(c)	3.7%	12.7%	22.3%
	Granulocytopenia (a)(b)	3.7%	11.6%	15.2%
	Lymphadenopathy	8.0%	11.1%	12.0%
Skin & Appendages Disorders	Pruritus	11.8%	9.0%	12.5%
Liver & Biliary System Disorders	SGPT increased (a)(b)	4.3%	19.6%	27.2%
	SGOT increased (a)(b)(c)	3.7%	10.1%	17.4%
Urinary System Disorders	Urinary tract infection	18.7%	18.0%	16.8%
Vision Disorders	Vision abnormal	7.0%	7.4%	13.0%
Secondary Terms	Fall	16.0%	16.9%	15.8%

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

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

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

Percentage of patients positive for neutralizing antibodies

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

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

Condyloma acuminata

Most common adverse events for patients treated for Condyloma acuminatum

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

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

DOSAGE AND ADMINISTRATION:

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

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

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

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

Reconstitution Table

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

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

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

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

Reconstitution Table

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

COMPOSITION

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

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

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

Liquid formulation

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

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

STABILITY AND STORAGE RECOMMENDATIONS

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

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

RECONSTITUTED SOLUTIONS

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

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

PARENTERAL PRODUCTS

See "Preparation of Solution" for table of reconstitution.

AVAILABILITY OF DOSAGE FORM

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

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

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

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

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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**.)

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 receiving hemodialysis treatments may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function. As with all patients, the titration schedule should be guided by clinical outcome (i.e. seizure control, avoidance of side effects) with the knowledge that patients with known renal impairment may require a longer time to reach steady-state at each dose. (See **DOSAGE AND ADMINISTRATION**.)

Decreased Hepatic Function

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

Information for Patients

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

Effects on Ability to Drive and Use Machines

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

Drug Interactions

Antiepileptic Drugs

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

The effect of topiramate on steady-state pharmacokinetics of phenytoin may be related to the frequency of phenytoin dosing. A slight increase in steady-state phenytoin plasma concentrations was observed, primarily in patients receiving phenytoin in two divided doses. The slight increase may be due to the saturable nature of phenytoin pharmacokinetics and inhibition of phenytoin metabolism ($CYP2C_{mp}$).

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)

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

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

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Table 3

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

Gastrointestinal: nausea, diarrhea, abdominal pain, constipation

Body as a Whole - General Disorders: fatigue

Urinary System: renal calculus

Skin and Appendages: rash

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

Geriatrics

See **PRECAUTIONS** section.

Patients with Renal Impairment

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

Patients Undergoing Hemodialysis

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

Patients with Hepatic Disease

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

AVAILABILITY OF DOSAGE FORMS

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

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

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

15 mg: "TOP" and "15 mg" on the side.
25 mg "TOP" and "25 mg" on the side.

Supplied: Bottles of 60 tablets with desiccant.
Bottles of 60 capsules without desiccant.

TOPAMAX is a Schedule F Drug.

Product Monograph available to physicians and pharmacists upon request.

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

Date of Issuance: April 2000
TXP1001013A

See pages A-4, A-5, A-20, A-21

IMITREX®
SUMATRIPTAN SUCCINATE
SUMATRIPTAN NASAL SPRAY

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

THERAPEUTIC CLASSIFICATION
Migraine Therapy

PHARMACOLOGIC CLASSIFICATION
5-HT_1 Receptor Agonist

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

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

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

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

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

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

* Statistically significant

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

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

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

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

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

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

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

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

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

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.** Product Monograph of ™IMITREX® (sumatriptan succinate/ sumatriptan); GlaxoSmithKline Inc. July 5, 2001. **2.** Cady R, McNeal S, O'Quinn S, Putman G. Effect of early intervention with sumatriptan on migraine pain: Retrospective analyses of data from three clinical trials. *Clinical Therapeutics* 2000;22(9):1035-1048.

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See page IBC

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PrCOPAXONE®
(glatiramer acetate injection)

20 mg, single use vials and 20 mg/1.0 mL, pre-filled syringes for Subcutaneous Injection

THERAPEUTIC CLASSIFICATION Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

COPAXONE® [glatiramer acetate for injection (formerly known as copolymer-1)] is a sterile, lyophilized mixture of synthetic polypeptides containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine with an average molar fraction of 0.141, 0.427, 0.095 and 0.338, respectively.

The mechanism(s) by which glatiramer acetate exerts its effect on Multiple Sclerosis (MS) is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in animals that is generally accepted as an experimental model of MS.

Studies in animals and *in vitro* systems suggest that upon its administration glatiramer acetate specific suppressor T cells are induced and activated in the periphery.

Because the immunological profile of glatiramer acetate remains to be fully elucidated, concerns exist about its potential to alter naturally occurring immune responses (see **PRECAUTIONS**).

Pharmacokinetics: Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support the assumption that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Nevertheless, larger fragments of glatiramer acetate can be recognized by glatiramer acetate reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some, may enter the systemic circulation intact.

Clinical Studies: The efficacy of COPAXONE® (glatiramer acetate for injection) was evaluated in two placebo-controlled trials in patients with Relapsing-Remitting MS (RR-MS). In a third placebo-controlled study the effects of glatiramer acetate on MRI parameters were assessed. In these studies, a dose of 20 mg/day was used. No other dose or dosing regimen has been studied in placebo-controlled trials of RR-MS.

The first trial was a pilot study Trial 1 (Trial BR-I) which was conducted at a single-center and was a double-blind, randomized, matched-pair, parallel group placebo-controlled trial.[15] Fifty patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n=25) or placebo (n=25) subcutaneously. The protocol-specified primary outcome measure was the proportion of patients who were relapse free during the 2-year duration of the trial, but two additional relevant outcomes were also specified as endpoints: frequency of attacks during the trial, and the change in the number of attacks compared to the rate of attacks in the 2 years prior to study entry. Results from this study (see Table 1) show that there was a statistically significant effect of glatiramer acetate on number of relapses.

TABLE 1 – Trial BR-1: Efficacy Results

Outcome	Trial I[a]		
	Glatiramer acetate n=25	Placebo n=25	p-Value
% Relapse Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate compared to pre-study	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

[a] The primary efficacy measure for **Trial I** was the proportion of patients who were relapse free during the 2 year duration of the trial (% **Relapse Free**). Analyses were based on the intent-to-treat population.

* Progression defined as an increase of at least 1 point on the DSS that persists for at least 3 consecutive months.

Trial II (01-9001) was a multicenter double-blind, randomized, placebo-controlled trial. Two hundred and fifty-one patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n=125) or placebo (n=126) subcutaneously.[16] Patients were diagnosed with RR-MS by standard criteria, and had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients had a score of no more than 5 on the Kurtzke Expanded Disability Scale Score (EDSS), a standard scale ranging from 0 (normal) to 10 (death due to MS). A score of 5 is defined as one at which a patient is still ambulatory but for whom full daily activities are impaired due to disability, a score of 6 is defined as one at which the patient is still ambulatory but requires assistance and a score of 7 on this scale means that the patient requires a wheelchair.

Patients were seen every 3 months for 2 years, as well as within several days of a presumed exacerbation. In order for an exacerbation to be confirmed, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the lesion for at least 48 hours).

The protocol-specified primary outcome measure was the mean number of relapses during treatment. Table 2 shows results of the analysis of primary as well as several secondary outcome measures at two years based on the intent-to-treat population.

TABLE 2 – Core (24-month) Double-Blind Study: Effect on Relapse Rate

Outcome	Trial II[a]		
	Glatiramer acetate n=125	Placebo n=126	p-Value
Mean No. of Relapses/2 years[b]	1.19	1.68	0.055
% Relapse Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Patients Progression Free[c]	98/125 (78%)	95/126 (75%)	0.48
Mean Change in EDSS	-0.05	+0.21	0.023

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

[b] Baseline adjusted mean.

[c] Progression defined as an increase of at least 1 point on the EDSS that persists for at least 3 consecutive months.

The effects of glatiramer acetate on relapse severity were not evaluated in either trial.

Both studies showed a beneficial effect of glatiramer acetate on relapse rate, and on this basis glatiramer acetate is considered effective.

The third study (9003) was a multi-national, multi-center, MRI-monitored study. A total of 239 patients with RR-MS (119 on glatiramer acetate and 120 on placebo) were randomized. Inclusion criteria were similar to those in Trial II (Study 01-9001) with the additional criteria that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated initially in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over nine months. Other MRI parameters were assessed as secondary endpoints. Table 3 summarizes the results for the parameters monitored during the nine-month double-blind phase for the intent-to-treat cohort. Because the link between MRI findings and the clinical status of patients is contentious, the prognostic value of the following statistically significant findings is unknown.

TABLE 3 – Nine-Month Double-Blind Phase: MRI Endpoints – Results

No.	Outcome	Glatiramer acetate n=113	Placebo n=115	p-Value
Primary Endpoint				
1.	Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	12	17	0.0037
Secondary Endpoints				
2.	Medians of the Cumulative Number of New T1 Gd-Enhancing Lesions	9	14	0.0347
3.	Medians of the Cumulative Number of New T2 Lesions	5	8	0.01
4.	Medians of the Cumulative Change from Baseline in volumes (mL) of T1 Gd-Enhancing Lesions	-0.309	0	0.0248
5.	Medians of the Cumulative Change from Baseline in volumes (mL) of T2 Lesions	8.852	13.566	0.0229
6.	Medians of the Cumulative Change from Baseline in volumes (mL) of T1 Hypointense Lesions	1.642	1.829	0.7311
7.	Proportion of T1 Gd-Enhancing Lesion-Free Patients	46.4%	32.2%	0.0653

The mean number of relapses in this 9-month study was 0.50 for the COPAXONE® group and 0.77 for the placebo group (p=0.0077).

INDICATIONS AND CLINICAL USE

For use in ambulatory patients with Relapsing-Remitting Multiple Sclerosis to reduce the frequency of relapses.

The safety and efficacy of COPAXONE® in chronic progressive MS have not been established.

CONTRAINDICATIONS

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

WARNINGS

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

Symptoms of Potentially Cardiac Origin: Approximately 26% of COPAXONE® patients in the pre-marketing multicenter controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain (see **ADVERSE REACTIONS: Chest Pain**). While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**), many did not. The pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New York Heart Association Class I and II) and thus the risks associated with COPAXONE® treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown.

COPAXONE® has been associated with an Immediate Post-Injection Reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**).

COPAXONE® has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE® in such patients.

Anaphylactoid reactions associated with the use of COPAXONE® have been reported in rare instances (<1/1000) during the post-marketing period. Some cases required treatment with epinephrine and other appropriate medical treatment.

PRECAUTIONS

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

Considerations Involving the Use of a Product Capable of Modifying Immune Responses: COPAXONE® is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. Whether COPAXONE® can alter normal human immune responses, such as the recognition of foreign antigens is unknown. It is therefore possible that treatment with COPAXONE® may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done. Continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled clinical trial of 125 RR-MS patients given glatiramer acetate 20 mg for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype – and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested. Nevertheless, anaphylaxis can be associated with the administration of almost any foreign substance and, therefore, this risk cannot be excluded.

Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats do not suggest any evidence of carcinogenic potential related to glatiramer acetate administered subcutaneously at dose levels of up to 30 mg/kg/day in rats and 60 mg/kg/day in mice (see **TOXICOLOGY: Carcinogenicity**). The relevance of these findings for humans is unknown (see **PRECAUTIONS: Considerations Involving the Use of a Product Capable of Modifying Immune Responses**).

Drug Interactions: Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with Interferon beta. However, 246 patients who failed on or who did not tolerate therapy with Interferon beta and were later treated with COPAXONE® within the framework of an open clinical trial did not report any serious or unexpected adverse events thought to be related to treatment.

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

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

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

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

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

ADVERSE REACTIONS

In the pre-marketing clinical trials, approximately 900 individuals have received at least one dose of COPAXONE® (glatiramer acetate for injection) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE® in clinical trials ranged from 6 months (693 patients) to 2 years (306 patients), and to over 7 years (69 patients) at a daily dose of 20 mg.

In controlled clinical trials, the most commonly observed adverse events associated with the use of COPAXONE® which occurred at a higher frequency than in placebo treated patients were: injection site reactions, vasodilation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety and hypertonia.

Of a total of 844 patients who could be evaluated for safety, approximately 8% discontinued treatment due to an adverse event. The adverse events most commonly associated with discontinuation were: injection site reaction (6.5%), vasodilation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness and tremor. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE® treatment included a case of life-threatening serum sickness.

Immediate Post-Injection Reaction: Approximately 10% of Multiple Sclerosis patients exposed to COPAXONE® in pre-marketing studies reported a post-injection reaction immediately following subcutaneous injection of COPAXONE®. Symptoms experienced could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria. These symptoms were invariably transient, self-limited, did not require specific treatment and in general, arose several months after initiation of treatment, although they may occur earlier in the course of treatment. A given patient may experience one or several episodes of these symptoms during treatment with COPAXONE®. Whether these episodes are mediated by an immunologic or non-immunologic mechanism, and whether several similar episodes seen in a given patient have identical mechanisms is unknown. In fact, whether or not this constellation of symptoms actually represents a specific syndrome is unknown. During the post-marketing period, there have been reports of patients with similar symptoms who received emergency medical care (see **WARNINGS**).

Chest Pain: Approximately 26% of glatiramer acetate patients in the multicenter pre-marketing controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. There has been only one episode of chest pain during which a full ECG was performed; the ECG showed no evidence of ischemia. Patients in clinical trials were free of significant cardiovascular disease (New York Heart Association Class I or II); therefore, the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown (see **WARNINGS: Symptoms of Potentially Cardiac Origin**).

Table 4 lists the adverse experiences after up to 35 months of treatment (> 27-33 months: COPAXONE®, n=84; Placebo, n=75; > 33 months: COPAXONE®, n=12; Placebo, n=24) in the pre-marketing multicenter placebo-controlled study (Trial II) in relapsing-remitting Multiple Sclerosis patients that occurred at an incidence of at least 2% among patients who received COPAXONE® and at an incidence that was at least 2% more than that observed in the same trial for placebo patients regardless of their causal relationship to treatment. No laboratory adverse experiences that met these criteria were reported.

It should be noted that the figures cited in Table 4 cannot be used to predict the incidence of side effects during the course of usual medical practice, where patient characteristics and other factors differ from those that prevailed in the clinical trials. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

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TABLE 4
Pre-marketing Controlled Trial in Patients with Multiple Sclerosis
Adverse Experiences ≥ 2% Incidence and ≥ 2% Above Placebo

	COPAXONE® n=125		Placebo n=126	
Adverse Experience	**n**	**%**	**n**	**%**
Body as a Whole				
Injection Site Pain	83	66.4	46	36.5
Asthenia	81	64.8	78	61.9
Injection Site Erythema	73	58.4	17	13.5
Injection Site Pruritus	48	38.4	5	4.0
Flu syndrome	38	30.4	34	27.0
Injection Site Inflammation	35	28.0	9	7.1
Back pain	33	26.4	28	22.2
Chest pain	33	26.4	13	10.3
Injection Site Mass	33	26.4	10	7.9
Injection Site Induration	25	20.0	1	0.8
Injection Site Welt	19	15.2	5	4.0
Neck pain	16	12.8	9	7.1
Face Edema	11	8.8	2	1.6
Injection Site Urticaria	9	7.2	0	0
Injection Site Hemorrhage	8	6.4	4	3.2
Chills	5	4.0	1	0.8
Cyst	5	4.0	1	0.8
Injection Site Reaction	4	3.2	1	0.8
Injection Site Atrophy	3	2.4	0	0
Abscess	3	2.4	0	0
Cardiovascular				
Vasodilatation	34	27.2	14	11.1
Palpitation	14	11.2	6	4.8
Migraine	9	7.2	5	4.0
Syncope	8	6.4	4	3.2
Digestive				
Nausea	29	23.2	22	17.5
Vomiting	13	10.4	7	5.6
Anorexia	6	4.8	3	2.4
Gastroenteritis	6	4.8	2	1.6
Oral Moniliasis	3	2.4	0	0
Tooth Caries	3	2.4	0	0
Hemic and Lymphatic				
Lymphadenopathy	23	18.4	12	9.5
Ecchymosis	15	12.0	12	9.5
Metabolic and Nutritional				
Peripheral Edema	14	11.2	7	5.6
Weight gain	7	5.6	0	0
Edema	5	4.0	1	0.8
Musculo-Skeletal				
Arthralgia	31	24.8	22	17.5
Nervous System				
Hypertonia	44	35.2	37	29.4
Tremor	14	11.2	7	5.6
Agitation	7	5.6	4	3.2
Confusion	5	4.0	1	0.8
Nystagmus	5	4.0	2	1.6
Respiratory				
Rhinitis	29	23.2	26	20.6
Dyspnea	23	18.4	8	6.4
Bronchitis	18	14.4	12	9.5
Skin and Appendages				
Sweating	15	12.0	10	7.9
Erythema	8	6.4	4	3.2
Skin Disorder	5	4.0	2	1.6
Skin Nodule	4	3.2	1	0.8
Wart	3	2.4	0	0
Special Senses				
Ear Pain	15	12.0	12	9.5
Eye Disorder	8	6.4	1	0.8
Urogenital System				
Urinary Urgency	20	16.0	17	13.5
Vaginal Moniliasis	16	12.8	9	7.1
Dysmenorrhea	12	9.6	9	7.1
Unintended Pregnancy	4	3.2	0	0
Impotence	3	2.4	0	0

Other events which occurred in at least 2% of patients but were present at equal or greater rates in the placebo group included: *Body as a whole:* Headache, injection site ecchymosis, accidental injury, abdominal pain, allergic rhinitis and malaise. *Digestive System:* Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth. *Musculo-Skeletal:* Myasthenia and myalgia. *Nervous System:* Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign, abnormal thinking, twitching, euphoria, and sleep disorder. *Respiratory System:* Pharyngitis, sinusitis, increased cough and laryngitis. *Skin and Appendages:* Acne, alopecia, and nail disorder. *Special Senses:* Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness. *Urogenital System:* Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender related differences. No clinically significant differences were identified. In these clinical trials 92% of patients were Caucasian, which is representative of the population of patients with Multiple Sclerosis. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE®. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE® and placebo groups in blinded clinical trials. No patient receiving COPAXONE® withdrew from any trial due to abnormal laboratory findings.

Other Adverse Events Observed During All Clinical Trials

COPAXONE® has been administered to approximately 900 individuals during clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using COSTART II dictionary terminology. All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and other events which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients. **Body as a whole:** *Frequent:* Injection site edema, injection site atrophy, abscess and injection site hypersensitivity. *Infrequent:* Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma and photosensitivity reaction. **Cardiovascular:** *Frequent:* Hypertension. *Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension and varicose veins. **Digestive:** *Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discolouration and duodenal ulcer. **Endocrine:** *Infrequent:* Goiter, hyperthyroidism, and hypothyroidism. **Gastrointestinal:** *Frequent:* Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis. **Hemic and Lymphatic:** *Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly. **Metabolic and Nutritional:** *Infrequent:* Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma. **Musculoskeletal:** *Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis. **Nervous:** *Frequent:* Abnormal dreams, emotional lability, and stupor. *Infrequent:* Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression and transient stupor. **Respiratory:** *Frequent:* Hyperventilation, hay-fever. *Infrequent:* Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration. **Skin and Appendages:** *Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy and warts. *Infrequent:* Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash. **Special Senses:** *Frequent:* Visual field defect. *Infrequent:* Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss. **Urogenital:** *Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious Papanicolaou smear, urinary frequency and vaginal hemorrhage. *Infrequent:* Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, breast pain, carcinoma cervix *in situ*, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Adverse Events Reported Post-Marketing and Not Previously Noted in Clinical Trials

Post-marketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE® (glatiramer acetate for injection) not mentioned above, that have been received since market introduction and that may have or not have causal relationship to the drug include the following:

Body as a whole: Sepsis, LE syndrome, hydrocephalus, enlarged abdomen, injection site hypersensitivity, allergic reaction, anaphylactoid reaction, bacterial infection, fever, infection. **Cardiovascular:** Thrombosis, peripheral vascular disease, pericardial effusion, myocardial infarct, deep thrombophlebitis, coronary occlusion, congestive heart failure, cardiomyopathy cardiomegaly, arrhythmia, angina pectoris, tachycardia. **Digestive:** Tongue edema, stomach ulcer hemorrhage, liver function abnormality, liver damage, hepatitis, eructation, cirrhosis of the liver, cholelithiasis, diarrhea, gastrointestinal disorder. **Hemic and Lymphatic:** Thrombocytopenia, lymphoma-like reaction, acute leukemia. **Metabolic and Nutritional:** Hypercholesteremia. **Musculoskeletal:** Rheumatoid arthritis, generalized spasm. **Nervous:** Myelitis, meningitis, CNS neoplasm, cerebrovascular accident, brain edema, abnormal dreams, aphasia, convulsion, neuralgia, anxiety, foot drop, nervousness, speech disorder, vertigo. **Respiratory:** Pulmonary embolus, pleural effusion, carcinoma of lung, hay fever, laryngismus. **Skin and Appendages:** Herpes simplex, pruritis, rash, urticaria. **Special Senses:** Glaucoma, blindness, visual field defect. **Urogenital:** Urogenital neoplasm, urine abnormality, ovarian carcinoma, nephrosis, kidney failure, breast carcinoma, bladder carcinoma, urinary frequency.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose with COPAXONE® has been reported in three patients. One patient injected four doses (80 mg total) of COPAXONE® at once. No sequelae were noted. Two other patients, a 28-year old male and a 37-year old female, were given 3 injections of 20 mg of COPAXONE® at one half hour intervals by error. Neither patient evidenced any change in blood pressure, heart rate, or temperature. Telephone follow-up several hours later produced no report of adverse experiences from either patient.

DOSAGE AND ADMINISTRATION

COPAXONE® should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Multiple Sclerosis.

The recommended dose of COPAXONE® (glatiramer acetate for injection or glatiramer acetate injection) for the treatment of relapsing-remitting MS is a daily injection of 20 mg given subcutaneously.

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

For the pre-filled syringe of COPAXONE®, please see the **INFORMATION FOR THE PATIENT: pre-filled syringe** for instructions on the preparation and injection of COPAXONE®.

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Glatiramer acetate

Chemical Name: Glatiramer acetate is the acetate salt of synthetic polypeptides.

Description: Glatiramer acetate is prepared by chemically reacting the activated derivatives of four amino acids: L-glutamic acid (L-Glu), L-alanine (L-Ala), L-tyrosine (L-Tyr), and L-lysine (L-Lys) in a specified ratio. The molar fraction of each amino acid residue ranges as follows: L-Glu 0.129-0.153, L-Ala 0.392-0.462, L-Tyr 0.086-0.100 and L-Lys 0.300-0374.

Structural Formula: Poly[L-Glu$^{13\text{-}15}$, L-Ala$^{39\text{-}46}$, L-Tyr$^{8.6\text{-}10}$, L-Lys$^{30\text{-}37}$]•nCH$_3$CO$_2$H (n=15-24)

Molecular Weight: The average molecular weight of the polypeptide is between 4,700 and 11,000 daltons, with at least 68 percent of the material within the range of 2,500 to 22,500 daltons.

Physical Form: White to slightly yellowish lyophilized material.

Solubility: Sparingly soluble in water, insoluble in acetone.

pH: The pH of a 0.5% w/v solution of glatiramer acetate in water is in the range of 5.5-8.0.

Composition: COPAXONE® (glatiramer acetate for injection) is a sterile, lyophilized drug product, intended for subcutaneous injection following reconstitution with Sterile Water for Injection. Each vial of lyophilized drug product contains 20 mg glatiramer acetate, plus a 2 mg overage to allow for losses in reconstitution and transfer, and 40 mg mannitol. Each vial of Sterile Water for Injection contains 1.1 mL of Sterile Water for Injection plus a 0.35 mL overage to allow for losses in reconstitution and transfer.

COPAXONE® (glatiramer acetate injection) is a single-use 20 mg/1.0 mL pre-filled syringe containing a sterile solution equivalent with the COPAXONE® reconstituted solution (i.e., 20 mg/mL glatiramer acetate and 40 mg mannitol in sterile water for injection).

Stability and Storage Recommendations: Vials of lyophilized COPAXONE® should be stored under refrigeration (2° - 8°C). COPAXONE® may also be stored at room temperature (15° - 30°C) for up to 14 days. The vials of diluent (Sterile Water for Injection) should be stored at room temperature.

The pre-filled syringes of COPAXONE® should be refrigerated immediately upon receipt (between 2° - 8°C). DO NOT FREEZE. If you cannot have refrigerator storage, pre-filled syringes of COPAXONE® can be stored at room temperature (15° - 30°C) for up to one week. Do not store pre-filled syringes at room temperature for longer than one week. Note: this drug is light sensitive, do not expose to light when not injecting. Each pre-filled syringe is for single use only.

Reconstituted Solutions: To reconstitute lyophilized COPAXONE®, prior to injection, use a sterile syringe and adapter to transfer the diluent supplied, Sterile Water for Injection, into the COPAXONE® vial. Gently swirl the vial of COPAXONE® and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist if it contains particulate matter. Soon after the product is completely dissolved, withdraw 1.0 mL of the solution into a sterile syringe. Remove the adapter, connect a 27-gauge needle and inject the solution subcutaneously. A vial is suitable for single use only; unused portions should be discarded. The reconstituted solution should not be left longer than 8 hours at room temperature.

Parenteral Products: COPAXONE® should be reconstituted only with the provided diluent, Sterile Water for Injection.

Vial Size	Volume of Diluent to be Added	Volume to be Injected	Nominal Concentration per mL
2 mL	1.1 mL	1.0 mL	20 mg

AVAILABILITY OF DOSAGE FORMS

COPAXONE® (glatiramer acetate for injection) is supplied as a 20 mg dose of sterile lyophilized glatiramer acetate with mannitol, packaged in single use 2 mL amber vials. A separate vial, containing 1.1 mL of diluent (Sterile Water for Injection) plus 0.35 mL of overage of diluent is included in the Self Injection Administration Package for each vial of drug. COPAXONE® (glatiramer acetate for injection) is available in packs of 32 amber vials of sterile lyophilized material for subcutaneous injection. The diluent (Sterile Water for Injection) for COPAXONE® is supplied in packs of 32 clear vials and is located in the Self Injection Administration Package.

COPAXONE® (glatiramer acetate injection) is a single-use 20 mg/1.0 mL pre-filled syringe containing a sterile solution equivalent with the COPAXONE® reconstituted solution (i.e., 20 mg/mL glatiramer acetate and 40 mg mannitol in sterile water for injection). COPAXONE® (glatiramer acetate injection) is available in packs of 30 single-use 20 mg/1.0 mL pre-filled glass syringes with 33 alcohol preps (swabs).

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1. Becton Dickinson. Prefilled Syringes: Market Research and End-Users' Perceptions. 1998. **2.** Erich and Lavidge Marketing Research Firm. Copaxone Time and Motion Study, Conventional Reconstitution vs. Pre-Filled Syringe. Jan 2002. **3.** Johnson KP, Brooks BR, Cohen JA et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: Results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurol* 1995;45:1268-1276. **4.** Bornstein MB, Miller A, Slagle S et al. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. *New Engl J Med* 1987;317:408-414. **5.** Khan O, Tselis A, Kamholz J et al. A prospective, open-label treatment trial to compare the effect of IFN ß-1a (Avonex®), IFN ß-1b (Betaseron®), and glatiramer acetate (Copaxone®) on the relapse rate in relapsing-remitting multiple sclerosis: results after 18 months of therapy. *Multiple Sclerosis* 2001;7:349-353. **6.** Miller A, Shapiro S, Gershtein R et al. Treatment of multiple sclerosis with Copolymer-1 (Copaxone®): Implicating mechanisms of Th1 to Th2/Th3 immune deviation. *J Neuroimmunol* 1998;92:113-121. **7.** Comi G, Filippi M, Wolinsky JS and the European/Canadian Glatiramer Acetate Study Group. European/Canadian Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Effects of Glatiramer Acetate on Magnetic Resonance Imaging-Measured Disease Activity and Burden in Patients with Relapsing Multiple Sclerosis. *Ann Neurol* 2001;49:290-297. **8.** COPAXONE® (glatiramer acetate) Product Monograph, Teva Neuroscience.

Product monograph available upon request.

TEVA NEUROSCIENCE

Teva Neuroscience
999 de Maisonneuve Blvd. West, Suite 550
Montreal, Quebec H3A 3L4

PAAB

See page A-25

ALTACE® ramipril

PHARMACOLOGIC CLASSIFICATION:
Angiotensin Converting Enzyme Inhibitor

ACTION AND CLINICAL PHARMACOLOGY
ALTACE (ramipril) is an angiotensin converting enzyme (ACE) inhibitor, which is used in the treatment of essential hypertension, and following acute myocardial infarction in stabilized patients with clinically confirmed heart failure.

Following oral administration, ALTACE is rapidly hydrolyzed to ramiprilat, its principal active metabolite.

Angiotensin-converting enzyme catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE activity leads to decreased levels of angiotensin II thereby resulting in decreased vasoconstriction and decreased aldosterone secretion. The latter decrease may result in a small increase in serum potassium (see PRECAUTIONS). Decreased levels of angiotensin II and the accompanying lack of negative feedback on renal renin secretion result in increases in plasma renin activity.

ACE is identical to kininase II. Thus, ramipril may also block the degradation of the vasodepressor peptide bradykinin, which may contribute to its therapeutic effect.

Pharmacokinetics and Metabolism
Following oral administration, ramipril is rapidly absorbed with peak plasma concentrations occurring within 1 hour. The extent of absorption of ramipril is 50-60% and is not significantly altered by the presence of food in the gastrointestinal tract, although the rate of absorption is reduced. Following absorption, ramipril is rapidly hydrolyzed in the liver to its active metabolite, ramiprilat. Peak plasma concentrations of ramiprilat are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat is 56%.

Ramipril is almost completely metabolized to the active metabolite ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive. After oral administration of ALTACE, about 60% of the parent drug and its metabolites is excreted in the urine, and about 40% is found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Plasma concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose-proportional. The 24-hour AUC for ramiprilat, however, is dose-proportional over the recommended dose range. The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44% respectively when 5 mg of oral ramipril was compared to 5 mg given intravenously.

Plasma concentrations of ramiprilat decline in a triphasic manner. The initial rapid decline, which represents distribution of the drug, has a half-life of 2-4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows two elimination phases. The apparent elimination phase has a half-life of 9-18 hours, and the terminal elimination phase has a prolonged half-life of >50 hours. After multiple daily doses of ramipril 5-10 mg, the half-life of ramiprilat concentrations was 13-17 hours, but was considerably prolonged at 2.5 mg (27-36 hours).

After once daily dosing, steady state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are higher than those seen after the first dose of ALTACE especially at low doses (2.5 mg).

The urinary excretion of ramipril, ramiprilat, and their metabolites is reduced in patients with impaired renal function. In patients with creatinine clearance <40 mL/min/1.73 m^2, increases in C_{max} and AUC of ramipril and ramiprilat compared to normal subjects were observed following multiple dosing with 5 mg ramipril (see DOSAGE AND ADMINISTRATION).

In patients with impaired liver function, plasma ramipril levels increased about 3-fold, although peak concentrations of ramiprilat in these patients were not different from those seen in patients with normal hepatic function.

A single dose pharmacokinetic study conducted in a limited number of elderly patients indicated that peak ramiprilat levels and the AUC for ramiprilat are higher in older patients (see PRECAUTIONS).

Pharmacodynamics
Administration of ALTACE to patients with mild to moderate essential hypertension results in a reduction of both supine and standing blood pressure usually with little or no orthostatic change or change in heart rate. Symptomatic postural hypotension is infrequent, although this may occur in patients who are salt- and/or volume-depleted (see WARNINGS).

In single dose studies, doses of 5-20 mg of ALTACE lowered blood pressure within 1-2 hours, with peak reductions achieved 3-6 hours after dosing. At recommended doses given once daily, antihypertensive effects have persisted over 24 hours.

The effectiveness of ALTACE appears to be similar in the elderly (over 65 years of age) and younger adult patients given the same daily doses.

In studies comparing the same daily dose of ALTACE given as a single morning dose or as a twice daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

While the mechanism through which ALTACE lowers blood pressure appears to result primarily from suppression of the renin-angiotensin-aldosterone system, ALTACE has an anti-hypertensive effect even in patients with low-renin hypertension.

The antihypertensive effect of angiotensin-converting enzyme inhibitors is generally lower in black patients than in non-blacks.

The antihypertensive effect of ALTACE and thiazide diuretics used concurrently is greater than that seen with either agent used alone.

Abrupt withdrawal of ALTACE has not resulted in rapid increase in blood pressure.

The effects of ramipril were assessed in patients who were at high risk for cardiovascular events, but did not have left ventricular dysfunction or heart failure. Heart Outcome Prevention Evaluation (HOPE) study included 9,297 patients older than 55 years of age with a history of coronary artery disease, stroke, peripheral vascular disease or diabetes mellitus plus at least one additional cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria). Patients were excluded if they had heart failure, low ejection fraction (<0.40), were taking an angiotensin converting enzyme inhibitor or vitamin E, had uncontrolled hypertension or overt nephropathy, or had had a myocardial infarction or stroke within four weeks before the study began. The patients were randomly assigned to receive ramipril 10 mg once daily or matching placebo for a mean of five years.

Due to the positive outcome the study was terminated prematurely by an independent monitoring board. The primary end point, the composite of death from cardiovascular causes, myocardial infarction and stroke was reached by a total of 651 ramipril treated patients (14%), as compared to 826 placebo treated patients (17.8%) (relative risk, 0.78; p<0.001). When analyzed separately, the rates of individual component of the composite primary outcome in patients treated with ramipril and placebo were as follows: death from cardiovascular causes 6.1% vs. 8.1% (RR 0.74, p<0.001), myocardial infarction 9.9% vs. 12.3% (RR 0.80, p<0.001) and stroke 3.4% vs. 4.9% of patients (RR 0.68, p<0.001), respectively.

Permanent discontinuation of treatment occurred in 28.9% of the ramipril treated patients versus 27.3% of placebo treated patients. The reasons for stopping the treatment, where the incidence was greater in the ramipril than in the placebo group, were cough (ramipril 7.3%, placebo 1.8%), hypotension/dizziness (ramipril 1.9%, placebo 1.5%) and edema (ramipril 0.4%, placebo 0.2%).

INDICATIONS AND CLINICAL USE: *Essential Hypertension.* Treatment of essential hypertension. It may be used alone or in association with thiazide diuretics.

ALTACE should normally be used in patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects.

ALTACE can also be tried as an initial agent in those patients in whom use of diuretics and/or beta-blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of ALTACE in renovascular hypertension have not been established and therefore, its use in this condition is not recommended.

The safety and efficacy of concurrent use of ALTACE with antihypertensive agents other than thiazide diuretics have not been established.

Treatment Following Acute Myocardial Infarction
ALTACE is indicated following acute myocardial infarction in clinically stable patients with signs of left ventricular dysfunction to improve survival and reduce hospitalizations for heart failure.

Sufficient experience in the treatment of patients with severe (NYHA class IV) heart failure immediately after myocardial infarction is not yet available. (See WARNINGS – Hypotension.)

MANAGEMENT OF PATIENTS AT INCREASED RISK OF CARDIOVASCULAR EVENTS: ALTACE may be used to reduce the risk of myocardial infarction, stroke or cardiovascular death in patients over 55 years of age who are at high risk of cardiovascular events because of a history of coronary artery disease, stroke, peripheral artery disease, or diabetes that is accompanied by at least one other cardiovascular risk factor such as hypertension, elevated total cholesterol levels, low high density lipoprotein levels, cigarette smoking, or documented microalbuminuria.

The incidence of the primary outcome (composite of myocardial infarction, stroke and death from cardiovascular causes) was reduced from 17.8% in the placebo-treated group to 14.0% in the ramipril-treated group (see ACTION AND CLINICAL PHARMACOLOGY).

GENERAL: In using ALTACE consideration should be given to the risk of angioedema (see WARNINGS).

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected ALTACE should be discontinued as soon as possible (see WARNINGS – Use in Pregnancy, and INFORMATION FOR THE PATIENT).

CONTRAINDICATIONS: ALTACE (ramipril) is contraindicated in patients who are hypersensitive to this drug, or to any ingredient in the formulation, or in those patients who have a history of angioedema.

WARNINGS: *Angioedema*: Angioedema has been reported in patients with ACE inhibitors, including ALTACE (ramipril). Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioe-dema of the face, tongue, or glottis occurs, ALTACE should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension: Symptomatic hypotension has occurred after administration of ALTACE, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with ALTACE should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of ALTACE is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response may not be a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion in hypertensive patients. However, lower doses of ALTACE and/or reduced concomitant diuretic therapy should be considered. *In patients receiving treatment following acute myocardial infarction, consideration should be given to discontinuation of ALTACE (see ADVERSE REACTIONS – Treatment Following Acute Myocardial Infarction, DOSAGE AND ADMINISTRATION – Treatment Following Acute Myocardial Infarction).*

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ALTACE cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease.

Use in Pregnancy: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ALTACE should be discontinued as soon as possible.

PRECAUTIONS: Renal Impairment: *As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.*

Use of ALTACE should include appropriate assessment of renal function.

ALTACE should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.

Anaphylactoid Reactions during Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid Reactions during Desensitization: There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Hyperkalemia and Potassium-Sparing Diuretics: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with ALTACE. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see PRECAUTIONS – Drug Interactions).

Surgery/Anesthesia: In patients undergoing surgery or anesthesia with agents producing hypotension, ALTACE may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it may be corrected by volume repletion.

Aortic Stenosis: There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Patients with Impaired Liver Function: Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with ALTACE (see ADVERSE REACTIONS). Should the patient receiving ALTACE experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of ALTACE should be considered when appropriate. There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ALTACE should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Pediatric Use: The safety and effectiveness of ALTACE in children have not been established; therefore use in this age group is not recommended.

Use in Elderly: Although clinical experience has not identified differences in response between the elderly (>65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics).

Patient Alertness: ALTACE may lower the state of patient alertness and/or reactivity, particularly at the start of treatment (see ADVERSE REACTIONS).

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of ALTACE, has been reported. Such possibility should be considered as part of the differential diagnosis of cough.

Drug Interactions: Diuretic therapy: Hypotension may result but can be minimized by discontinuing diuretic or increasing salt intake prior to ramipril treatment and/or reducing initial dose. Agents increasing serum potassium: Use potassium sparing diuretics with caution and monitor frequently. Agents causing renin release: ALTACE antihypertensive effect increased. Lithium: Lithium levels may be increased. Administer lithium with caution and monitor levels frequently. Antacids: The bioavailability of ALTACE and the pharmacokinetics of ramiprilat were not affected. Digoxin: No change in ramipril, ramiprilat or digoxin serum levels. Warfarin: The co-administration of ALTACE with warfarin did not alter the anticoagulant effects. Acenocoumarol: No significant changes. Non-steroidal anti-inflammatory agents (NSAID): The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of NSAIDs (*e.g. indomethacin*).

ADVERSE REACTIONS: *Essential Hypertension.* Serious adverse events *occurring in North American placebo-controlled clinical trials with* ALTACE monotherapy in hypertension (n=972) were: hypotension (0.1%); myocardial infarction (0.3%); cerebrovascular accident (0.1%); edema (0.2%); syncope (0.1%). Among all North American ALTACE patients (n=1,244), angioedema occurred in patients treated with ALTACE and a diuretic (0.1%).

The most frequent adverse events occurring in these trials with ALTACE monotherapy in hypertensive patients (n=651) were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%); nausea (1.8%); peripheral edema (1.8%); somnolence (1.7%); impotence (1.5%); rash (1.4%); arthritis (1.1%); dyspnea (1.1%). Discontinuation of therapy due to clinical adverse events was required in 5 patients (0.8%).

In placebo-controlled trials, an excess of upper respiratory infection and flu syndrome was seen in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ALTACE patients, with about 4% of these patients requiring discontinuation of treatment. Approximately 1% of patients treated with ALTACE monotherapy in North American controlled clinical trials (n=972) have required discontinuation because of cough.

Treatment Following Acute Myocardial Infarction

Adverse events (except laboratory abnormalities) in a controlled clinical trial of post-AMI patients with clinical signs of heart failure considered possibly/probably related to ALTACE and occurring in more than 1% of stabilized patients (n=1,004) were: hypotension (10.7%); increased cough (7.6%); dizziness/vertigo (5.6%); nausea/vomiting (3.8%); angina pectoris (2.9%); postural hypotension (2.2%); syncope (2.1%); heart failure (2.0); severe/resistant heart failure (2.0%); myocardial infarct (1.7%); vomiting (1.6%); headache (1.2%); abnormal kidney function (1.2%); abnormal chest pain (1.1%); diarrhea (1.1%).

Isolated cases of death have been reported with the use of ramipril that appear to be related to hypotension (including first dose effects), but many of these are difficult to differentiate from progression of underlying disease (see WARNINGS – Hypotension). Discontinuation of therapy due to adverse reactions was required in 368/1,004 post-AMI patients taking ramipril (36.7%), compared to 401/982 patients receiving placebo (40.8%).

Clinical Laboratory Test Findings: increased creatinine; increases in blood urea nitrogen (BUN); decreases in hemoglobin or hematocrit; hyponatraemia; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; proteinuria and significant increases in serum potassium.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available regarding overdosage of ALTACE (ramipril) in humans. Two cases of overdosage have been reported.

In the case of an overdose with ramipril, the most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion with normal saline. It is not known if ramipril or ramiprilat can be removed from the body by hemodialysis.

DOSAGE AND ADMINISTRATION

Essential Hypertension: Dosage of ALTACE (ramipril) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with ALTACE may need to be adjusted.

Monotherapy: The recommended initial dosage of ALTACE in patients not on diuretics is 2.5 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range is 2.5 to 10 mg once daily. A daily dose of 20 mg should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ALTACE.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of ALTACE and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with ALTACE to reduce the likelihood of hypotension (see WARNINGS). If the diuretic cannot be discontinued, an initial dose of 1.25 mg ALTACE should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of ALTACE should subsequently be titrated (as described above) to the optimal response.

Use in Renal Impairment: For patients with a creatinine clearance below 40 mL/min/ 1.73 m^2 (serum creatinine above 2.5 mg/dL), the recommended initial dose is 1.25 mg ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg. In patients with severe renal impairment (creatinine clearance below 10 mL/min/1.73 m^2) the maximum total daily dose of 2.5 mg ALTACE should not be exceeded.

Treatment Following Acute Myocardial Infarction:

Initiation of therapy requires consideration of concomitant medication and baseline blood pressure and should be instituted under close medical supervision, usually in a hospital, three to ten days following an acute myocardial infarction in haemodynamically stable patients with clinical signs of heart failure.

The recommended initial dosage of ALTACE is 2.5 mg given twice a day (b.i.d.), one in the morning and one in the evening. If tolerated, and depending on the patient's response, dosage may be increased by doubling at intervals of one to three days. The maximum daily dose of ALTACE should not exceed 5 mg twice daily (b.i.d). After the initial dose of ALTACE, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If a patient becomes hypotensive at this dosage, it is recommended that the dosage be lowered to 1.25 mg b.i.d. following effective management of the hypotension. (see WARNINGS – Hypotension).

Patients who have been fluid or salt depleted, or treated with diuretics are at *an increased risk of hypotension (see WARNINGS – Hypotension).* An excessive fall in blood pressure may occur particularly in the following: after the initial dose of ALTACE; after every first increase of dose of ALTACE; after the first dose of a concomitant diuretic and/or when increasing the dose of the concomitant diuretic. If appropriate, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension (see PRECAUTIONS – Drug Interactions). Consideration should be given to reducing the initial dose to 1.25 mg of ALTACE in these patients.

Use in Renal Impairment: In patients with impaired renal function (creatinine clearance of 20-50mL/min/1.73 m^2 body surface area), the initial recommended dosage is generally 1.25 mg of ALTACE once daily. This dosage may be increased with caution up to 1.25 mg of ALTACE twice daily, depending upon clinical response and tolerability.

Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and severe renal failure. (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism, PRECAUTIONS – Renal Impairment).

Use in Hepatic Impairment: Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and hepatic dysfunction. Dose reduction and careful monitoring of these patients is required (see ACTIONS AND CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism, PRECAUTIONS – Patients with Impaired Liver Function).

Management of Patients at Increased Risk of Cardiovascular Events: Recommended initial dose: 2.5 mg of ALTACE once daily. Depending on the tolerability, the dose is gradually increased. It is recommended to double the dose after one week of treatment and – after another three weeks – to increase it to 10 mg. Usual maintenance dose: 10 mg of ALTACE daily (see ACTION AND CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Dosage recommendations for special risk groups such as patients with renal or hepatic impairment, or at an increased risk of hypotension (fluid or salt depletion, treated with diuretics) are to be followed as previously described (SEE WARNINGS and PRECAUTIONS).

PHARMACEUTICAL INFORMATION

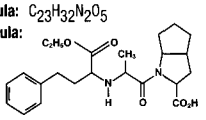
I. DRUG SUBSTANCE

Proper name: Ramipril

Chemical name: 2-[N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-(1S,3S,5S)-2-azabicyclo[3.3.0]octane-3-carboxylic acid

Empirical formula: $C_{23}H_{32}N_2O_5$

Structural formula:



Molecular weight: 416.52

Description: A white to off-white crystalline powder with a melting point of 105°C to 112°C. Slightly soluble in water and freely soluble in ethanol and methanol.

II. DOSAGE FORM

a) Composition

ALTACE (ramipril) capsules 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg contain the medicinal ingredient ramipril in quantities of 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg respectively.

The qualitative formulation for all potencies of ALTACE is: ramipril, pregelatinized starch NF (as filler, gliding agent and disintegration agent) and empty gelatin capsules.

Empty gelatin capsules for all potencies of ALTACE are composed of gelatin NF and coloring agents specific to each potency (see below).

POTENCY	CAP	BODY
1.25 mg	Yellow iron oxide Titanium dioxide	Titanium dioxide
2.5 mg	Yellow iron oxide FD & C red no. 3 Titanium dioxide	Titanium dioxide
5.0 mg	FD & C blue no. 2 FD & C red no. 3 Titanium dioxide	Titanium dioxide
10.0 mg	FD & C blue no. 2 FD & C red no. 3 Black iron oxide Titanium dioxide	Titanium dioxide

b) Stability and storage recommendations

Store ALTACE (ramipril) in original container at room temperature, below 25°C and not beyond the date indicated on the container.

AVAILABILITY: No. 4 hard gelatin capsules:

- 1.25 mg (white/yellow);
- 2.5 mg (white/orange);
- 5 mg (white/red);
- 10 mg (white/blue).

ALTACE capsules 1.25 mg, 2.5 mg, 5 mg and 10 mg are packaged in cartons of 30 (2 x 15 blister-packed) capsules.

Product monograph available upon request.

References:

1. ALTACE Product Monograph. **2.** The Heart Outcomes Prevention Evaluation Study Investigators (HOPE) Trial. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342(3):145-53.

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Brief Prescribing Information

BETASERON®

Interferon beta-1b

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

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

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

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

INDICATIONS AND CLINICAL USE

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

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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Nervous System		
Dizziness	28%	35%
Hypertonia	24%	26%
Depression	24%	25%
Anxiety	13%	15%
Nervousness	5%	8%
Somnolence	3%	6%
Confusion	2%	4%
Speech disorder	1%	3%
Convulsion	0%	2%
Hyperkinesia	0%	2%
Amnesia	0%	2%
Respiratory System		
Sinusitis	26%	36%
Dyspnea*	2%	8%
Laryngitis	2%	6%
Skin and Appendages		
Sweating*	11%	23%
Alopecia	2%	4%
Special Senses		
Conjunctivitis	10%	12%
Abnormal vision	4%	7%
Urogenital System		
Dysmenorrhea	11%	18%
Menstrual disorder*	8%	17%
Metrorrhagia	8%	15%
Cystitis	4%	8%
Breast pain	3%	7%
Menorrhagia	3%	6%
Urinary urgency	2%	4%
Fibrocystic breast	1%	3%
Breast neoplasm	0%	2%
Cardiovascular System		
Vasodilatation	4%	6%
Peripheral vascular disorder	5%	5%
Chest pain	4%	5%
Migraine	3%	4%
Hypotension	4%	2%
Hypertension*	2%	4%
Palpitation	3%	2%
Syncope	3%	2%
Hemorrhage	2%	2%
Tachycardia	1%	2%
Digestive System		
Nausea	13%	13%
Constipation	12%	12%
Diarrhea	10%	7%
Gastroenteritis	5%	6%
Vomiting	6%	4%
Dysphagia	5%	4%
Gastrointestinal disorder	5%	4%
Tooth disorder	4%	4%
Dyspepsia	4%	4%
Anorexia	2%	4%
Fecal incontinence	3%	2%
Liver function test abnormal	1%	3%
Gastritis	2%	2%
Flatulence	1%	3%
Sore throat	1%	2%
Colitis	2%	0%
Gastrointestinal pain	0%	2%
Gingivitis	0%	2%
Hemic and Lymphatic System		
Leukopenia*	5%	10%
Anemia	5%	2%
Ecchymosis	2%	1%
Lymphadenopathy	1%	3%
Injection Site		
Injection site reaction*	10%	46%
Injection site inflammation*	4%	48%
Injection site pain	5%	9%
Injection site necrosis*	0%	5%
Injection site hemorrhage	2%	2%
Metabolic and Nutritional Disorders		
Peripheral edema	7%	7%
Weight loss	3%	2%
SGPT increased	2%	2%
Hypercholesteremia	2%	1%
Musculoskeletal System		
Myasthenia	40%	39%
Arthralgia	20%	20%
Myalgia*	9%	23%
Bone fracture (not spontaneous)	5%	3%
Muscle cramps	3%	3%
Spontaneous bone fracture	3%	3%
Arthritis	1%	2%
Joint disorder	1%	2%
Nervous System		
Headache	41%	47%
Neuropathy	41%	38%
Paresthesia	39%	35%
Hypertonia*	31%	41%
Abnormal gait	34%	34%
Depression	31%	27%
Ataxia	23%	19%
Dizziness	14%	14%
Incoordination	13%	11%
Insomnia	8%	12%
Vertigo	12%	8%
Emotional lability	11%	8%
Paralysis	10%	8%
Somnolence	8%	8%
Tremor	9%	6%
Sweating increased	6%	6%
Neuralgia	7%	5%
Movement disorder	6%	5%
Sleep disorder	5%	6%
Anxiety	5%	6%
Hypesthesia	4%	6%
Nervousness	3%	4%
Speech disorder	5%	2%
Dysarthria	4%	2%
Spastic paralysis	1%	3%
Convulsion	2%	2%
Hyperesthesia	2%	2%
Amnesia	3%	1%
Dry mouth	2%	1%
Hemiplegia	2%	1%
Thinking abnormal	2%	1%
Myoclonus	2%	0%
Respiratory System		
Rhinitis	32%	28%
Pharyngitis	20%	16%
Bronchitis	12%	9%
Cough increased	10%	5%
Sinusitis	6%	6%
Pneumonia	5%	5%
Dyspnea	2%	3%
Upper respiratory tract infection	2%	3%
Asthma	2%	1%
Voice alteration	2%	1%
Skin and Appendages		
Rash*	12%	20%
Pruritus	6%	6%
Skin disorder	4%	4%
Eczema	4%	2%
Herpes simplex	2%	3%
Alopecia	2%	2%
Acne	2%	2%
Dry skin	3%	1%
Subcutaneous hematoma	3%	1%
Breast pain	2%	1%
Herpes zoster	2%	1%
Seborrhea	2%	1%
Special Senses		
Abnormal vision	15%	11%
Amblyopia	10%	7%
Diplopia	9%	7%
Eye pain	5%	4%
Otitis media	3%	2%
Conjunctivitis	3%	2%
Eye disorder	2%	3%
Deafness	3%	1%
Optic neuritis	2%	2%
Ear disorder	2%	1%
Tinnitus	2%	1%
Urogenital System		
Urinary tract infection	25%	22%
Urinary incontinence	15%	8%
Urinary tract disorder	10%	7%
Cystitis	9%	7%
Urinary urgency	7%	8%
Menstrual disorder	13%	9%
Increased urinary frequency	5%	6%
Metrorrhagia	6%	12%
Urinary retention	6%	4%
Vaginitis	4%	3%
Amenorrhea	4%	3%
Dysuria	2%	2%
Impotence	4%	7%
Menopause	4%	2%
Menorrhagia	4%	2%
Nocturia	1%	2%
Vaginal moniliasis	2%	2%
Kidney pain	2%	0%
Pyelonephritis	0%	2%
Prostatic disorder	1%	2%

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

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

2. Secondary-progressive MS: The incidence of adverse events that occurred in at least 2% of patients treated with 8 MIU BETASERON or placebo for up to three years, 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%

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

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

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

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

DOSAGE AND ADMINISTRATION FOR SUBCUTANEOUS USE ONLY

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

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

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

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

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

Withdraw 1 mL of reconstituted solution from the vial into a sterile syringe fitted with a 27-gauge ½-inch needle and inject the solution subcutaneously. Sites for self-injection include abdomen, buttocks and thighs. A vial is suitable for single use only; unused portions should be discarded (See **BETASERON® [interferon beta-1b] INFORMATION FOR THE PATIENT** section for **SELF-INJECTION PROCEDURE**.)

AVAILABILITY OF DOSAGE FORMS

BETASERON (interferon beta-1b) is presented in single-use vials of lyophilized powder containing 0.3 mg (9.6 MIU) interferon beta-1b, 15 mg Albumin Human USP, and 15 mg Mannitol, USP. BETASERON is supplied in cartons containing 15 vials of medication and 15 vials of diluent (2 mL of Sodium Chloride 0.54% solution, per vial).

Product Monograph available upon request.
B10204E5

REFERENCES:

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

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EXELON*
(rivastigmine)

(Rivastigmine as the Hydrogen Tartrate Salt)
Capsules – 1.5 mg, 3 mg, 4.5 mg, 6 mg
Oral Solution – 2 mg/mL

PHARMACOLOGICAL CLASSIFICATION Cholinesterase Inhibitor

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 and oral solution 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. EXELON is contraindicated in patients with severe liver impairment since it has not been studied in this population. **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 non-steroidal 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**). EXELON is contraindicated in patients with severe liver impairment since it has not been studied in this population (see **CONTRAINDICATIONS**). **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. acetaminophen) (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)		
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
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. **SYMPTOMS AND TREATMENT OF OVERDOSAGE Symptoms:** Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterised by severe nausea, vomiting, salivation, sweating, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bracycardia and/or syncope may also occur. **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 and oral solution 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. 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. **Oral Solution:** The prescribed amount of solution should be withdrawn from the container using the oral dosing syringe supplied. EXELON oral solution may be swallowed directly from the syringe or first mixed with a small glass of water, cold fruit juice or soda. Patients should be instructed to stir and drink the mixture. EXELON oral solution and capsules may be interchanged at equal doses. **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. **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.Oral solution (2 mg/mL): EXELON oral solution is available in amber glass bottles with a dip tube and self-aligning plug. The oral solution is packaged with a dispenser set which consists of an assembled oral dosing syringe that allows dispensing a maximum volume of 3 mL corresponding to a 6 mg dose, with a plastic tube container. Each bottle contains 120 mL of a clear, yellow solution.

Product Monograph available on request.

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ONCE-A-WEEK

AVONEX®

(Interferon beta-1a)

IM injection

PRESCRIBING INFORMATION

THERAPEUTIC CLASSIFICATION

Immunomodulator

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General

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

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

Laboratory Tests

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

Drug Interactions

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

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

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

Use in Pregnancy

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

Nursing Mothers

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

Pediatric Use

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

Information to Patients

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

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

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

ADVERSE EVENTS

The safety data describing the use of AVONEX® (Interferon beta-1a) in MS patients are based on the placebo-controlled trial in which 158 patients randomized to AVONEX® were treated for up to 2 years (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 ($p \leq 0.05$).

DOSAGE AND ADMINISTRATION

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

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

AVAILABILITY OF DOSAGE FORMS

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

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

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4. Data on file, PRB#8154-1, Biogen, Inc., November 20, 1997.

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BIOGEN®

CANADA

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Pr Reminyl*

Galantamine hydrobromide tablets

PRESCRIBING INFORMATION

PrREMINYL*

galantamine hydrobromide tablets

4 mg, 8 mg, 12 mg galantamine base

Cholinesterase Inhibitor

CLINICAL PHARMACOLOGY

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

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

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

Pharmacokinetics

Absorption

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

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

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

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

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

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

Distribution

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

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

Metabolism

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

Elimination

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

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

CYP2D6 Poor Metabolizers

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

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

Hepatic Impairment

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

Renal Impairment

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

Patients with Alzheimer's Disease

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

Gender and Race

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

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

Clinical Trials

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

Results for 2 of these studies are presented in this section. The data shown below were obtained from the Intent-To-Treat population (ITT analysis, i.e. all patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete the study, their last observation while on treatment was carried forward and used at endpoint).

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

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

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

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

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

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

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

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

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

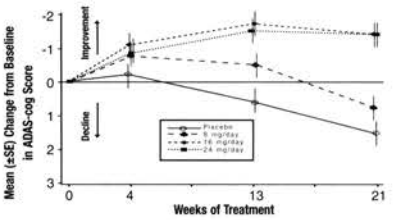
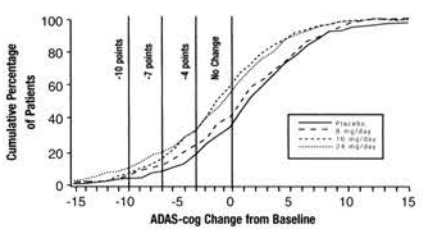


Figure 2 illustrates the cumulative percentages of patients from each of the four treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been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

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

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



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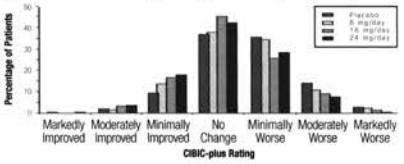
Treatment	Change in ADAS-cog			
	-10	-7	-4	0
Placebo	3.7%	7.8%	19.0%	43.9%
8 mg/day	4.5%	11.4%	22.7%	47.7%
16 mg/day	6.4%	15.0%	33.1%	67.3%
24 mg/day	8.8%	19.8%	32.4%	62.6%

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

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



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

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

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

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog score for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean difference in the ADAS-cog change scores for the REMINYL-treated patients compared to the patients on placebo were 3.2 and 2.8 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not statistically significantly different from each other.

Figure 4: Time-course of the Changes from Baseline in ADAS-cog Score (ITT Population)

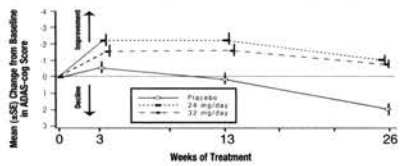
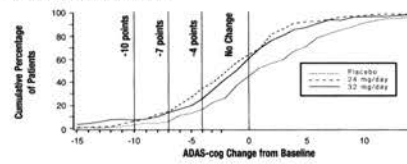


Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL groups are more likely to show the greater improvements. Curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

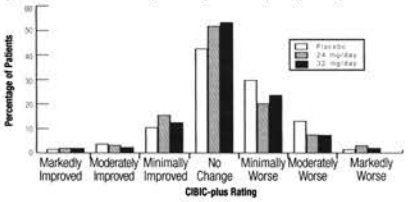
Figure 5: Cumulative Percentage of Patients with Specified Changes from Baseline in ADAS-cog Scores (ITT Population)



Treatment	Change in ADAS-cog			
	-10	-7	-4	0
Placebo	2.3%	5.6%	16.4%	45.5%
24 mg/day	5.8%	14.0%	34.3%	63.8%
32 mg/day	7.7%	13.4%	25.8%	61.2%

Effects on the CIBIC-plus: Figure 6 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups. The mean REMINYL-placebo differences for these groups of patients in the mean rating were 0.22 and 0.17 units for 24 and 32 mg/day of REMINYL, respectively. The mean ratings for both groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 6: Distribution of CIBIC-plus Ratings Week 26 (ITT Population)



Age, gender and race: Patient's age, gender or race did not predict outcome of treatment.

INDICATIONS AND CLINICAL USE

REMINYL (galantamine hydrobromide) is indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. REMINYL has not been studied in controlled clinical trials for longer than 6 months.

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

CONTRAINDICATIONS

REMINYL (galantamine hydrobromide) is contraindicated in patients with known hypersensitivity to galantamine hydrobromide, other tertiary alkaloid derivatives or to any excipients used in the formulation.

WARNINGS

Anesthesia

REMINYL (galantamine hydrobromide), as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Neurological Conditions

Seizures: In placebo-controlled trials with REMINYL, cases of seizure were reported; there was no increase in incidence compared with placebo. Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's Disease. The risk/benefit of REMINYL treatment for patients with a history of seizure disorder must therefore be carefully evaluated.

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

Pulmonary Conditions

Like other cholinomimetic drugs, REMINYL should be prescribed with care for patients with a history of asthma or obstructive pulmonary disease.

Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and heart block. These actions may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction disorders, or to patients taking other drugs concomitantly which significantly slow heart rate. In clinical trials, patients with serious cardiovascular disease were excluded. Caution should be exercised in treating patients with active coronary artery disease or congestive heart failure. It is recommended that REMINYL not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes.

In randomized controlled trials, bradycardia was reported at 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo, and it rarely led to treatment discontinuation. No increased incidence of heart block was observed at the recommended doses. Patients treated with galantamine up to 24 mg/day at the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo, 0.7% [2/286]; 4 mg b.i.d., 0.4% [3/692]; 8 mg b.i.d., 1.3% [7/552]; 12 mg b.i.d., 2.2% [6/273]).

A 6-week cardiovascular safety clinical trial (GAL-USA-16; n=139) was performed to investigate the effect of galantamine at doses up to 32 mg/day. This dosing regimen was: 8 mg/day in Week 1, 16 mg/day in Week 2, 24 mg/day in Weeks 3 and 4, and 32 mg/day in Weeks 5 and 6. Heart block/pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients. It should be noted that a forced 1-week dose escalation was used in this study, which is not recommended. Whether these cardiac effects are attenuated by slower titration rates is not known. Particular caution is warranted during titration where the majority of pauses occurred in the above study.

Gastrointestinal Conditions

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g. those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). In controlled clinical studies with REMINYL, patients with symptomatic peptic ulceration were excluded. Clinical studies of REMINYL have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see ADVERSE REACTIONS).

REMINYL, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting and diarrhea, anorexia and weight loss. These effects appeared more frequently at higher doses (see ADVERSE REACTIONS), with nausea and vomiting being more prevalent in women and patients with lower body weight and correspondingly higher plasma drug concentrations. Females are more sensitive to the cholinergic adverse effects associated with cholinesterase inhibitors and in general are more likely to experience nausea and vomiting than are males. In most cases, these effects were of mild to moderate intensity and transient and have resolved during continued REMINYL treatment or upon treatment discontinuation.

Weight Loss

Cholinesterase inhibitors as well as Alzheimer's Disease can be associated with significant weight loss. In controlled clinical trials, the use of REMINYL was associated with weight loss. Weight decrease occurred early during treatment and was related to dose. Weight loss of ≥7% occurred more frequently in patients treated with REMINYL and in female patients than in patients receiving placebo. Where weight loss may be of clinical concern, body weight should be monitored.

Genitourinary

Although not observed in clinical trials of REMINYL, cholinomimetics may cause bladder outflow obstruction.

PRECAUTIONS

Concomitant Use with Other Drugs

Use with Anticholinergics

Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors

A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Use with other Psychoactive Drugs

Few patients in the REMINYL (galantamine hydrobromide) clinical trials received neuroleptics, antidepressants or anticonvulsants, there is thus limited information concerning the interaction of REMINYL with these drugs.

Use in Patients ≥85 Years Old

In controlled clinical studies, the number of patients aged 85 years or over who received REMINYL at therapeutic doses of 16 or 24 mg/day was 123. Of these patients, 70 received the maximum recommended dose of 24 mg/day. There is limited safety information for REMINYL in this patient population.

Since cholinomimetics as well as Alzheimer's Disease can be associated with significant weight loss, caution is advised regarding the use of REMINYL in elderly patients with low body weight, especially in those ≥85 years old.

Use in Elderly Patients with Serious Comorbid Disease

There is limited information on the safety of REMINYL treatment in patients with mild to moderate Alzheimer's Disease and serious/significant comorbidity. The use of REMINYL in Alzheimer's Disease patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Dose escalation in this patient population should proceed with caution.

Renally and Hepatically Impaired Patients

There is limited information on the pharmacokinetics of REMINYL in renally and hepatically impaired patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics). It is therefore recommended that dose escalation with REMINYL in Alzheimer's Disease patients with renal impairment (creatinine clearance of 9 to 60 mL/min) or hepatic impairment be undertaken with caution and under conditions of close monitoring for adverse effects (see DOSAGE AND ADMINISTRATION, Special Populations). In patients with a creatinine clearance of less than 9 mL/min and in patients with severe hepatic impairment (Child-Pugh score of 10-15), the use of REMINYL is not recommended.

Drug-Drug Interactions

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide.

Effect of Other Drugs on the Metabolism of REMINYL

Pharmacokinetic studies to assess the potential of REMINYL for interaction with cimetidine, ranitidine, ketoconazole, erythromycin, paroxetine, warfarin and digoxin were limited to short-term, mostly single-dose studies in young healthy volunteers. Similar studies in elderly patients were not done.

In vitro

CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide, whereas CYP2D6 is involved in the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged in urine, no single pathway appears predominant.

In vivo

Cimetidine and Ranitidine: Galantamine was administered as a single dose of 4 mg on Day 2 of a 3-day treatment with either cimetidine (800 mg daily; n=6 males and 6 females) or ranitidine (300 mg daily; n=6 males and 6 females). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the pharmacokinetics of galantamine.

Ketoconazole: Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg b.i.d. for 4 days, increased the AUC of galantamine by 30% when subjects were treated with galantamine 4 mg b.i.d. for 8 days (n=8 males and 8 females).

Erythromycin: Erythromycin, a moderate inhibitor of CYP3A4 at a dose of 500 mg q.i.d. for 4 days increased the AUC of galantamine by 10% when subjects received galantamine 4 mg b.i.d. for 6 days (n=8 males and 8 females).

Paroxetine: Paroxetine, a strong inhibitor of CYP2D6, increased the AUC of 4 mg b.i.d., 8 mg b.i.d. and 12 mg b.i.d. galantamine by 40%, 45% and 48%, respectively, in 16 healthy volunteers (8 males and 8 females) who received galantamine together with 20 mg/day paroxetine.

Effect of Galantamine on the Metabolism of Other Drugs

In vitro

Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

In vivo

Warfarin: Galantamine at 12 mg b.i.d. had no effect on the pharmacokinetics of R- and S-warfarin (25 mg single dose) or on the prothrombin time (n=16 males). The protein binding of warfarin was unaffected by galantamine.

Digoxin: Galantamine at 12 mg b.i.d. had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were co-administered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia (n=8 males and 8 females).

Nicotinic Receptor Modulation

Single *in vitro* applications of galantamine dose-dependently modulate the effect on nicotinic receptors, having a positive allosteric (sensitizing) effect at concentrations below 0.28 µg/mL (1 µM) and an inhibitory effect at higher concentrations. Chronic *in vitro* or *in vivo* studies on nicotinic receptor modulation have not been conducted.

It is unknown whether galantamine has an effect on the pharmacodynamic action of other drugs that act on cholinergic nicotinic receptors (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times on an exposure [AUC] basis), and 30 mg/kg/day (12 times the MRHD on a mg/m² basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m² basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m² and AUC basis).

Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m² basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m² basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

Pregnancy

In a teratology study in which rats were dosed from Day 14 (females) or Day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the MRHD on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through Day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis.

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

Nursing Mothers

It is not known whether REMINYL is excreted in human breast milk and therefore REMINYL should not be used in nursing mothers.

Pediatric Use

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

ADVERSE REACTIONS

A total of 2287 patients with mild to moderate Alzheimer's Disease were treated with REMINYL (galantamine hydrobromide) in Phase III controlled clinical studies using either a 1-week or 4-week dose-escalation period, and 761 patients received REMINYL 24 mg/day, the maximum recommended maintenance dose. The number of patients who completed the studies was 1686 (72%). The mean duration of treatment for all REMINYL groups was 130 days (range 1-214 days).

Adverse Events Leading to Discontinuation

Overall, 19% (441/2287) of patients treated with REMINYL discontinued from Phase III controlled clinical trials due to adverse events compared to 8% (98/1159) in the placebo group. For patients treated with REMINYL, the rate of discontinuation due to adverse events was 14% for males and 22% for females.

In the 4-week dose-escalation fixed-dose study (GAL-USA-10), 8% (55/692) of patients treated with REMINYL withdrew due to adverse events compared to 7% (20/286) in the placebo group. During the dose-escalation phase of this study the incidence of discontinuations due to adverse events was 4% for placebo, 5% for REMINYL 16 mg/day and 6% for REMINYL 24 mg/day. During the maintenance phase, 4% of patients who received placebo, 3% of patients who received REMINYL 16 mg/day and 4% of patients who received REMINYL 24 mg/day withdrew from this study due to adverse events.

Table 1 shows the most frequent adverse events leading to discontinuation for study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used.

Table 1: Most frequent adverse events leading to discontinuation in a placebo-controlled, double-blind trial with a 4-week dose-escalation schedule (GAL-USA-10)

Adverse Events	Recommended 4-week dose escalation		
	Placebo n=286	16 mg/day n=279	24 mg/day n=273
Nausea	<1%	2%	4%
Vomiting	0%	1%	3%
Anorexia	<1%	1%	<1%
Dizziness	<1%	2%	1%
Syncope	0%	0%	1%

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

The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate of placebo in study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used are shown in Table 2. These events were primarily gastrointestinal and tended to occur at a lower rate with 16 mg/day, the initial recommended maintenance dose.

Table 2: Most frequent adverse events in a randomized placebo-controlled clinical trial with a 4-week dose increment during dose-escalation and maintenance phases (GAL-USA-10)

Adverse Events	Weeks 1-12†			Weeks 13-21		
	Placebo n=286	16 mg/day n=279	24 mg/day n=273	Placebo n=259	16 mg/day n=243	24 mg/day n=241
Nausea	5%	11%	13%	<1%	4%	6%
Vomiting	<1%	5%	6%	<1%	2%	6%
Diarrhea	5%	9%	4%	2%	5%	2%
Anorexia	2%	5%	5%	1%	2%	5%

† Dose escalation occurred with 4 weeks per dose increment.

The majority of these adverse events occurred during the dose-escalation period. Nausea and vomiting, the most frequent adverse events, occurred more frequently at higher doses, lasted 5-7 days in most cases, and the majority of patients had one episode. The incidence of weight loss in this study was, during dose escalation (Weeks 1-12): placebo, 1%; 16 mg/day, 3%; 24 mg/day, 2%; and during the maintenance phase (Weeks 13-21): placebo, <1%; 16 mg/day, 3%; 24 mg/day, 3%.

Dose escalation should be cautious and maintenance dosing should remain flexible and be adjusted according to individual needs.

Adverse Events Reported in Controlled Trials

The reported adverse events in REMINYL trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour and the types of patients treated may differ.

Table 3 lists the most common adverse events (adverse events occurring with an incidence of 2% with REMINYL treatment and in which the incidence was greater than with placebo treatment) for four placebo-controlled trials for patients treated with 16 or 24 mg/day of REMINYL. The combined values presented in Table 3 were derived from trials using a 1-week or the recommended 4-week dose-escalation period.

Table 3: Adverse events reported in at least 2% of patients with Alzheimer's Disease administered REMINYL and at a frequency greater than with placebo (combined 1- and 4-week dose-escalation data)

Body System / Adverse Events	Placebo (n=801)	REMINYL† (n=1040)
Body as a whole - general disorders		
Fatigue	3%	5%
Syncope	1%	2%
Central & peripheral nervous system disorders		
Dizziness	6%	9%
Headache	5%	8%
Tremor	2%	3%
Gastro-intestinal system disorders		
Nausea	9%	24%
Vomiting	4%	13%
Diarrhea	7%	9%
Abdominal pain	4%	5%
Dyspepsia	2%	5%
Heart rate and rhythm disorders		
Bradycardia	1%	2%
Metabolic and nutritional disorders		
Weight decrease	2%	7%
Psychiatric disorders		
Anorexia	3%	9%
Depression	5%	7%
Insomnia	4%	5%
Somnolence	3%	4%
Red blood cell disorders		
Anemia	2%	3%
Respiratory system disorders		
Rhinitis	3%	4%
Urinary system disorders		
Urinary tract infection	7%	8%
Hematuria	2%	3%

† Adverse events in patients treated with 16 or 24 mg/day of REMINYL in three placebo-controlled trials with a 1-week dose-escalation period and a 26-week fixed-dose REMINYL treatment, and one placebo-controlled trial with the recommended 4-week dose-escalation period and a 21-week fixed-dose REMINYL treatment are included.

No clinically relevant abnormalities in laboratory values were observed. In a cardiovascular safety clinical trial (GAL-USA-16), pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients during the dose-escalation period (see WARNINGS).

Other Adverse Events Observed During Clinical Trials

REMINYL has been administered to 3055 patients with Alzheimer's Disease during clinical trials worldwide.

A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's Disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years. To establish the rate of adverse events, data from all patients for any dose of REMINYL in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All events occurring in approximately 0.1% of patients are included, except for those already listed elsewhere in labelling, WHO terms too general to be informative, or relatively minor events. Events are classified by body system and listed using the following definitions: *frequent adverse events* - those occurring in at least 1/100 patients; *infrequent adverse events* - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to REMINYL treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole - General Disorders: *Frequent:* chest pain.

Cardiovascular System Disorders: *Frequent:* hypertension; *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure.

Central & Peripheral Nervous System Disorders: *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia.

Gastrointestinal System Disorders: *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *Rare:* esophageal perforation.

Heart Rate & Rhythm Disorders: *Infrequent:* AV block, palpitation, atrial fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T-wave inversion, ventricular tachycardia.

Metabolic & Nutritional Disorders: *Infrequent:* hyperglycemia, alkaline phosphatase increased, NPN increased.

Platelet, Bleeding & Clotting Disorders: *Infrequent:* purpura, epistaxis, thrombocytopenia.

Psychiatric Disorders: *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium.

Urinary System Disorders: *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

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

In a postmarketing report, one patient who had been taking 4 mg of galantamine daily inadvertently ingested eight 4 mg tablets (32 mg total) on the tenth day of treatment. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment. ECG obtained just prior to initiation of galantamine treatment was normal.

Treatment

REMINYL (galantamine hydrobromide) has a plasma half-life of approximately 7-8 hours. It is recommended that, in case of asymptomatic overdose, no further dose of REMINYL should be administered and the patient should be monitored.

As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the following signs of cholinergic crisis may develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Tertiary anticholinergics such as atropine may be used as an antidote for REMINYL overdosage. Intravenous atropine sulphate titrated to effect is recommended at an initial dose of 0.5 to 1.0 mg i.v., with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics. It is not known whether REMINYL and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.

Continued on page A-50

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COMTAN*
(entacapone)

Tablets, 200 mg

THERAPEUTIC CLASSIFICATION Adjunct to levodopa and DDC inhibitor/COMT-Inhibitor

ACTION AND CLINICAL PHARMACOLOGY COMTAN (entacapone) is a reversible, selective and mainly peripherally acting inhibitor of catechol-O-methyltransferase (COMT). COMTAN has no antiparkinsonian effect of its own and is designed for concomitant administration with levodopa preparations.

COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a cathecol structure. Physiological substrates of COMT include dopa, catecholamines (dopamine, norepinephrine, epinephrine) and their hydroxylated metabolites. In the presence of a decarboxylase inhibitor, COMT becomes the major enzyme which is responsible for the metabolism of levodopa to 3-methoxy-4-hydroxy-l-phenylalanine (3-OMD).

The mechanism of action of entacapone is believed to be related to its ability to inhibit COMT and thereby alter the plasma pharmacokinetics of levodopa. When administered with levodopa and a dopa decarboxylase (DDC) inhibitor (carbidopa or benserazide), entacapone decreases the degradation of levodopa in the peripheral tissues further by inhibiting the metabolism of levodopa to 3-OMD through the COMT pathway. This leads to more sustained plasma concentrations of levodopa. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain leading to greater effects on the signs and symptoms of Parkinson's Disease. The higher levodopa levels also lead to increased levodopa adverse effects, sometimes requiring a decrease in the dose of levodopa.

In animals, while entacapone enters the CNS to a minimal extent, it has been shown to inhibit central COMT activity. In humans, entacapone inhibits the COMT enzyme in peripheral tissues. The effects of entacapone on central COMT activity in humans have not been studied.

PHARMACODYNAMICS

Effect of entacapone on erythrocyte COMT activity Studies in healthy volunteers and patients with Parkinson's disease have shown that entacapone dose-dependently and reversibly inhibits human erythrocyte COMT activity after oral administration. Following single doses of 200 and 800 mg of entacapone, maximal inhibition of erythrocyte COMT activity was 64% and 82%, respectively.

Effect of entacapone on the pharmacokinetics of levodopa and its metabolites When 200 mg entacapone is administered together with levodopa/carbidopa, it increases the area under the curve (AUC) of levodopa by approximately 35% and the elimination half-life of levodopa is prolonged from 1.3 h to 2.4 h. In general, the average peak levodopa plasma concentration and the time of its occurrence (T_{max} of 1 hour) are unaffected. The onset of effect occurs after the first administration and is maintained during long-term treatment.

In a dose-response study in patients with Parkinson's disease, the maximal effect was obtained with a single dose of 200 mg entacapone. Doses of entacapone greater than 200 mg did not further improve the bioavailability of levodopa. Studies in healthy volunteers and in patients with Parkinson's disease show that entacapone dose-dependently decreases the formation of 3-OMD from levodopa. The chronic use of entacapone (200 mg, 3 to 10 times daily) in patients with Parkinson's disease, decreases the AUC of 3-OMD by 42 to 61%.

PHARMACOKINETICS AND METABOLISM OF ENTACAPONE Entacapone pharmacokinetics are linear over a dose range of 5 to 200 mg. A slight non linearity in AUC was seen at doses greater than or equal to 400 mg in a single dose, dose-response, study in patients with Parkinson's disease. The pharmacokinetics of entacapone are independent of levodopa/DDC coadministration.

Absorption There are large intra- and interindividual variations in the absorption of entacapone.

Entacapone is rapidly absorbed from the GI tract, reaching peak concentrations (C_{max}) in the plasma in approximately one hour. The drug has an extensive first-pass metabolism with bioavailability of about 35% following oral administration of a 200 mg dose. C_{max}, after a single 200 mg dose of entacapone, is approximately 1.2 µg/mL. Food does not affect the absorption of entacapone to any significant extent.

Distribution and protein binding The volume of distribution of entacapone at steady state after i.v. injection is small (20 L). Entacapone does not distribute widely into tissues due to its high plasma protein binding. Based on *in vitro* studies, the plasma protein binding of entacapone is 98% over the concentration range of 0.4 to 50 µg/mL. Entacapone binds mainly to serum albumin.

Metabolism/Elimination Entacapone undergoes extensive metabolism, mainly in the liver. The main metabolic pathway of entacapone in humans is the isomerization to the *cis*-isomer, followed by direct glucuronidation of the parent and *cis*-isomer; the glucuronide conjugate is inactive.

The elimination of entacapone occurs mainly by non-renal metabolic pathways. It is estimated that 80-90% of the dose is excreted in feces, although this has not been confirmed in man. Approximately 10-20% is excreted in urine. Only traces of entacapone are found as unchanged drug in urine. The major part (95%) of the drug excreted in urine is conjugated with glucuronic acid. Of the metabolites found in urine only about 1% have been formed through oxidation.

The total body clearance of entacapone, after i.v. administration, is about 800 mL/min. It is eliminated with a short elimination half-life; the half-life for β-phase being about 0.5 hours and for the γ-phase about 2.5 hours. The β-phase is predominant, and the γ-phase accounts for approximately 8% of the plasma-time-concentration curve (AUC) following i.v. administration.

Hepatic Impairment The metabolism of the drug is slowed in patients with mild to moderate (Child-Pugh grading Class A and B) hepatic insufficiency caused by cirrhotic disease. In these patients, the AUC and C_{max} values were approximately two-fold greater than those in demographically-matched healthy volunteers. As there is no clinical trial data to establish a safe and effective dosing regimen for hepatically impaired patients, entacapone should be not be administered to patients with hepatic impairment (see **CONTRAINDICATIONS**).

Renal Impairment The pharmacokinetics of entacapone were evaluated in healthy volunteers and in patients with moderately (Cl_{cr} 0.60 - 0.89 mL/sec/1.73 m²) and severely (Cl_{cr} 0.20 - 0.44 mL/sec/1.73 m²) impaired renal function. After a single oral dose of 200 mg, the pharmacokinetics of entacapone were not significantly changed in patients with moderate to severe renal insufficiency.

Age, gender and race Entacapone pharmacokinetics are independent of age. No formal gender studies have been conducted. Racial representation in clinical trials was largely limited to Caucasians (there were only 4 blacks in one US trial and no Asians in any of the clinical trials); no conclusions can therefore be reached about the effect of entacapone on groups other than Caucasian.

Studies Assessing Potential Drug Interactions *Effect of entacapone on the metabolism of other drugs* Protein binding: Entacapone is highly protein bound (98%). *In vitro* studies have shown that entacapone, at therapeutic concentrations, does not displace drugs of which a large proportion is bound to plasma proteins (e.g. warfarin, salicylic acid, phenylbutazone, and diazepam). On the other hand, entacapone is not markedly displaced by any of these drugs at therapeutic concentrations.

CLINICAL TRIALS The effectiveness of COMTAN as an adjunct to levodopa/DDC therapy in the treatment of Parkinson's disease was demonstrated in three separate 24-week randomized, placebo-controlled, double-blind, multicenter studies in 676 patients with mild to moderate Parkinson's disease (average Hoen and Yahr score: 1.5-3). In two of these studies (Nordic Study and North American "SEESAW" Study), the patients' disease was "fluctuating", i.e. was characterized by documented periods of "On" (periods with relatively good functioning) and "Off" (periods of relatively poor functioning), despite optimum levodopa therapy. In the third trial (German-Austrian "CELOMEN" Study) patients were not required to have been experiencing fluctuations. On average the patients evaluated had been treated with levodopa/DDC inhibitor therapy for 8.3 years and 86% were treated with other antiparkinsonian medication (dopamine agonists, selegiline, amantadine, anticholinergics) in addition to a levodopa/DDC inhibitor.

In the two studies in patients with Parkinson's disease with documented episodes of end-of-dose motor fluctuations despite optimal levodopa therapy, patients were randomized to receive placebo (n=188) or 200 mg entacapone (n=188) with each daily dose of levodopa/dopa decarboxylase inhibitor (carbidopa or benserazide; average 4 to 6 doses per day). The formal double-blind portion of both trials was 6 months. Patients recorded the time spent in the "On" and "Off" states in home diaries periodically throughout the duration of the trial. In the Nordic Study the primary outcome measure was the total mean time spent in the "On" state during an 18-hour diary recorded day, in the North American "SEESAW" study, the primary outcome measure was the proportion of awake time spent over 24 hours in the "On" state.

In addition to the primary outcome measure, as secondary measures, the amount of time spent in the "Off" state was evaluated and patients were also evaluated in subparts of the Unified Parkinson's Disease Rating Scale (UPDRS), an investigator's and patients' global assessment of clinical condition, a 7-point subjective scale designed to assess global functioning in Parkinson's Disease and for change in daily levodopa/DDC dose. Results for the primary efficacy measure for these two studies are shown in Table 1.

TABLE 1: Primary Outcome Measures: Hours of awake time "On" (Nordic Study); Percent of Awake time "On" (North American "SEESAW" study).

Nordic Study

	Placebo (n=86) Mean (± SD)	Entacapone (n=85) Mean (± SD)	Difference
Baseline*	9.2 ± 2.5	9.3 ± 2.2	
Week 8-24*†	9.4 ± 2.6	10.7 ± 2.2	1h 20 min (8.3%) $CI_{95\%}$ 45 min, 1h 56 min

North American "SEESAW" Study

	Placebo (n=102)	Entacapone (n=103)	Difference
Baseline**	60.8 ± 14.0	60.0 ± 15.2	
Week 8-24**‡	62.8 ± 16.8	66.8 ± 14.5	4.5% (0 h 35 min) $CI_{95\%}$ 0.93%, 7.97%

*daily ON time (h); †Values represent the average of weeks 8, 16 and 24, by protocol-defined outcome measure. **Proportion ON time%; ‡Values represent the average of weeks 8, 16 and 24, by protocol-defined outcome measure.

Effects on "On" time did not differ by age, weight, disease severity at baseline, levodopa dose and concurrent treatment with dopamine agonists or selegiline.

Corresponding significant decreases in "Off" time were also noted. Change from baseline in hours of awake time "Off" in the Nordic Study were: -1.3 hours for the entacapone group; 0 hours for the placebo group and in the North American "SEESAW" Study were: -1.2 hours for the entacapone group; -0.3 for the placebo group.

Withdrawal of entacapone: In the North American "SEESAW" Study, abrupt withdrawal of entacapone, without alteration of the dose of levodopa/carbidopa, resulted in significant worsening of fluctuations, compared to placebo. In some cases, symptoms were slightly worse at baseline, but returned to approximately baseline severity within two weeks following levodopa dose increase on average by 80 mg. In the Nordic Study, similarly, a significant worsening of Parkinsonian symptoms were observed after entacapone withdrawal, as assessed two weeks after drug withdrawal. At this phase the symptoms were approximately baseline severity following levodopa dose increase by about 50 mg.

In the third placebo controlled trial (Austrian-German "CELOMEN" Study), as in the other two trials, patients were randomized to receive 200 mg entacapone or placebo with each dose of levodopa/dopa decarboxylase inhibitor (up to 10 times daily). The CELOMEN study was primarily designed as a safety trial. Measures of effectiveness in this study were the UPDRS Parts II and III and total daily "On" time (see Table 2).

TABLE 2:

Outcome Measures: UPDRS and Hours of awake time "On" (Austrian-German "CELOMEN" Study).

UPDRS ADL*

	Placebo (n=104) Mean (± SD)	Entacapone (n=191) Mean (± SD)	Difference
Baseline	12.0 ± 5.8	12.4 ± 6.1	
Week 24	12.4 ± 6.5	11.1 ± 6.3	-1.35 CI_{95} -2.54, -0.16

UPDRS MOTOR*

	Placebo (n=102)	Entacapone (n=190)	Difference
Baseline	24.1 ± 12.1	24.9 ± 12.9	
Week 24	24.3 ± 12.9	21.7 ± 12.1	-2.83 CI_{95} -4.95, -0.71

Hours of Awake Time "On" (Home diary)**

	Placebo (n=60)	Entacapone (n=114)	Difference
Baseline	10.1 ± 2.5	10.2 ± 2.6	
Week 24	10.6 ± 3.0	11.8 ± 2.7	1.08 CI_{95} 0.13, 2.03

*Total population; score change at endpoint. **Fluctuating population, with 5-10 doses.

INDICATIONS AND CLINICAL USE COMTAN (entacapone) is indicated as an adjunct to levodopa/carbidopa or levodopa/benserazide preparations to treat patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing-off" (see CLINICAL PHARMACOLOGY: Clinical Trials).

COMTAN's effectiveness has not been systematically evaluated in patients with idiopathic Parkinson's Disease who do not experience end-of-dose "wearing-off".

Since COMTAN is to be used in combination with a levodopa/dopa-decarboxylase inhibitor, the prescribing information for levodopa/carbidopa and levodopa/benserazide are also applicable when COMTAN is added to the treatment regimen.

CONTRAINDICATIONS COMTAN (entacapone) is contraindicated in patients with known hypersensitivity to entacapone or to the excipients of the drug product.

COMTAN should not be given concomitantly with non-selective monoamine oxidase (MAO) inhibitors (e.g. phenelzine and tranylcypromine). The combination of selective MAO-A and selective MAO-B inhibitors is equivalent to non-selective MAO-inhibition, therefore, they should not both be given concomitantly with COMTAN and levodopa preparations. Non-selective MAO inhibitors must be discontinued at least two weeks prior to initiating therapy with entacapone.

Selective MAO-B inhibitors should not be used at higher than recommended doses (e.g. selegeline 10 mg/day) when co-administered with COMTAN (see **PRECAUTIONS**, **Drug Interactions**, Selegeline).

COMTAN is contraindicated in patients with a previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis.

COMTAN is contraindicated in patients with liver impairment.

COMTAN is contraindicated in patients with pheochromocytoma due to the increased risk of hypertensive crisis.

WARNINGS ***Drugs metabolized by Catechol-O-methyltransferase (COMT):*** When a single 400 mg dose of entacapone was given together with intravenous isoprenaline (isoproterenol) and epinephrine without coadministered levodopa/dopa decarboxylase inhibitor, the overall mean maximal changes in heart rate during infusion were about 50% and 80% higher than with placebo, for isoprenaline and epinephrine, respectively.

Therefore, drugs known to be metabolized by COMT, such as isoproterenol, epinephrine, norepinephrine, dopamine, dobutamine, alpha-methyldopa, apomorphine, isoetherine and bitolterol should be administered with caution in patients receiving entacapone regardless of the route of administration (including inhalation), as their interaction may result in increased heart rates, possibly arrhythmias, and excessive changes in blood pressure.

Ventricular tachycardia was noted in a 32 year old healthy male volunteer in an interaction study after epinephrine infusion and oral entacapone administration. Treatment with propranolol was required. A causal relationship to entacapone administration appears probable but cannot be attributed with certainty.

PRECAUTIONS Rhabdomyolysis secondary to severe dyskinesias or Neuroleptic Malignant Syndrome (NMS) has been observed rarely in patients with Parkinson's disease.

NMS, including rhabdomyolysis and hyperthermia, is characterised by motor symptoms (rigidity, myoclonus, tremor), mental status changes (e.g., agitation, confusion, coma), hyperthermia, autonomic dysfunction (tachycardia, labile blood pressure) and elevated serum creatine phosphokinase (CPK) which may be a consequence of rhabdomyolysis. In individual cases, only some of these symptoms and/or findings may be evident.

Neither NMS nor rhabdomyolysis have been reported in association with COMTAN (entacapone) treatment from controlled trials in which entacapone was discontinued abruptly. Since the introduction into the market, a rare number of cases with some similar signs and symptoms have been reported in association with COMTAN treatment. Nevertheless, because NMS has been reported rarely in Parkinson's disease patients when other dopaminergic medications were withdrawn abruptly, prescribers should exercise caution when discontinuing COMTAN treatment. When considered necessary, withdrawal should proceed slowly, and if signs and/or symptoms occur despite a slow withdrawal of entacapone, an increase in levodopa dosage may be necessary.

COMTAN enhances the effects of levodopa. Therefore, to reduce levodopa-related dopaminergic adverse effects, e.g. dyskinesias, nausea, vomiting and hallucinations, it may be necessary to adjust the levodopa dosage within the first days to first weeks following the initiation of COMTAN treatment.

COMTAN has no antiparkinsonian effect of its own and therefore should only be used as an adjunct to levodopa/carbidopa or levodopa/benserazide treatment. The warnings and precautions given for levodopa/carbidopa and levodopa/benserazide treatment should therefore be taken into account when COMTAN is used.

If COMTAN treatment is discontinued, it is necessary to adjust the dosing of other parkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the parkinsonian symptoms (see DOSAGE AND ADMINISTRATION).

Orthostatic Hypotension/Syncope COMTAN may aggravate levodopa-induced orthostatic hypotension. COMTAN should be given with caution to patients who are treated with drugs which may cause orthostatic hypotension. In controlled clinical trials approximately 1.2% of patients who received 200 mg COMTAN and 0.8% of patients treated with placebo reported at least one episode of syncope. Reports of syncope were generally more frequent in patients in both treatment groups who had an episode of documented hypotension.

Diarrhea In clinical trials, diarrhea was reported as an adverse event in 60 of 603 (10.0%) and 16 of 400 (4.0%) of patients treated with 200 mg COMTAN and placebo, respectively. In patients treated with COMTAN diarrhea was generally mild to moderate in

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severity (8.6%) but was reported as severe in 1.3%. Diarrhea resulted in withdrawal in 10 of 603 (1.7%) patients (1.2% with mild to moderate diarrhea and 0.3% with severe diarrhea). Diarrhea generally resolved after discontinuation of COMTAN. Two patients with diarrhea required hospitalization. Typically, diarrhea presents within 4 to 12 weeks after entacapone is started, but it may appear as early as the first week and as late as many months after the initiation of treatment.

Dyskinesia COMTAN may potentiate the dopaminergic side effects of levodopa and may cause and/or exacerbate preexisting dyskinesia. Although decreasing the dose of levodopa may ameliorate this side effect, many patients in controlled trials continued to experience frequent dyskinesias despite a reduction in their dose of levodopa. The rates of withdrawal for dyskinesia were 1.5% and 0.8% for 200 mg COMTAN and placebo, respectively.

Hallucinations Dopaminergic therapy in Parkinson's disease patients has been associated with hallucinations. In clinical trials, hallucinations developed in approximately 4% of patients treated with 200 mg COMTAN or placebo. Hallucinations led to drug discontinuation and premature withdrawal from clinical trials in 0.8% and 0% of patients treated with 200 mg COMTAN and placebo, respectively. Hallucinations led to hospitalization in 1.0% and 0.3% of patients in the 200 mg COMTAN and placebo groups, respectively.

Hyperpyrexia and Confusion Cases of a symptom complex resembling the neuroleptic malignant syndrome characterized by elevated temperature, muscular rigidity, altered consciousness, and elevated CPK have been reported in association with the rapid dose reduction or withdrawal of other dopaminergic drugs. Several cases with similar signs and symptoms have been reported in association with COMTAN therapy, although no information about dose manipulation is available. The complicated nature of these cases makes it difficult to determine what role, if any, COMTAN may have played in their pathogenesis. No cases have been reported following abrupt withdrawal or dose reduction of entacapone treatment during clinical studies.

Prescribers should exercise caution when discontinuing entacapone treatment. When considered necessary, withdrawal should proceed slowly. If a decision is made to discontinue treatment with COMTAN, recommendations include monitoring the patient closely and adjusting other dopaminergic treatments as needed. This syndrome should be considered in the differential diagnosis for any patient who develops a high fever or severe rigidity. Tapering COMTAN has not been systematically evaluated.

Fibrotic Complications Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot derived dopaminergic agents. These complications may resolve when the drug is discontinued, but complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, it is unknown whether other, non-ergot derived drugs (e.g., entacapone) that increase dopaminergic activity can cause them. It should be noted that the expected incidence of fibrotic complications is so low that even if entacapone caused these complications at rates similar to those attributable to other dopaminergic therapies, it is unlikely that it would have been detected in a cohort of the size exposed to entacapone. Four cases of pulmonary fibrosis were reported during clinical development of entacapone; three of these patients were also treated with pergolide and one with bromocriptine. The duration of treatment with entacapone ranged from 7 to 17 months.

Renal Toxicity In a 1-year toxicity study, entacapone (plasma exposure 20 times that in humans receiving the maximum recommended daily dose of 1600 mg) caused an increased incidence in male rats of nephrotoxicity that was characterized by regenerative tubules, thickening of basement membranes, infiltration of mononuclear cells and tubular protein casts. These effects were not associated with changes in clinical chemistry parameters, and there is no established method for monitoring for the possible occurrence of these lesions in humans. Although this toxicity could represent a species-specific effect, there is not yet evidence that this is so.

Hepatic Findings Three comparative nonclinical toxicological studies were conducted in rats with special emphasis on liver toxicity. Rats were treated with entacapone or tolcapone (another COMT inhibitor) at oral doses ranging from 200 mg/kg/day to 600 mg/kg/day from 8 to 15 days. In rats treated with entacapone no microscopic findings were noted in liver at any of the doses tested (plasma exposure at the highest dose of 600 mg/kg/day corresponds to 26 times that in humans receiving the maximum recommended daily dose of 1600 mg). In contrast, rats treated with tolcapone showed signs of hepatotoxicity (centrilobular hypertrophy, necrosis, vacuolation) on histopathological examination at doses of 400 mg/kg/day and 600 mg/kg/day (plasma exposure at 500 mg/kg/day corresponds to 26 times that in humans at the maximum recommended daily dose of 600 mg). The relevance of these findings to man is unknown.

Urine Discolouration COMTAN may cause a harmless intensification in the color of the patient's urine to brownish-orange.

Special Populations *Hepatic Impairment* **(see CONTRAINDICATIONS)**

Renal Impairment The pharmacokinetics of entacapone were not significantly changed in patients with moderate to severe renal insufficiency and there is no need for dose adjustment (see PHARMACOKINETICS AND METABOLISM OF COMTAN). There is no experience with entacapone in patients receiving dialysis.

Carcinogenesis Two-year carcinogenicity studies have been conducted in the mouse at dosages up to 600 mg/kg/day and in the rat at dosages up to 400 mg/kg/day. In the rat, the only drug-related finding was an increased incidence of renal tubular adenomas and carcinomas noted in males at doses of 400 mg/kg/day. Plasma exposures (AUC) associated with this dose were approximately 20 times higher than estimated plasma exposures of humans receiving the maximum recommended daily dose of entacapone (8 x 200 mg = 1600 mg). In the mouse study, there was a high incidence of premature mortality in animals receiving the highest dose of entacapone (600 mg/kg/day, corresponding to 2 times the maximum recommended human dose on a mg/m^2 basis). Thus, the mouse study does not allow adequate assessment of carcinogenicity. Although no treatment related tumors were observed in animals receiving lower doses, the carcinogenic potential of entacapone has not been fully evaluated.

The carcinogenic potential of COMTAN in combination with levodopa/DDC has not been studied.

Mutagenesis Entacapone was mutagenic and clastogenic in the *in vitro* mouse lymphoma/thymidine kinase assay in the presence and absence of metabolic activation, and was clastogenic in cultured human lymphocytes in the presence of metabolic activation. Entacapone, either alone or in combination with Sinemet, was not clastogenic in the *in vivo* mouse micronucleus test or mutagenic in the bacterial reverse mutation assay (Ames test).

Pregnancy There are no studies or clinical experience of the use of COMTAN in pregnant women. Use of COMTAN in women of child-bearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child. Reproduction studies have been performed in rats and rabbits at doses up to 1000 mg/kg/day and 300 mg/kg/day, respectively, of entacapone. Increased incidence of fetal variations were evident in litters from rats treated at the highest dose in the absence of overt maternal toxicity. The maternal plasma drug exposure (AUC) associated with this dose was approximately 34 times the estimated plasma exposure in humans receiving the maximal recommended dose of 8 x 200 mg (1600 mg/day). Increased frequencies of abortion and late/total resorptions and decreased fetal weights were observed in litters of rabbits treated with maternotoxic doses of 100 mg/kg/day (plasma AUC 0.4 times those in humans receiving the maximal recommended daily dose) or greater. There was no evidence of teratogenicity in these studies.

However, when entacapone was administered to female rats prior to mating and during early gestation, an increased incidence of fetal eye anomalies (macrophthalmia, microphthalmia, anophthalmia) was observed in litters of dams treated with doses of 160 mg/kg/day (plasma AUCs 7 times those in humans receiving the maximal recommended daily dose) or greater, in the absence of maternal toxicity. Administration of up to 700 mg/kg/day (plasma AUCs 28 times those in humans receiving the maximal recommended daily dose) to female rats during the later part of gestation and throughout lactation produced no evidence of developmental impairments in the offspring.

Entacapone is always given concomitantly with levodopa/carbidopa, which is known to cause visceral and skeletal malformations in rabbits. The teratogenic potential of entacapone with levodopa/carbidopa was not assessed in animals.

No effect on fertility was observed in male and female rats treated with up to 700 mg/kg/day of COMTAN (exposure achieved approximately 28 times higher than that in man after the maximum recommended daily dose of 8 x 200 mg/day).

Nursing mothers Studies in rats have shown that entacapone is excreted in milk. It is not known whether entacapone is excreted in human milk. Since the safety of COMTAN in infants is unknown, women should not breast-feed during treatment with COMTAN.

Pediatric Use The safety and efficacy of COMTAN in pediatric patients has not been established and use in patients below the age of 18 is not recommended.

Occupational Hazards: Psychomotor Performance COMTAN together with levodopa may cause dizziness and symptomatic orthostatism. Patients should be cautioned about operating machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Drug Interactions ***Protein binding*** Entacapone is highly protein bound (98%). *In vitro* studies have shown that entacapone, at therapeutic concentrations, does not displace drugs of which a large proportion is bound to plasma proteins (e.g. warfarin, salicylic acid, phenylbutazone and diazepam). Entacapone is not markedly displaced by any of these drugs at therapeutic concentrations (see ACTIONS AND CLINICAL PHARMACOLOGY).

Drugs metabolized by the Catechol-O-methyltransferase (COMT): see **WARNINGS.**

Non-selective MAO inhibitors: See **CONTRAINDICATIONS.**

Selegiline In two multiple-dose interaction studies in patients with Parkinson's disease, no interactions between COMTAN and selegiline (10 mg) were observed in the presence of coadministered levodopa/dopa decarboxylase inhibitor. More than 400 parkinsonian patients in phase 2 and 3 studies used selegiline in combination with entacapone and levodopa/DDC inhibitor without any apparent interactions (also see **CONTRAINDICATIONS**).

The experience on the clinical use of COMTAN with several drugs including, tricyclic antidepressants, noradrenaline reuptake inhibitors (desipramine, maprotiline and venlafaxine) and catechol-structured drugs that are metabolized by COMT is limited. Therefore, patients should be carefully monitored when COMTAN is administered in combination with these drugs (see **CONTRAINDICATIONS and WARNINGS**).

No interaction of COMTAN with carbidopa were observed with the recommended dosage regimen; however, high single doses (in excess of 400 mg of COMTAN) may decrease the bioavailability of carbidopa.

Pharmacokinetic interaction studies with benserazide have not been conducted.

COMTAN increases the bioavailability of levodopa from standard levodopa/benserazide preparations 5-10% more than from standard levodopa/carbidopa preparations. Consequently, undesirable dopaminergic effects may be more frequent when entacapone is added to levodopa/benserazide treatment. A larger reduction of the levodopa dose may be required when COMTAN treatment is initiated in patients receiving levodopa/benserazide (see DOSAGE and ADMINISTRATION).

As most COMTAN excretion is via the bile, caution should be exercised when drugs known to interfere with biliary excretion, glucuronidation, and intestinal beta-glucuronidase are given concurrently with COMTAN. These include probenicid, cholestyramine, and some antibiotics (e.g. erythromycin, rifampicin, ampicillin and chloramphenicol).

Imipramine In a single-dose study in healthy volunteers, no interactions between COMTAN and imipramine were observed in the absence of coadministration of levodopa/dopa decarboxylase inhibitor.

Hormone levels: Levodopa is known to depress prolactin secretion and increase growth hormone levels. Treatment with COMTAN coadministered with levodopa/dopa decarboxylase inhibitor does not change these effects.

Laboratory Tests COMTAN is a chelator of iron. The impact of entacapone on the body's iron stores is unknown; however, a tendency towards decreased serum iron concentrations was noted in a clinical trial. In a controlled clinical study serum ferritin levels (as marker of iron deficiency and subclinical anemia) were not changed with entacapone compared to placebo after one year of treatment and there was no difference in the rates of anemia or decreased hemoglobin levels.

The laboratory tests required during extended levodopa therapy should be normally conducted also during COMTAN treatment.

ADVERSE REACTIONS A total of 1450 patients with Parkinson's Disease received COMTAN (entacapone) during the pre-marketing clinical trials. Approximately 14% of the 603 patients given entacapone in the double-blind placebo-controlled trials discontinued treatment due to adverse events compared to 9% of the 400 patients who received placebo. The most frequent causes of discontinuation in decreasing order for COMTAN vs placebo are: psychiatric reasons (2% vs 1%), diarrhea (2% vs 0%), dyskinesia/hyperkinesia (2% vs 1%), nausea (2% vs 1%), abdominal pain (1% vs 0%), and aggravation of Parkinson's Disease symptoms (1% vs 1%).

Incidence of Adverse Events in Placebo Controlled Trials The most frequently observed adverse events reported with COMTAN were dyskinesias/hyperkinesia (29%/10%), nausea (14%), abnormal urine (intensification of the color of urine, 13%), diarrhea (10%), dizziness (10%) and abdominal pain (9%). Dyskinesia, nausea and abdominal pain, may be more common with higher doses (> 1400 mg/day) than with lower doses of COMTAN.

Adverse events related to the treatment with COMTAN are usually mild to moderate in severity, leading only rarely to discontinuation of the treatment.

Table 3

Adverse events, irrespective of causal relationship to study drug, occurring in ≥ 1% of COMTAN patients during controlled Phase 3 studies.

Adverse Events by body system	COMTAN (n=603) % of patients	Placebo (n=400) % of patients
Autonomic Nervous System Disorders		
Hypotension postural	4.3	4.0
Body As A Whole – General Disorders		
Fatigue	6.1	3.5
Pain	6.0	4.5
Back pain	5.0	3.0
Sweating increased	3.6	3.0
Asthenia	1.8	1.3
Weight decrease	1.7	0.5
Fever	1.3	0.5
Syncope	1.0	0.8
Central & Peripheral Nervous System Disorders		
Dyskinesia	25.2	14.8
Hyperkinesia	9.5	5.0
Hypokinesia	8.6	7.5
Dizziness	7.5	6.0
Ataxia	1.2	0.5
Speech disorder	1.2	0.8
Gastrointestinal System Disorders		
Nausea	13.8	7.5
Diarrhea	10.0	4.0
Abdominal pain	8.1	4.5
Constipation	6.3	4.3
Vomiting	4.0	1.0
Mouth dry	3.0	0.3
Dyspepsia	2.3	0.8
Flatulence	1.5	0.3
Anorexia	1.5	1.3
Gastrointestinal disorders	1.0	0.3
Gastritis	1.0	0.3
Musculoskeletal System Disorders		
Arthralgia	1.8	1.5
Platelet, Bleeding & Clotting Disorders		
Purpura	1.5	0.8
Psychiatric Disorders		
Hallucinations	4.1	4.0
Paroniria	2.2	1.8
Anxiety	2.0	1.3
Agitation	1.7	0.3
Confusion	1.7	1.5
Somnolence	1.7	0.3
Amnesia	1.3	0.8
Sleep disorder	1.3	0.8
Reproductive Disorders, Male		
Prostatic disorder	1.0	0.3
Resistance Mechanism Disorders		
Infection bacterial	1.3	0.0
Respiratory System Disorders		
Dyspnoea	2.7	1.3
Bronchitis	1.2	1.0
Skin And Appendages Disorders		
Rash	3.6	3.0
Special Senses Other, Disorders		
Taste perversion	1.0	0.3
Urinary System Disorders		
Urine abnormal	9.5	0.0
Cystitis	1.2	0.5

Adverse Events reported in <1% of patients treated with COMTAN in Phase 3 trials:

Body As A Whole – General Disorders: malaise, hot flushes, temperature changed sensation, aspiration, oedema generalised, carpal tunnel syndrome, leg pain;

Cardiovascular Disorders, General: hypertension, heart valve disorders;

Central & Peripheral Nervous System Disorders: hypoaesthesia, muscle contractions involuntary, eye abnormality, hypotonia;

Endocrine Disorders: hyperthyroidism;

Gastrointestinal System Disorders: gastroenteritis, oesophagitis, tooth disorder, saliva increased, dysphagia, faeces discoloured, diverticulitis, change in bowel habits, faecal abnormality;

Heart Rate And Rhythm Disorders: extrasystoles, bradycardia, bundle branch block, fibrillation atrial;

Liver & Biliary System Disorders: gamma-gt increased, cholelithiasis, bilirubinaemia, cholangitis;

Metabolic & Nutritional Disorders: hyperglycaemia, hypoglycaemia, phosphatase alkaline increased, hypercholesterolaemia,

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Musculoskeletal System Disorders: bursitis, arthritis, tendinitis;
Myo-, Endo-, Pericardial & Valve Disorders: angina pectoris;
Platelet, Bleeding & Clotting Disorders: epistaxis, thrombocytopenia;
Psychiatric Disorders: nervousness, thinking abnormal, concentration impaired, dreaming abnormal, delusion, paranoid reaction;
Reproductive Disorders, Female: breast fibroadenosis;
Reproductive Disorders, Male: impotence, sexual function abnormal;
Resistance Mechanism Disorders: herpes simplex;
Respiratory System Disorders: pneumonia, pharyngitis, sinusitis;
Secondary Terms – Events: inflicted injury;
Skin And Appendages Disorders: pruritus, skin disorder, dermatitis, eczema, dermatitis fungal;
Special Senses Other, Disorders: taste loss;
Urinary System Disorders: urinary incontinence, haematuria, albuminuria, dysuria, nocturia, renal pain;
Vascular (Extracardiac) Disorders:, skin cold clammy, claudication intermittent;
Vision Disorders: diplopia, conjunctivitis, cataract, photopsia;
White Cell & Res Disorders: leucopenia.

The following adverse events were reported only once but are considered clinically important: hepatic function abnormal, hepatic enzymes increased (> 3 times ULN), cholecystitis and allergic reaction.

Laboratory Findings Slight decreases in hemoglobin, erythrocyte count and hematocrit have been reported during entacapone treatment. The underlying mechanism may involve decreased absorption of iron from the gastrointestinal tract. During long-term treatment (6 months) with entacapone a clinically significant decrease in haemoglobin has been observed in 1.5% of patients.

Post-Introduction Reports Voluntary reports of adverse events that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following: erythematous or maculopapular rash and urticaria. Rare (>1/10,000 and < 1/1000) reports of clinically significant increases in liver enzymes have been received.

SYMPTOMS AND TREATMENT OF OVERDOSAGE The COMT inhibition by COMTAN (entacapone) is dose-dependent; a massive overdose of COMTAN may, therefore, produce a 100% inhibition of COMT enzyme in man, and thereby prevent the metabolism of endogenous and exogenous catechols. No cases of either accidental or intentional overdose have been reported with COMTAN. The highest single dose of entacapone administered to humans was 800 mg, resulting in a plasma concentration of 14.1 µg/mL. The highest daily dose given to man in clinical studies has been 2400 mg per day (400 mg six times daily, n = 15 patients with Parkinson's Disease) for 14 days and 800 mg tid for 7 days in 8 healthy volunteers. At this daily dose, the peak plasma concentrations of entacapone averaged 2.0 µg/mL (at 45 min, compared to 1.0 and 1.2 µg/mL with 200 mg entacapone at 45 min). Abdominal pain and loose stools were the most commonly observed adverse events during this study.

Symptoms The acute toxicity of COMTAN is low, LD_{50} in rats and mice is > 2000 mg/kg. Signs of acute toxicity in animals included piloerection, hypoactivity, salivation and orange-yellow urine. Respiratory difficulty, ataxia or tonic convulsions were reported in the late stage of the toxicity reaction. In these studies, the lethal concentrations of entacapone in plasma were 80-130 µg/mL. The highest individual plasma concentration of COMTAN measured in man was 14.1 µg/mL following an 800 mg single dose.

Management of overdose: Hospitalization is advised and general supportive care is indicated. Management is symptomatic; there is no known antidote to COMTAN. The drug is rapidly absorbed and eliminated with a short mean residence time. There is no experience with dialysis or hemoperfusion, and these procedures are unlikely to be of benefit, because COMTAN is highly bound to plasma proteins. An immediate gastric lavage and repeated doses of charcoal over time may hasten the elimination of COMTAN by decreasing the absorption/reabsorption of COMTAN from GI tract. The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. In managing overdosage, the possibility of interaction among drugs, especially catechol-structured drugs, should be borne in mind.

DOSAGE AND ADMINISTRATION

Method of Administration COMTAN (entacapone) has no antiparkinsonian effect of its own and therefore should always be administered simultaneously with each levodopa/carbidopa or levodopa/benserazide dose. The efficacy of COMTAN as an adjunct to controlled-release levodopa/dopa decarboxylase inhibitor preparations has not been established.

COMTAN is taken orally with or without food. (See ACTION AND CLINICAL PHARMACOLOGY).

Dosage The recommended dose of COMTAN is one 200 mg tablet administered concomitantly with each levodopa/carbidopa or levodopa/benserazide dose up to 8 times daily (1600 mg/day).

Because entacapone enhances the bioavailability and therefore the central effects of levodopa, it may be necessary to adjust the dosage of levodopa during the initial days to weeks of entacapone therapy in order to reduce levodopa-related dopaminergic side effects, e.g., dyskinesias, nausea, vomiting and hallucinations. In some cases, it may be necessary to reduce the daily dosages of levodopa by about 10-30%. This can be achieved through either reducing the dose of the levodopa preparation itself, or by extending the interval between doses, according to the clinical condition of the patient.

In clinical trials, the majority of patients required a decrease in daily levodopa dose if their daily dose of levodopa had been greater than or equal to 800 mg, or if patients had moderate or severe dyskinesias before beginning treatment. The average reduction in daily levodopa dose for patients in clinical trials requiring levodopa dose reduction was about 25% (more than 58% of patients with levodopa doses above 800 mg daily required such a reduction).

COMTAN increases the bioavailability of levodopa from standard levodopa/benserazide preparations slightly (5-10%) more than from standard levodopa/carbidopa preparations. Therefore, patients who are taking standard levodopa/benserazide preparations may need a larger reduction of levodopa dose when entacapone is initiated.

Patients with Impaired Hepatic Function As there is no clinical trial data to establish a safe and effective dosing regimen for hepatically-impaired patients, entacapone should be not be administered to patients with hepatic impairment (see **CONTRAINDICATIONS)**

Patients with Impaired Renal Function No dose adjustment of COMTAN is necessary in patients with moderate to severe renal insufficiency. There is no experience with COMTAN in patients receiving dialysis therapy.

Elderly No dose adjustment is required in elderly patients.

Discontinuation of COMTAN Rapid withdrawal or abrupt reduction in the COMTAN dose could lead to emergence of signs and symptoms of Parkinson's disease (see Clinical Pharmacology, Clinical Trials) and may lead to hyperpyrexia and confusion, a symptom complex resembling neuroleptic malignant syndrome (see **PRECAUTIONS**, **Hyperpyrexia and Confusion**). This syndrome should be considered in the differential diagnosis for any patient who develops high fever or severe rigidity. If a decision is made to discontinue treatment with COMTAN, patients should be monitored closely and other dopaminergic treatments should be adjusted as needed. Although tapering COMTAN has not been systematically evaluated, it seems prudent to withdraw patients slowly if the decision to discontinue treatment is made.

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: entacapone

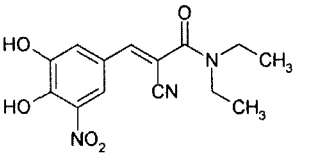
Chemical Name: *(E)*-α-Cyano-*N,N*-diethyl-3, 4-dihydroxy-5-nitrocinnamamide

Empirical Formula: $C_{14}H_{15}N_3O_5$

Molecular Weight: 305.28

Description: Entacapone is a yellow or greenish yellow, non-hygroscopic powder. It is practically insoluble in water and in acidic aqueous medium, but slightly soluble in organic solvents. The pKa value is approximately 4.5. The partition coefficient in 1-octanol/phosphate buffer pH 7.4 is -0.25. Its melting point is approximately 163°C.

Structural Formula:



Composition: COMTAN 200 mg film-coated tablets contain 200 mg of the active ingredient entacapone. The non-medicinal ingredients are: **Core:** croscarmellose sodium, hydrogenated vegetable oil, magnesium stearate, mannitol, microcrystalline cellulose. **Coating:** glycerol 85%, hydroxypropylmethyl cellulose, magnesium stearate, polysorbate 80, red iron oxide, sucrose, titanium dioxide, yellow iron oxide.

Storage Store at room temperature (15° and 30°C).

AVAILABILITY OF DOSAGE FORMS COMTAN (entacapone) 200 mg is a brownish-orange, unscored, oval-shaped film-coated tablet embossed with "COMTAN" on one side. COMTAN tablets are available in bottles of 30, 60, 100 and 500 tablets.

Product monograph is available upon request.

*Comtan is a registered trademark.

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See page OBC

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DOSAGE AND ADMINISTRATION

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

Adults

The dosage of REMINYL shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day given in a b.i.d. regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL might provide additional benefit for some patients.

The recommended starting dose of REMINYL is 4 mg twice a day (8 mg/day). After a minimum of 4 weeks of treatment, if this dose is well tolerated, the dose should be increased to 8 mg twice a day (16 mg/day). A further increase to 12 mg twice a day (24 mg/day) after a minimum of 4 weeks at the previous dose may be considered following appropriate assessment of clinical benefit and tolerability.

REMINYL should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be warned that if therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

The abrupt withdrawal of REMINYL in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of REMINYL are lost, however, when the drug is discontinued.

Concomitant Treatment

In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered.

Special Populations

Dose escalation for elderly patients (>85 years old) with low body weight (especially females) or serious comorbid diseases should be undertaken with particular caution.

Hepatic Impairment

Galantamine plasma levels may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), dosing should proceed cautiously and should not exceed 8 mg twice a day (16 mg/day). In patients with severe hepatic impairment (Child-Pugh score of 10-15), the use of REMINYL is not recommended (see PRECAUTIONS).

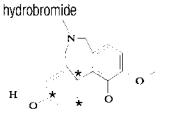
Renal Impairment

For patients with renal impairment (creatinine clearance of 9 to 60 mL/min), dose escalation should proceed cautiously and the maintenance dose should generally not exceed 16 mg/day. In patients with a creatinine clearance less than 9 mL/min, the use of REMINYL is not recommended (see PRECAUTIONS).

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

PHARMACEUTICAL INFORMATION

Drug Substance

Trade Name:	REMINYL
Common Name:	galantamine hydrobromide
Chemical Name:	(4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide
Structural Formula:	 [4aS-(4aα,6β,8aR*)] Hydrobromide (1:1)
Molecular Formula:	$C_{17}H_{21}NO_3 \cdot HBr$
Molecular Weight:	368.27
Ionization Constant:	pKa=8.2 (azepine moiety)
Partition Coefficient:	log P=1.09, between n-octanol and an aqueous buffer solution at pH=12.0
Melting Point:	257.3°C
Description:	Galantamine hydrobromide is a white to almost white powder. It is freely soluble in water (pH=5.2), 0.1 N hydrochloric acid (pH=1.0) and 0.1 N sodium hydroxide (pH=8.3).

Composition

REMINYL (galantamine hydrobromide) tablets are available in three strengths containing 4, 8, 12 mg of galantamine per tablet, as galantamine hydrobromide. The inactive ingredients are lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, propylene glycol, talc, and titanium dioxide. The 4 mg tablet also contains yellow ferric oxide. The 8 mg tablet also contains red ferric oxide. The 12 mg tablet also contains red ferric oxide and FD & C yellow #6 (also known as orange yellow S aluminum lake).

Stability and Storage Recommendations

REMINYL tablets should be stored between 15°C–30°C.

AVAILABILITY OF DOSAGE FORMS

REMINYL (galantamine hydrobromide), expressed as galantamine base, is available as film-coated tablets in the following strengths:

4 mg tablets which are off-white, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G4" on the other side;
8 mg tablets which are pink, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G8" on the other side;
12 mg tablets which are orange-brown, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G12" on the other side.
REMINYL is available in bottles of 60 tablets and in blisters of 56 tablets per carton.

Product Monograph available to healthcare professionals upon request.

JANSSEN-ORTHO

19 Green Belt Drive, Toronto, Ontario M3C 1L9

Date of Issuance: March 2002
RMPI031006A

Member R&D PAAB

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The Lawson Health Research Institute, based in London, Ontario, Canada, is seeking applications for a dynamic and unique NURSE SCIENTIST with research interests and a proven track-record in Cerebrovascular Disease and Stroke management, the origins of disease or preventative strategies. The successful application will hold the title of ì **Heart and Stroke Foundation of Ontario Endowed Research Chair in Cerebrovascular Nursing**. This opportunity is for a five year funding term with option of renewal, where scientific excellence is the sole criteria for renewal.

The Chair develops and implements a program of innovative nursing research that promotes best nursing practices for stroke locally, provincially, nationally and internationally. The Chair provides leadership in nursing research, advances evidence-based practice and works within a collaborative practice model. This position allows for access to stroke patients across the full continuum of care, at a variety of collaborating agencies including the London Health Sciences Centre and St. Josephís Health Care London.

This position will support the teaching and research mission of the Heart & Stroke Foundation of Ontario and the Ministry of Health and Long Term Care Coordinated Stroke Strategy, the Research Programs at the Lawson Health Research Institute and the School of Nursing, Faculty of Health Sciences at the University of Western Ontario.

The successful applicant will be required to maintain a base of peer-reviewed operating grants on which he/she is the Principal Investigator. The position will allow 75% of time for research with 25% of time in mentoring graduate students and advanced practice nurses. The successful applicant will hold an academic appointment with the School of Nursing, Faculty of Health Sciences and the Faculty of Medicine and Dentistry at the University of Western Ontario.

Qualifications:

PhD in Nursing or related cognate program. At least one graduate degree must be in nursing.
Evidence of an established program of nursing research in stroke at the senior scientist level, including experience as an independent investigator and evidence of successful research funding. Applicants with a program of research in any area other than stroke, but in a relevant area, may also be considered.
Current registration or eligibility for registration with the College of Nurses of Ontario.
Evidence of a track record of success in facilitating collaboration and academic and clinical linkages.
Canadian citizenship, permanent resident status or eligibility to obtain a Canadian Working Permit.

Applications should be addressed to Chair, Search Committee, Endowed Chair in Cerebrovascular Nursing Research, c/o Dr. Joseph J. Gilbert, Chief Administrative Officer, Lawson Health Research Institute, 375 South Street, London, ON, Canada, N6A 4G5. Email: lhscri@lhsc.on.ca. Application is open until the position is filled.

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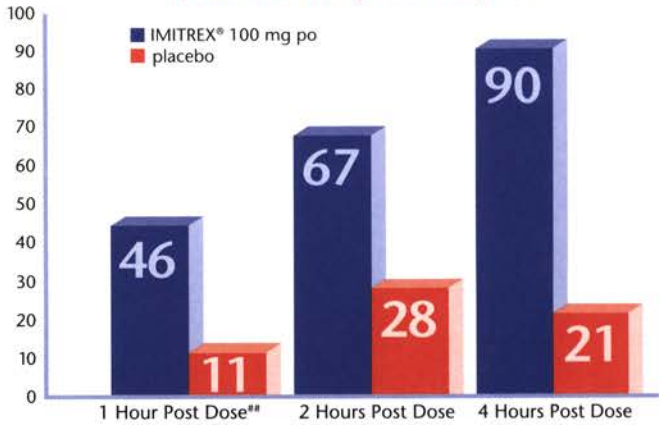
OUR GOAL: ZERO PAIN™† IN MIGRAINE

- IMITREX® is effective at any stage of migraine pain[1Δ]
- IMITREX® at the first sign of pain reduced most attacks to ZERO[2‡]
- Nearly 1 out of 2 attacks reduced to ZERO PAIN™ at 1 hour
- 2 out of 3 attacks reduced to ZERO PAIN™ at 2 hours
- 9 out of 10 attacks reduced to ZERO PAIN™ at 4 hours

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



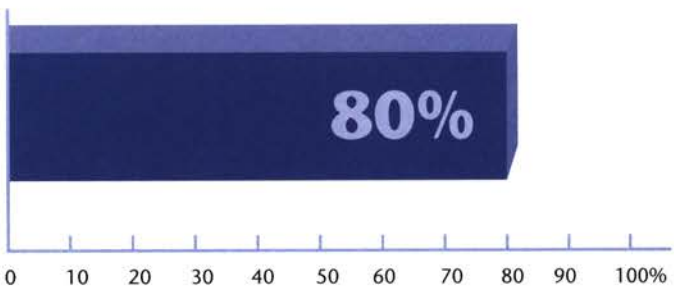
Adapted from Cady *et al.* ($p<0.05$ at 1, 2 & 4 hours)

**2 and 4 hour post dose time points were the primary endpoints.

SUCCESS WITH JUST ONE DOSE[2]

- When IMITREX® was taken at first sign of pain‡, 80% of migraine attacks did not require a second dose[2]
- Reduced need for a second dose = Potential cost savings (acquisition cost only)

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



IMITREX® (sumatriptan succinate/sumatriptan) is a selective 5-HT_1 receptor agonist indicated for the acute treatment of migraine attacks with or without aura.[1] IMITREX® is not indicated for prophylactic therapy of migraine, or for the management of hemiplegic, basilar or ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache.[1]

IMITREX® is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX®. IMITREX® is also contraindicated in patients with uncontrolled or severe hypertension.

The most common adverse events with IMITREX® 100 mg tablets included: nausea (11.0% vs. 5.8% placebo), malaise/fatigue (9.5% vs. 5.1% placebo), sensations (body regions unspecified) (9.0% vs. 4.5% placebo).

† Refers to 0 (zero) on a 4 point pain scale where 0=no pain, 1=mild pain, 2=moderate pain and 3=severe pain.[2]
Δ IMITREX® should not be used prophylactically. Administration during migraine aura prior to other symptoms occurring may not prevent the development of a headache.[1]
‡ Early intervention = treatment initiated at first sign of pain - when pain was mild, before progression to moderate-severe pain.
# Based on a retrospective analysis, 92 patients treated 118 headaches at first sign of pain, where the original prospective study did not pre-define this end-point. Further investigation using prospective analysis is required to prove clinical significance.

IMITREX®
SUMATRIPTAN SUCCINATE
SUMATRIPTAN

A faster way back.™*

GlaxoSmithKline

* Onset of action: 10-15 min. subcutaneous, 15 min. nasal spray, 30 min. tablet.

For brief prescribing information see pages A-35, A-36

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