Interferon beta-1a

Rebif®

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

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTIONS AND CLINICAL PHARMACOLOGY

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

Interferon beta-1a acts through various mechanisms:

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

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

Relapsing-Remitting Multiple Sclerosis

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

PRISMS STUDY

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

The main criteria for inclusion were:

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

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

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

Effect on exacerbation

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

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

The results after one year of treatment were also significant.

Effect on time to first progression in disability

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

Effect on multiple sclerosis pathology as detected by MRI scans

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

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

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

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

Additional analyses were conducted in order to study the efficacy of Rebif® in populations of patients with adverse predictive outcome factors, who were likely to be at higher risk for progression in disability. The primary predictive factor examined was baseline EDSS >3.5. Patients in this cohort have a more severe degree of disability and are at higher risk for progression than those with lower EDSS: natural history studies have shown that patients at EDSS levels of 4.0 to 5.0 spend less time at these EDSS levels than at lower levels of disability. Treatment with Rebif® at both doses significantly reduced the mean exacerbation count per patient compared to placebo treatment. Progression in this group of patients is of particular concern, as it involves development of difficulty in ambulation. The 132 µg weekly dose significantly prolonged time to confirmed progression whereas the 66 µg weekly dose did not. Both doses of Rebif® significantly affected percent change from baseline in MRI burden of disease in the high-EDSS cohort, and the 132 µg weekly dose significantly reduced the number of T2 active lesions in this population. The efficacy results in this cohort of patients with established disability confirms that the 132 µg weekly dose has a marked effect on progression in disability and the underlying pathology of the disease.

Effect on exacerbation (High-EDSS cohort)

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

*Log-linear model

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

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

*excludes patients lost to follow-up without progression

Progression in disability: statistical comparisons

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

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

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

*ANOVA on the ranks

Number of T2 Active Lesions (High-EDSS cohort)

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

*ANOVA on the ranks

CROSS-OVER STUDY

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

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

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

Six-months observation vs six-months treatment:

Treatment with Rebif® at both doses used in this study, achieved a statistically significant reduction in both the MRI evidence of MS activity in the brain and the clinical relapse rate versus the corresponding observation periods. This pattern of improvement was also reflected in additional MRI measures. In the biannual T2-weighted scans, a reduction in the mean number of new lesions and in the mean number of enlarging lesions was demonstrated.

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

Two-year results: At the end of this study, 62 patients continued treatment for a further 18 months. Each of these patients continued to receive the dose to which they were randomized. Validation of the results of the 2 year treatment period is ongoing, however, the results from the continuation of treatment at both doses demonstrate that Rebif® maintained its dose-dependent effect in reducing the relapse rate and the brain lesion volume detected by T2 weight MRI scans compared to the observation period, which corroborates the findings of the longer, placebo-controlled study.

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

Study	# patients/ % previously treated	# lesions treated	Treatment	Results
1	25/80%	3	0.12 or 3.67 µg of Rebif®/lesion, or placebo, 3 times per week for 3 weeks	Rebif® at a dose of 3.67 µg/ lesion is efficacious, as evidenced by the induction of complete disappearance of lesions and the reduction in the area of lesions. The 0.12 µg dose of Rebif® did not show advantages over placebo treatment.
2	100/72%	6	3.67 µg of Rebif®/lesion, or placebo, 3 times per week for 3 weeks	There was a significant increase in Major Response rate at Month 3 in patients who received Rebif® vs placebo (p<0.0001). The Complete Response rate at Month 3 was significantly in favour of patients who received Rebif® (ps0.0162).
3	100/52%	8	3.67 µg of Rebif®/lesion, or placebo, 3 times per week for 3 weeks	For the Israeli centre, the results from Week 6, supported by those from study Day 19 demonstrate the efficacy of Rebif®. Because of the study design and the non-compliance with the study protocol at the German centre, indications of efficacy were not supported by the results from the analyses where patients from both centres were pooled.
4	124/72%	6	3.67 µg of Rebif®/lesion, or placebo, 3 times per week for 3 weeks	This study showed that Rebif® was effective with the proportion of patients achieving a complete or Partial Response at Day 19 and Week 6, and a significant reduction in the total area of lesions on Day 19 and Week 6. Because of the study design, the effect of Rebif® at Month 3 was not demonstrated.

INDICATIONS AND CLINICAL USE

Multiple Sclerosis: Rebif® (Interferon beta-1a) is indicated for the treatment of relapsing-remitting multiple sclerosis in patients with an EDSS between 0 and 5.0, to reduce the number and severity of clinical exacerbations, slow the progression of physical disability, reduce the requirement for steroids, and reduce the number of hospitalizations for treatment of multiple sclerosis. The efficacy has been confirmed by T1-Gd enhanced and T2 (burden of disease) MRI evaluations. Evidence of efficacy beyond 2 years is not known since the primary evidence of efficacy derives from 2-year trials.

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

Laboratory Tests

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

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

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

ADVERSE REACTIONS

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

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

	Placebo	Rebif® 66 µg / weekly	Rebif® 132 µg / weekly
Adverse Events			
Injection site disorders (all)	**38.5**	**89.9**	**92.4**
Upper respiratory tract infections	**85.6**	**75.1**	**74.5**
Headache	62.6	64.6	70.1
Flu-like symptoms	51.3	56.1	58.7
Fatigue	35.8	32.8	41.3
Depression	27.8	20.6	23.9
Fever	**15.5**	**24.9**	**27.7**
Back pain	21.4	19.6	23.4
Myalgia	19.8	24.9	25.0
Nausea	23.0	24.9	24.5
Insomnia	21.4	19.6	23.4
Diarrhoea	18.7	17.5	19.0
Laboratory Test Abnormalities			
Lymphopenia	11.2	20.1	28.8
Leukopenia	3.7	12.7	22.3
Granulocytopenia	3.7	11.6	15.2
AST increase	3.7	10.1	17.4
ALT increase	4.3	19.6	27.2

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

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

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

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

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

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

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

Percentage of patients positive for neutralizing antibodies

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

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

Condyloma acuminata

Most common adverse events for patients treated for Condyloma Acuminatum

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

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

DOSAGE AND ADMINISTRATION:

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

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

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

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

Reconstitution Table

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

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

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

Preparation of Solution: Lyophilized formulation (Condyloma acuminatum) Reconstitute the contents of a vial of Rebif® in sterile diluent in order to obtain a final concentration of 3.67 µg per 0.1 mL solution. The reconstituted solution should be used immediately.

Reconstitution Table

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

COMPOSITION

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

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

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

Liquid formulation

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

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

STABILITY AND STORAGE RECOMMENDATIONS

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

Liquid formulation: Refer to the date indicated on the labels for the expiry date. Rebif® liquid in a pre-filled syringe should be stored at 2-8°C. Do not freeze.

RECONSTITUTED SOLUTIONS

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

PARENTERAL PRODUCTS

See "Preparation of Solution" for table of reconstitution.

AVAILABILITY OF DOSAGE FORM

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

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

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

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

Product Monograph available to Healthcare Professionals on request.

serono
biotech & beyond

PAAB

See pages A-31

Interféron bêta-1a

Rebif®

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

CLASSIFICATION THÉRAPEUTIQUE

Immunomodulateur

MODES D'ACTION ET PHARMACOLOGIE CLINIQUE

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

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

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

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

Sclérose en plaques (SEP) rémittente

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

ÉTUDE PRISMS

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

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

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

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

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

Effet sur les poussées évolutives

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

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

Les résultats après un an de traitement étaient également significatifs

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

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

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

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

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

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

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

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

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

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

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

*Modèle log-linéaire

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

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

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

Progression de l'invalidité: comparaisons statistiques

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

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

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

*Analyse de la variance – rangs

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

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

*Analyse de la variance – rangs

ÉTUDE SELON LE MODÈLE CROISÉ

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

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

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

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

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

	Dosage	Période d'observation	Période de Traitement	% de Réduction	valeur de p
Nbre de poussées évolutives/patient	33 µg/sem 99 µg/sem	0,914 0,788	0,429 0,242	53% 69%	p=0,007 p=0,003
Nbre de patients n'ayant eu aucune poussée évolutive	33 µg/sem 99 µg/sem	15/35 17/33	23/35 26/33		p=0,059 p=0,02
Nbre de lésions/ mois/patient	33 µg/sem 99 µg/sem	3,47 2,42	1,77 0,86	49% 64%	p<0,001 p<0,001
Volume des lésions/patient	33 µg/sem 99 µg/sem	557 mm³ 379 mm³	220 mm³ 100 mm³	61% 73%	p<0,001 p<0,001
Nbre moyen total de nouvelles lésions observées par T2	33 µg/sem 99 µg/sem	5,67 3,93	1,97 1,18	65% 70%	p<0,001 p<0,001
Nbre moyen total de lésions élargies observées par T2	33 µg/sem 99 µg/sem	2,26 1,81	0,97 0,45	57% 75%	p=0,001 p=0,004

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

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

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

INDICATIONS ET USAGE CLINIQUE

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

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

CONTRE-INDICATIONS

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

MISES EN GARDE

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

Sclérose en plaques rémittente

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

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

Condylome

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

PRÉCAUTIONS

Généralités

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

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

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

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

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

Grossesse et allaitement

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

Pédiatrie

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

Patients atteints de maladies et d'états particuliers

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

Interaction médicamenteuse

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

Analyses de laboratoire

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

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

Renseignements à donner aux patients

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

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

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

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

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

RÉACTIONS INDÉSIRABLES

Sclérose en plaques

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

	Placebo	Rebif® 66 µg / sem	Rebif® 132 µg / sem
EFFETS INDÉSIRABLES			
Réactions au point d'injection (toutes)	36,5	80,9	92,4
Infections des voies respiratoires hautes	66,8	78,1	74,5
Céphalée	62,6	64,6	70,1
Syndrome pseudo-grippal	51,3	56,1	58,7
Fatigue	38,8	32,6	41,3
Dépression	27,8	20,6	23,9
Fièvre	19,8	24,8	27,7
Mal de dos	21,4	19,6	23,4
Myalgie	19,8	24,9	25,0
Rhinite	23,0	24,9	24,5
Infection	21,4	19,6	23,4
Diarrhée	18,7	12,3	19,0
ANOMALIES LORS DES ÉPREUVES DE LABORATOIRE			
Lymphocytopénie	11,2	20,1	20,6
Leucopénie	9,3	12,7	22,3
Granulocytopénie	3,7	11,6	15,2
Augmentation des ASAT	3,7	10,1	17,4
Augmentation des ALAT	4,3	19,6	27,2

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

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

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

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

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

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

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

Pourcentage de patients ayant des anticorps neutralisants

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

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

Condyloma acuminé

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

Système organique/ Terme privilégié		Essai 1 n = 25	Essai 2 n = 52	Essai 3 n = 50	Essai 4 n = 65
Troubles à caractère général touchant l'organisme entier	Asthénie	24,0 %	3,8 %	30,0 %	15,4 %
	Fièvre	8,0 %	21,2 %	4,0 %	0,0 %
	Syndrome grippal	4,0 %	7,7 %	24,0 %	26,1 %
	Réaction au point d'injection	8,0 %	11,5 %	-	-
	Inflammation au point d'injection	-	5,8 %	-	-
	Céphalée	28,0 %	42,3 %	20,0 %	36,9 %
	Malaise/ rempart	-	13,4 %	-	-
	Mal de dos	-	9,6 %	-	10,8 %
	Douleur	-	-	-	9,2 %
	Douleur pelvienne	8,0 %	-	6,0 %	-
	Frissons		28,8 %	-	9,2 %
	Malaise	-	1,9 %	16,0 %	1,5 %
	Douleur au point d'injection	4,0 %	36,5 %	66,0 %	13,8 %
	Tuméfaction non inflammatoire	-	7,7 %	-	-
	Fatigue	-	28,8%	-	-
Appareil digestif	Nausée	8,0 %	17,3 %	-	7,8 %
	Vomissements	8,0 %	1,9 %	-	3,0 %
Appareil locomoteur	Myalgie	12,0 %	3,8 %	2,0 %	9,2 %
	Endolorissement musculaire	-	26,9 %	-	-
	Douleur musculaire	-	1,9 %	-	-
Appareil respiratoire	Pharyngites	16,0 %	0,0 %	-	3,0 %

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

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

SYMPTÔMES ET TRAITEMENT DU SURDOSAGE

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

POSOLOGIE ET ADMINISTRATION

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

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

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

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

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

Tableau de reconstitution

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

Préparation de la solution : formulation liquide

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

CONDYLOME ACUMINÉ:

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

Préparation de la solution : formulation lyophilisée (condylome acuminé)

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

Tableau de reconstitution

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

COMPOSITION

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

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

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

Formulation liquide : La formulation liquide est fournie dans des seringues contenant 0,5 mL de solution. Chaque seringue contient de l'interféron bêta-1a, de l'albumine (humaine), du mannitol et du tampon d'acétate de sodium 0,01M, comme indiqué dans le tableau ci-dessous. La solution ne contient pas de préservateur.

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

STABILITÉ ET RECOMMANDATIONS CONCERNANT LA CONSERVATION

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

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

SOLUTIONS RECONSTITUÉES

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

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

PRODUITS PARENTÉRAUX

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

PRÉSENTATION DES FORMES POSOLOGIQUES

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

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

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

Référence :

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

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

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See IFC

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	175%	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, lightness, 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, photophobia, 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 user. The appearance, namely colour, shape and size of the IMITREX® Nasal Spray device is a trademark of Glaxo Group Limited. Glaxo Wellcome Inc., licensed user.

References:

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

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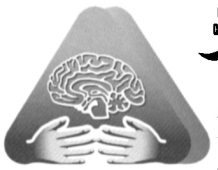


PRESCRIBING INFORMATION

Aggrenox® Capsules

(Dipyridamole / Acetylsalicylic Acid)

200 mg Extended Release Dipyridamole /
25 mg Immediate Release Acetylsalicylic Acid (ASA)

THERAPEUTIC CLASSIFICATION

Antiplatelet Agent

ACTION AND CLINICAL PHARMACOLOGY

Blood platelets participate actively in the pathogenesis of atherosclerotic lesions and thrombosis which is the principle cause of most strokes and transient ischemic attacks (TIAs). Platelets are believed to adhere to denuded, dysfunctional endothelium and to release mitogenic substances, such as platelet-derived growth factor (PDGF), that foster the lesion's progression to rupture and thrombosis. The antithrombotic action of AGGRENOX is the result of the additive antiplatelet effects of dipyridamole and acetylsalicylic acid (ASA).

DIPYRIDAMOLE

Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes *in vitro* and *in vivo*; the inhibition occurs in a dose dependent manner at therapeutic plasma concentrations (0.5-1.9 μg/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A_2-receptor thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3', 5'-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor (PAF), collagen and adenosine diphosphate (ADP). Reduced platelet aggregation reduces platelet consumption towards normal levels.

Dipyridamole also inhibits phosphodiesterase (PDE) in various tissues. While the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cyclic-3', 5'-guanosine monophosphate-PDE (cGMP-PDE), thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, now identified as nitric oxide).

ASA

ASA inhibits platelet aggregation by irreversible inhibition of platelet cyclo-oxygenase and thus inhibits the generation of thromboxane A_2, a powerful inducer of platelet aggregation and vasoconstriction. In studies of platelet activity inhibition, 25 mg ASA was administered b.i.d. to 5 subjects for 2.5 days. Complete inhibition of collagen-induced aggregation was achieved by the 5th dose of ASA, and maximal effect persisted up to 2-3 days following stoppage of drug.

PHARMACOKINETICS

There are no significant interactions between ASA and dipyridamole. The kinetics of the components are unchanged by their co-administration as AGGRENOX. AGGRENOX is not interchangeable with the individual components of ASA and dipyridamole.

Dipyridamole

Absorption: The dissolution and absorption of dipyridamole from AGGRENOX Capsules is independent of the pH of the gastrointestinal tract. Peak plasma levels are achieved in 1.5 - 2 hours after administration. The absolute bioavailability of dipyridamole from AGGRENOX is about 70%. With a daily maintenance dose of 400 mg of the extended release formulation, peak plasma levels at steady state are between 1.5 - 3 μg/mL and trough levels are between 0.4 - 0.8 μg/mL.

Pharmacokinetic studies to determine the effect of food have not been conducted with AGGRENOX.

Distribution: Due to its high lipophilicity, dipyridamole distributes to many organs; however it has been shown that the drug does not cross the blood brain barrier to any significant extent.

Metabolism and Elimination: Dipyridamole is metabolized in the liver. In plasma, about 80% of the total amount is present as parent compound and 20% as monoglucuronide. Most of the glucuronide metabolite (about 95%) is excreted via bile into the feces, with some evidence of enterohepatic circulation. Renal excretion of parent compound is negligible and urinary excretion of the glucuronide metabolite is low (about 5%). The dominant half-life for elimination after oral or intravenous administration is about 40 minutes.

Pharmacokinetics of Dipyridamole in Special Populations:

Geriatric Patients: Plasma concentrations (determined as area under the curve, AUC) of dipyridamole in healthy elderly subjects (> 65 years) are about 30-50% higher than in subjects younger than 55 years, on treatment with AGGRENOX. The difference is caused mainly by reduced clearance.

Hepatic Dysfunction: Patients with mild to severe hepatic insufficiency show no change in plasma concentrations of dipyridamole compared to healthy volunteers, but show an increase in the pharmacologically inactive monoglucuronide metabolite. Dipyridamole can be dosed without restriction as long as there is no evidence of liver failure.

Renal Dysfunction: Renal excretion of dipyridamole is very low (about 5%). In patients with creatinine clearances ranging from about 15 mL/min to > 100 mL/min, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite.

ASA

Absorption: The rate of absorption of ASA from the gastrointestinal tract is dependent on the dosage form, the presence or absence of food, gastric pH, and other physiologic factors. Since ASA produces its pharmacodynamic effect via the irreversible acetylating of platelets, the time course of its pharmacodynamic activity is not dependent on the pharmacokinetics of ASA but rather on the lifespan of the platelets (approximately 8-10 days). Therefore, small differences in the pharmacokinetics of ASA, such as variations in its absorption rate or in elimination, are largely irrelevant to its pharmacologic activity with chronic administration. ASA undergoes moderate hydrolysis to salicylic acid in the liver and the gastrointestinal wall, with 50% - 75% of an administered dose reaching the systemic circulation as intact ASA. Peak plasma levels of ASA are achieved 0.5 - 1 hour after administration of a 50 mg ASA daily dose from AGGRENOX (given as 25 mg b.i.d.). Peak mean plasma concentration at steady state is 319 (175-463 ng/mL).

Distribution: ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10 L). At low plasma concentrations (< 100 μg/mL), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system, breast milk, and fetal tissues. Early signs of salicylate overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approximating 200 μg/mL. (See **ADVERSE REACTIONS; OVERDOSAGE**)

Metabolism: ASA is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 15-30 minutes. Plasma levels of ASA are essentially undetectable 1-2 hours after dosing and peak salicylic acid concentrations occur within 1-2 hours of administration of ASA. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 g), the plasma half-life may be increased to over 20 hours.

Elimination: The elimination of salicylic acid follows first order kinetics at lower doses, with a resultant half-life of approximately 2-3 hours. Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5% to > 80%. Alkalinization of the urine is a key concept in the management of salicylate overdose. (See **OVERDOSAGE**) Following therapeutic doses, about 10% is excreted as salicylic acid and 75% as salicyluric acid, in urine.

Pharmacokinetics of ASA in Special Populations:

Hepatic Dysfunction: Due to the ASA component, AGGRENOX is to be avoided in patients with severe hepatic insufficiency.

Renal Dysfunction: Due to the ASA component, AGGRENOX is to be avoided in patients with severe renal failure (glomerular filtration rate less than 10 mL/min).

INDICATIONS AND CLINICAL USE

AGGRENOX is indicated for the prevention of stroke in patients who have had a previous stroke or a transient ischemic attack (TIA).

CONTRAINDICATIONS

AGGRENOX is contraindicated in patients with hypersensitivity to dipyridamole, ASA or any of the other product components.

Due to the ASA component, AGGRENOX is also contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps.

WARNINGS

ALCOHOL WARNING: Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking AGGRENOX, due to the ASA component.

PEPTIC ULCER DISEASE: Patients with a history of active peptic ulcer disease should avoid using AGGRENOX, which can cause gastric mucosal irritation, and bleeding, due to the ASA component.

PEDIATRIC USE: Safety and effectiveness of AGGRENOX in pediatric patients has not been studied. Therefore, AGGRENOX should not be used in pediatric patients.

PREGNANCY: There are no adequate and well-controlled studies of AGGRENOX in pregnant women. Because animal reproduction studies are not always predictive of human response, AGGRENOX should be given during the first two trimesters of pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Due to the ASA component, AGGRENOX should not be prescribed during the third trimester of pregnancy.

PRECAUTIONS

GENERAL

AGGRENOX should be used with caution in patients with severe coronary artery disease (e.g., unstable angina or recently sustained myocardial infarction), due to the vasodilatory effect of the dipyridamole component. Chest pain may be aggravated in patients with underlying coronary artery disease who are receiving dipyridamole.

For stroke or TIA patients for whom ASA is indicated to prevent recurrent myocardial infarction (MI) or angina pectoris, the dose of ASA in AGGRENOX has not been proven to provide adequate treatment for these cardiac indications.

ASA should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of ASA in certain viral illnesses.

Due to the ASA component, AGGRENOX should be avoided in patients with severe renal failure (glomerular filtration rate less than 10 mL/min) and in patients with severe hepatic insufficiency.

AGGRENOX should be used with caution in patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders, due to the fact that even low doses of ASA can inhibit platelet function leading to an increase in bleeding time.

GI side effects include stomach pain, heartburn, nausea, vomiting, diarrhea, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

CARCINOGENESIS AND IMPAIRMENT OF FERTILITY

Carcinogenesis: In carcinogenicity studies in rats and mice with the combination of dipyridamole and ASA at the ratio of 1:6 over a period of 125 and 105 weeks respectively, no significant tumorigenic effect was observed at maximum doses of 450 mg/kg (corresponding to a share of 75 mg/kg of dipyridamole, 9 times the maximum recommended daily human dose for a 50 kg person on a mg/kg basis [or 1.5-2.1 times on a mg/m² basis]), and 375 mg/kg ASA, 375 times the maximum recommended daily human dose for a 50 kg person on a mg/kg basis (or 58-83 times on a mg/m² basis).

Fertility: Fertility studies with dipyridamole revealed no evidence of impaired fertility in rats at oral dosages of up to 1,250 mg/kg, 156 times the maximum recommended human dose on a mg/kg basis for a 50 kg person (or 35 times on a mg/m² basis). ASA inhibits ovulation in rats.

NURSING MOTHERS

Dipyridamole and ASA are excreted in human breast milk in low concentrations. Therefore, caution should be exercised when AGGRENOX is administered to a nursing woman.

LABORATORY TESTS

ASA has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria and prolonged bleeding time. Over the course of the 24-month study (ESPS-2), patients treated with AGGRENOX showed a decline (mean change from baseline) in hemoglobin of 0.25 g/dl, hematocrit of 0.75%, and erythrocyte count of 0.13 x 10^6/mm³.

DRUG INTERACTIONS

Adenosine: Dipyridamole has been reported to increase the plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage may be necessary.

Cholinesterase inhibitors: The dipyridamole component of AGGRENOX may counteract the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis.

The following drug interactions are associated with the ASA component of AGGRENOX:

Angiotensin converting enzyme (ACE) inhibitors: Due to the indirect effect of the ASA component on the renin-angiotensin conversion pathway, the hyponatremic and hypotensive effects of ACE inhibitors may be diminished by concomitant administration of AGGRENOX.

Acetazolamide: Due to the ASA component, concurrent use of AGGRENOX and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant therapy (heparin and warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and effects on platelets. ASA can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. The ASA component of AGGRENOX can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: The ASA component of AGGRENOX can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of AGGRENOX due to inhibition of renal prostaglandins by ASA, leading to decreased renal blood flow and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of AGGRENOX due to inhibition of renal prostaglandins by ASA, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: The ASA component of AGGRENOX can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renally impaired.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Due to the ASA component, the concurrent use of AGGRENOX with other NSAIDs may increase bleeding or lead to decreased renal function.

Oral hypoglycemics: AGGRENOX may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.

Uricosuric agents (probenecid and sulfinpyrazone): The ASA component of AGGRENOX antagonizes the uricosuric action of uricosuric agents.

ADVERSE REACTIONS

A 24-month, multicentre, double-blind, randomised study (ESPS-2) was conducted to compare the efficacy and safety of AGGRENOX with placebo, extended release dipyridamole alone and ASA alone. The study was conducted in a total of 6,602 male and female patients who had experienced a previous ischemic stroke or transient ischemia of the brain within three months prior to randomisation.

Table 1 presents the incidence of adverse events that occurred in 1% or more of patients treated with AGGRENOX where the incidence was also greater than those patients treated with placebo.

Table 1: Incidence of Adverse Events in ESPS-2*

Body System/Preferred Term	Individual Treatment Group			
	AGGRENOX	ER-DP Alone	ASA Alone	Placebo
Total Number of Patients	1650	1654	1649	1649
Total Number (%) of Patients With at Least One On-Treatment Adverse Event	1319(79.9%)	1305(78.9%)	1323(80.2%)	1304(79.1%)
Central & Peripheral Nervous System Disorders				
Headache	647(39.2%)	634(38.3%)	558(33.8%)	543(32.9%)
Convulsions	28(1.7%)	15(0.9%)	28(1.7%)	26(1.6%)
Gastro-Intestinal System Disorders				
Dyspepsia	303(18.4%)	288(17.4%)	299(18.1%)	275(16.7%)
Abdominal Pain	289(17.5%)	255(15.4%)	262(15.9%)	239(14.5%)
Nausea	264(16.0%)	254(15.4%)	210(12.7%)	232(14.1%)
Diarrhea	210(12.7%)	257(15.5%)	112(6.8%)	161(9.8%)
Vomiting	138(8.4%)	129(7.8%)	101(6.1%)	118(7.2%)
Hemorrhage Rectum	26(1.6%)	22(1.3%)	16(1.0%)	13(0.8%)
Melena	31(1.9%)	10(0.6%)	20(1.2%)	13(0.8%)
Hemorrhoids	16(1.0%)	13(0.8%)	10(0.6%)	10(0.6%)
GI Hemorrhage	20(1.2%)	5(0.3%)	15(0.9%)	7(0.4%)
Body as a Whole – General Disorders				
Pain	105(6.4%)	88(5.3%)	103(6.2%)	99(6.0%)
Fatigue	95(5.8%)	93(5.6%)	97(5.9%)	90(5.5%)
Back Pain	76(4.6%)	77(4.7%)	74(4.5%)	65(3.9%)
Accidental Injury	42(2.5%)	24(1.5%)	51(3.1%)	37(2.2%)
Malaise	27(1.6%)	23(1.4%)	26(1.6%)	22(1.3%)
Asthenia	29(1.8%)	19(1.1%)	17(1.0%)	18(1.1%)
Syncope	17(1.0%)	13(0.8%)	16(1.0%)	8(0.5%)
Psychiatric Disorders				
Amnesia	39(2.4%)	40(2.4%)	57(3.5%)	34(2.1%)
Confusion	18(1.1%)	9(0.5%)	22(1.3%)	15(0.9%)
Anorexia	19(1.2%)	17(1.0%)	10(0.6%)	15(0.9%)
Somnolence	20(1.2%)	13(0.8%)	18(1.1%)	9(0.5%)
Musculo-Skeletal System Disorders				
Arthralgia	91(5.5%)	75(4.5%)	91(5.5%)	76(4.6%)
Arthritis	34(2.1%)	25(1.5%)	17(1.0%)	19(1.2%)
Arthrosis	18(1.1%)	22(1.3%)	13(0.8%)	14(0.8%)
Myalgia	20(1.2%)	16(1.0%)	11(0.7%)	11(0.7%)
Respiratory System Disorders				
Coughing	25(1.5%)	18(1.1%)	32(1.9%)	21(1.3%)
Upper Respiratory Tract Infection	16(1.0%)	9(0.5%)	16(1.0%)	14(0.8%)
Cardiovascular Disorders, General				
Cardiac Failure	26(1.6%)	17(1.0%)	30(1.8%)	25(1.5%)
Platelet, Bleeding & Clotting Disorders				
Hemorrhage NOS	52(3.2%)	24(1.5%)	46(2.8%)	24(1.5%)
Epistaxis	39(2.4%)	16(1.0%)	45(2.7%)	25(1.5%)
Purpura	23(1.4%)	8(0.5%)	9(0.5%)	7(0.4%)
Any Bleeding**	144(8.7%)	77(4.7%)	135(8.2%)	74(4.5%)
Severity of bleeding:***				
Mild	84(5.1%)	53(3.2%)	82(5.0%)	52(3.2%)
Moderate	33(2.0%)	18(1.1%)	33(2.0%)	15(0.9%)
Severe	23(1.4%)	4(0.2%)	19(1.2%)	5(0.3%)
Fatal	4(0.2%)	2(0.1%)	1(0.1%)	2(0.1%)
Neoplasm				
Neoplasm NOS	28(1.7%)	16(1.0%)	23(1.4%)	20(1.2%)
Red Blood Cell Disorders				
Anemia	27(1.6%)	16(1.0%)	19(1.2%)	9(0.5%)

* Reported by >1% of patients during AGGRENOX treatment where the incidence was greater than those treated with placebo.
** Bleeding at any site, reported during follow-up and within 15 days after eventual stroke or treatment cessation.
*** Severity of bleeding: mild = requiring no special treatment; moderate = requiring specific treatment but no blood transfusion; severe = requiring blood transfusion.
Note: ER-DP = Extended Release Dipyridamole 400 mg/day; ASA = Acetylsalicylic Acid 50 mg/day.
Note: The dosage regimen for all treatment groups is b.i.d.
Note: NOS = not otherwise specified.

Discontinuation due to adverse events in ESPS-2 was 27.8% for AGGRENOX, 28.2% for extended release dipyridamole, 23.2% for ASA, and 23.7% for placebo.

Rare Adverse Reactions:

Adverse reactions that occurred in less than 1% of patients treated with AGGRENOX in the ESPS-2 study and that were medically judged to be possibly related to either dipyridamole or ASA are listed below.

Body as a Whole: allergic reaction, fever. *Cardiovascular*: hypotension, flushing. *Central Nervous System*: coma, dizziness, paraesthesia. *Gastrointestinal*: gastritis, ulceration and perforation. *Hearing & Vestibular Disorders*: tinnitus, and deafness. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism. *Heart Rate and Rhythm Disorders*: tachycardia, palpitation, arrhythmia, supraventricular tachycardia. *Liver and Biliary System Disorders*: cholelithiasis, jaundice, abnormal hepatic function. *Metabolic & Nutritional Disorders*: hyperglycemia, thirst. *Platelet, Bleeding and Clotting Disorders*: hematoma, gingival bleeding, cerebral hemorrhage, intracranial hemorrhage, subarachnoid hemorrhage. *Note*: There was one case of pancytopenia recorded in a patient within the AGGRENOX treatment group, from which the patient recovered without discontinuation of AGGRENOX. *Psychiatric Disorders*: agitation. *Reproductive*: uterine hemorrhage. *Respiratory*: hyperpnea, asthma, bronchospasm, hemoptysis, pulmonary edema. *Special Senses*: taste loss. *Skin and Appendages Disorders*: pruritus, urticaria. *Urogenital*: renal insufficiency and failure, hematuria.

POST-MARKETING EXPERIENCE

The following is a list of additional adverse reactions that have been reported either in the literature or are from post-marketing spontaneous reports for either dipyridamole or ASA.

Body as a Whole: hypothermia

Cardiovascular: angina pectoris

Central Nervous System: cerebral edema

Fluid and Electrolyte: hyperkalemia, metabolic acidosis, respiratory alkalosis

Gastrointestinal: pancreatitis, Reye's syndrome

Hearing and Vestibular Disorders: hearing loss

Hypersensitivity: acute anaphylaxis, laryngeal edema

Liver and Biliary System Disorders: hepatitis

Musculoskeletal: rhabdomyolysis

Metabolic & Nutritional Disorders: hypoglycemia, dehydration

Platelet, Bleeding and Clotting Disorders: prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia

Reproductive: prolonged pregnancy and labour, stillbirths, lower birth weight infants, antepartum and postpartum bleeding

Respiratory: tachypnea

Skin and Appendages Disorders: rash, alopecia, angioedema

Urogenital: interstitial nephritis, papillary necrosis, proteinuria

Laboratory Changes

Over the course of the 24-month study (ESPS-2), patients treated with AGGRENOX showed a decline (mean change from baseline) in hemoglobin of 0.25 g/dl, hematocrit of 0.75%, and erythrocyte count of 0.13 x 10^6/mm^3.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Because of the dose ratio of dipyridamole to ASA, overdosage of AGGRENOX is likely to be dominated by signs and symptoms of dipyridamole overdose. For real or suspected overdose, a Poison Control Centre should be contacted immediately. Careful medical management is essential.

Dipyridamole

Symptoms: Based upon the known hemodynamic effects of dipyridamole, symptoms such as feeling warm, flushes, sweating, restlessness, feeling of weakness and dizziness may occur. A drop in blood pressure and tachycardia might also be observed.

Treatment: Symptomatic treatment is recommended, possibly including a vasopressor drug. Gastric lavage should be considered. Since dipyridamole is highly protein bound, dialysis is not likely to be of benefit.

ASA

Symptoms: In mild overdosage these may include rapid and deep breathing, nausea, vomiting, vertigo, tinnitus, flushing, sweating, thirst and tachycardia. In more severe cases acid-base disturbances including respiratory alkalosis and metabolic acidosis can occur. Severe cases may show fever, hemorrhage, excitement, confusion, convulsion or coma and respiratory failure.

Treatment: It consists of prevention and management of acid-base and fluid and electrolyte disturbances. Renal clearance is increased by increasing urine flow and by alkaline diuresis but care must be taken in this approach not to aggravate further the metabolic acidosis that develops and the hypokalemia. Acidemia should be prevented by administration of adequate sodium-containing fluids and sodium bicarbonate. Hypoglycemia is an occasional accompaniment of salicylate overdosage and can be managed by administration of glucose solutions. If a hemorrhagic diathesis is evident, give vitamin K. Hemodialysis may be useful in complex acid-base disturbances particularly in the presence of abnormal renal function.

DOSAGE AND ADMINISTRATION

For oral administration. The recommended dose of AGGRENOX is one capsule twice daily, one in the morning and one in the evening, with or without food. The capsules should be swallowed whole without chewing.

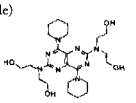
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Dipyridamole

Chemical Name: 2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido(5,4-d) pyrimidine (= dipyridamole)

Structural Formula:



Molecular Formula: $C_{24}H_{40}N_8O_4$

Molecular Weight: 504.63

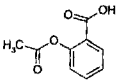
Description: Dipyridamole is an odourless yellow crystalline substance, having a bitter taste. It is soluble in dilute acids, methanol and chloroform, and is practically insoluble in water.

Melting Point: 162-168°C

Proper Name: acetylsalicylic acid (ASA)

Chemical Name: benzoic acid, 2-(acetyloxy)-

Structural Formula:



Molecular Formula: $C_9H_8O_4$

Molecular Weight: 180.16

Description: ASA is an odourless, white, needle-like crystalline or powdery substance. When exposed to moisture, ASA hydrolyzes into salicylic and acetic acids, and gives off a vinegary odour. It is highly lipid soluble and slightly soluble in water.

COMPOSITION

Each hard gelatin capsule contains 200 mg dipyridamole as extended release pellets (a mixture of two release rate pellets), and 25 mg ASA as an immediate release sugar-coated tablet.

Non-medicinal ingredients (in alphabetical order): acacia, aluminium stearate, colloidal silicon dioxide, corn starch, dimethicone, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin.

Capsule shell contains gelatin, red iron oxide and yellow iron oxide, titanium dioxide and water.

STABILITY AND STORAGE RECOMMENDATIONS

Store at 15 to 30°C. Protect from excessive moisture.

AVAILABILITY OF DOSAGE FORMS

AGGRENOX is available as a hard gelatin capsule, with a red cap and an ivory-coloured body, containing yellow extended release pellets incorporating dipyridamole and a round white tablet incorporating immediate-release ASA. The capsule body is imprinted in red with the Boehringer Ingelheim logo and with "01A".

AGGRENOX is supplied in polypropylene tubes containing 60 capsules.

Product Monograph available upon request.

References:

1. Albers GW, Amarenco J, Easton DJ, Sacco RL, Teal P. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke. Sixth ACCP Consensus Conference on Antithrombotic Therapy. *CHEST* 2001;119:300S-320S.
2. Diener HC *et al.* European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *Journal of the Neurological Sciences* 1996;143:1-13. 3. Aggrenox® Product Monograph, Boehringer Ingelheim (Canada) Ltd. 4. Diener HC, *et al.* European Stroke Prevention Study 2. Efficacy and Safety Data. *Journal of the Neurological Sciences* 1997;151:S1-S77.

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See pages A-3, A-32

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BRIEF PRESCRIBING INFORMATION
CONSULT FULL PRODUCT MONOGRAPH FOR COMPLETE PRESCRIBING INFORMATION

Pr Topamax

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

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

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

WARNINGS

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

Central Nervous System Effects

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

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

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

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_{min}).

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

Effects of Other Antiepileptic Drugs on TOPAMAX Phenytoin and carbamazepine decrease the plasma concentration of TOPAMAX. The addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX may require adjustment of the dose of TOPAMAX. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of TOPAMAX, and therefore, does not warrant dosage adjustment of TOPAMAX.

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

Table 1
Drug Interactions with TOPAMAX Therapy

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

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	0	5.1
Emotional Lability	5	5.1
Confusion	3	4.1
Psychomotor Slowing	2	3.1
Reproductive Disorders, Female		
Leukorrhea	0.0	2.3
Resistance Mechanism Disorders		
Infection Viral	3.0	7.1
Infection	3.0	3.1
Respiratory System Disorders		
Upper Respiratory Tract Infection	36.6	36.7
Pneumonia	1.0	5.1
Skin and Appendages Disorders		
Skin Disorder	2.0	3.1
Alopecia	1.0	2.0
Dermatitis	0.0	2.0
Hypertrichosis	1.0	2.0
Rash Erythematous	0.0	2.0
Urinary System Disorders		
Urinary Incontinence	2.0	4.1
Vision Disorders		
Eye Abnormality	1.0	2.0
Vision Abnormal	1.0	2.0
White Cell and RES Disorders		
Leukopenia	0.0	2.0

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

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

[c] Not Otherwise Specified

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

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

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

Post-Marketing Adverse Reactions

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

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

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

Metabolic and Nutritional: weight decrease

Autonomic Nervous System: vomiting

Vision: vision abnormal

Gastrointestinal: nausea, diarrhea, abdominal pain, constipation

Body as a Whole - General Disorders: fatigue

Urinary System: renal calculus

Skin and Appendages: rash

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

Geriatrics

See **PRECAUTIONS** section.

Patients with Renal Impairment

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

Patients Undergoing Hemodialysis

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

Patients with Hepatic Disease

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

AVAILABILITY OF DOSAGE FORMS

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

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

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

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

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

TOPAMAX is a Schedule F Drug.

Product Monograph available to physicians and pharmacists upon request.

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

Date of Issuance: April 2000
TXPI001013A

See pages A-10, A-11, A-22, A-23

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-1b are species-restricted and, therefore, the most pertinent pharmacological information on BETASERON (interferon beta-1b) is derived from studies of human cells in culture and *in vivo*.

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

Clinical Trials: The efficacy of 8 MIU BETASERON, administered subcutaneously every other day, has been studied in one placebo-controlled clinical trial in relapsing-remitting MS patients (n=124) and a placebo-controlled trial in secondary-progressive MS patients (n=360).

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

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

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

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

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

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

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

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

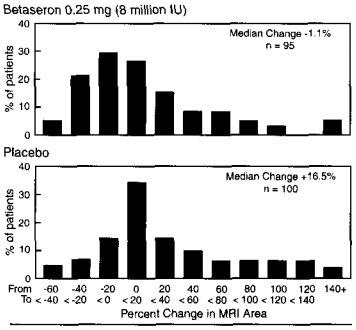
Over the 2-year period, there were 25 MS-related hospitalizations in the 0.25 mg (8 MIU) BETASERON-treated group compared to 48 hospitalizations in the placebo group. In comparison, non-MS hospitalizations were evenly distributed between the groups, with 16 in the 0.25 mg (8 MIU) BETASERON group and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

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

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

MRI scanning is viewed as a useful means to visualize changes in white matter that are believed to be a reflection of the pathologic changes that, appropriately located within the central nervous system (CNS), account for some of the signs and symptoms that typify relapsing-remitting MS. The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in lesion area often do not correlate with clinical exacerbations probably because many of the lesions affect so-called "silent"

Figure 1: Distribution of Change in MRI Area



regions of the CNS. Moreover, it is not clear what fraction of the lesions seen on MRI become foci of irreversible demyelinization (i.e., classic white matter plaques). The prognostic significance of the MRI findings in this study has not been evaluated.

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

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

2. Secondary-Progressive MS: The effectiveness of BETASERON administered subcutaneously at a dose of 0.25 mg (8 MIU) every other day for 3 years was studied in a European multicenter (32 sites), randomized, double-blind, placebo-controlled trial in patients with secondary-progressive MS.

The study included patients between 18 and 55 years of age who had clinically definite or laboratory-supported definite MS for not less than one year. Disease had to be in the secondary-progressive phase and deterioration could not be exclusively related to incomplete recovery from relapses. EDSS score at study entry was between 3.0 and 6.5 and patients had to have a history of at least two clearly identified relapses, or deterioration of at least 1 EDSS point (or 0.5 points between EDSS scores of 6.0 to 7.0) within the preceding 24 months.

The primary efficacy endpoint was time to confirmed progression in disability, as determined by an increase by one point on the EDSS from baseline if the entry score was 3.0 to 5.5, or 0.5 points on the EDSS if the baseline score was 6.0 or 6.5. The increased score had to be maintained for three months before progression was confirmed. Secondary efficacy endpoints included time to becoming wheelchair-bound (EDSS 7.0) and annual relapse rate.

Although the study was designed with a treatment duration of three years, a prospectively planned interim analysis of efficacy was performed after all patients had completed 2 years in the study. This resulted in a decision by an independent Advisory Board to terminate the study early. Approximately 85% of all EDSS data for the three year study duration were available for the interim analysis of the primary endpoint. The primary analysis of efficacy was based on all patients randomized to treatment (Intent to Treat). The primary statistical method for the primary endpoint was a non-parametric analysis of covariance with stratification for centre and adjustment for baseline EDSS.

Results presented below are for the dataset at study termination.

During the study, assessment of the EDSS was performed by a physician not otherwise involved in the treatment of the patient. All EDSS physicians were regularly trained to guarantee a maximally standardized assessment of the EDSS. All efforts were undertaken to maintain the blinding, e.g., standard clothing to cover injection sites was obligatory.

A total of 718 patients (358 on placebo and 360 on BETASERON) were enrolled. In both treatment groups, the proportion of female patients exceeded that of males (Placebo: 64.2% vs. 35.8%; BETASERON: 58.1% vs. 41.9%), but this difference was not statistically significant. The mean time on treatment was 886 days for placebo and 909 days for BETASERON. Eighty-eight (88) patients were lost to follow-up; the remainder were followed up until the end of study irrespective of continuation of study drug. Over the 3-year study period, treatment was discontinued prematurely by 117 (32.7%) placebo patients and 103 (29.6%) BETASERON patients. Lack of efficacy, adverse events and non-compliance were the most common reasons for ending treatment in 15.6%, 6.4% and 7.5% of the placebo group and in 7.5%, 14.2% and 3.3% of the BETASERON group, respectively. The treatment groups were well-balanced for all relevant baseline values, including EDSS at baseline, and time since evidence of secondary-progressive disease.

There was a statistically significant difference in time to confirmed progression in disability in favour of BETASERON (p=0.0046), as shown in Table 2. The delay in progression in disability became apparent after 9 months of treatment and was statistically significant from month 12 onwards. The proportion of patients with confirmed progression in disability was reduced from 60.9% in the placebo group to 51.9% in the BETASERON group (p=0.0245).

The treatment effect was consistent across all baseline EDSS levels studied; however, the difference in the proportion of patients having confirmed progression in disability between BETASERON and placebo-treated patients was lower for patients with study entry EDSS values of ≥6.0, compared to the other EDSS categories (EDSS ≤3.5: 15.0%; EDSS 4.0-5.5: 11.3% and EDSS ≥6.0: 3.5%). Although the proportion of male patients in the BETASERON group with confirmed progression in disability was slightly higher than that of female patients, piecewise logistic regression analysis did not reveal any significant treatment by gender interaction (p=0.4335).

Kaplan-Meier plots (post-hoc analysis) of the data are shown in Figure 2. The Kaplan-Meier estimate of the percentage of patients progressing by the end of 3 years was 53.9% for placebo and 45.3% for BETASERON-treated patients.

The time to becoming wheelchair-bound (EDSS = 7.0) was also significantly prolonged (p=0.0047) and the proportion of patients becoming wheelchair-bound was reduced from 28.5% in the placebo group to 18.6% in the BETASERON group (p=0.0069).

BETASERON reduced the relapse rate by 26.3% over the entire study period (p=0.0034). The proportion of patients with moderate or severe relapses was reduced from 54.2% in the placebo group to 47.2% in the BETASERON group (p=0.0508). The mean annual rate of moderate or severe relapses was 0.44 and 0.31 in the placebo and the BETASERON group, respectively (p=0.0037).

The incidence of hospitalizations due to MS was reduced: 44.4% of placebo patients required hospitalization due to MS vs. 36.1% in the BETASERON group (p=0.0003). The number of patients with steroid courses was 73.2% and 62.5% of patients in the placebo and BETASERON group respectively (p=0.0010).

In addition to clinical measures, annual magnetic resonance imaging (MRI) was performed. All patients underwent a T2-weighted MRI scanning at baseline and yearly thereafter, while a subgroup of patients (Placebo, n = 61; BETASERON, n = 64) underwent monthly scans in months 1-6 and 19-24 in addition to the annual scans scheduled for the general study population. Results of secondary and tertiary MRI endpoints showed significant differences between treatment groups in favor of BETASERON (see Table 2). The exact relationship between MRI findings and the clinical status of patients is unknown.

Serum samples were collected throughout the study to test for the development of neutralizing antibodies (NAB) against interferon beta-1b. Analyses were performed to assess the association between NAB status (measured by an MxA neutralization assay) and treatment response as measured by clinical and MRI outcome measures. Confirmed NAB titers of 1:20, 1:100 and 1:400 were observed in 28%, 14% and 8% of patients, respectively. Despite continued therapy with BETASERON, 50% of the NAB-positive patients were found to have negative titers subsequent to the first development of confirmed quantifiable titers. The relationship between antibody formation and clinical efficacy is not known.

Table 1: 2-Year Study Results

Primary and Secondary Endpoints

Efficacy Parameters	Treatment Groups			Statistical Comparisons p-value		
Primary Clinical Endpoints	**Placebo (n=123)**	**0.05 mg (1.6 MIU) (n=125)**	**0.25 mg (8 MIU) (n=124)**	**Placebo vs 0.05 mg (1.6 MIU)**	**0.05 mg (1.6 MIU) vs 0.25 mg (8 MIU)**	**Placebo vs 0.25 mg (8 MIU)**
Annual exacerbation rate	1.31	1.14	0.90	0.005	0.113	0.0001
Proportion of exacerbation-free patients†	16%	18%	25%	0.609	0.286	0.094
Exacerbation frequency per patient 0†	20	22	29	0.151	0.077	0.001
1	32	31	39			
2	20	28	17			
3	15	15	14			
4	15	7	9			
≥5	21	16	8			
Secondary Endpoints††						
Median number of months to first on-study exacerbation	5	6	9	0.299	0.097	0.010
Rate of moderate or severe exacerbations per year	0.47	0.29	0.23	0.020	0.257	0.001
Mean number of moderate or severe exacerbation days per patient	44.1	33.2	19.5	0.229	0.064	0.001
Mean change in EDSS score‡ at endpoint	0.21	0.21	-0.07	0.996	0.108	0.144
Mean change in Scripps score‡‡ at endpoint	-0.53	-0.50	0.66	0.641	0.051	0.126
Median duration per exacerbation (days)	36	33	35.5	ND	ND	ND
% change in mean MRI lesion area at endpoint	21.4%	9.8%	-0.9%	0.015	0.019	0.0001

ND Not done.

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

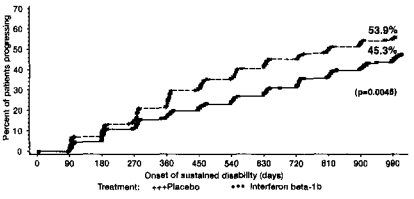
†† Sequelae and Functional Neurologic Status, both required by protocol, were not analyzed individually but are included as a function of the EDSS.

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

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

Figure 2

Onset of Progression in Disability by Time in Study.
(Kaplan-Meier Methodology: Post-hoc Analysis).



Estimate of the Percentage of Patients Progressing by the End of 3 Years.

Note: The p value of 0.0046 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given timepoint.

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Table 2
Secondary-Progressive MS Study Results
Summary of Key Efficacy Endpoints

	Treatment Groups		p-value
	Placebo (n=358)	Betaseron 0.25 mg (8 MIU) (n=360)	
Primary Endpoints			
Time to Confirmed Progression in Disability[1]			0.0046
Year 1	0.70	0.81	0.0032
Year 2	0.53	0.64	0.0013
Month 33	0.44	0.53	0.0066
Secondary Clinical Endpoints			
Time to becoming wheelchair-bound[2]			0.0047
Year 1	0.90	0.96	0.0139
Year 2	0.81	0.86	0.0096
Month 36	0.69	0.80	0.0047
Proportion of patients becoming wheelchair-bound	28.5%	18.6%	0.0069
Mean annual relapse rate	0.57	0.42	0.0034
MRI: mean percent change in T2 lesion volume (baseline to last scan)	15.4	-2.1	<0.0001
MRI: mean number of newly active lesions (months 1-6)	10.24 (n=61)	3.57 (n=64)	<0.0001
Tertiary Endpoints			
Proportion of patients with confirmed progression	60.9%	51.9%	0.0245
Mean endpoint EDSS	5.93	5.58	0.0065
Median time to first relapse (days)	385	644	0.0088
MRI: mean number of persistently enhancing lesions (months 1-6)	3.10 (n=61)	1.02 (n=64)	0.0009
MRI: mean number of persistently enhancing lesions (months 19-24)	3.04 (n=53)	0.36 (n=56)	0.0004

[1]Probability of remaining progression-free during the interval.
[2]Probability of not becoming wheelchair-bound during the interval.

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 3. In the following table, terms so general as to be uninformative, and those events where a drug cause was remote have been excluded.

Table 3: 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%

Table 3: Adverse Events and Laboratory Abnormalities

Adverse Event	Placebo n=123	0.25 mg (8 MIU) n=124
Hemic and Lymphatic System		
– Lymphocytes < 1500/mm^3	67%	82%
– ANC < 1500/mm^3*	6%	18%
– WBC < 3000/mm^3*	5%	16%
– Lymphadenopathy	11%	14%
Metabolic and Nutritional Disorders		
– ALT (SGPT) > 5 times baseline*	6%	19%
– Glucose < 55 mg/dL	13%	15%
– Total bilirubin > 2.5 times baseline	2%	6%
– Urine protein > 1+	3%	5%
– AST (SGOT) > 5 times baseline*	0%	4%
– Weight gain	0%	4%
– Weight loss	2%	4%
Musculoskeletal System		
– Myalgia*	28%	44%
– Myasthenia	10%	13%
Nervous System		
– Dizziness	28%	35%
– Hypertonia	24%	26%
– Depression	24%	25%
– Anxiety	13%	15%
– Nervousness	5%	8%
– Somnolence	3%	6%
– Confusion	2%	4%
– Speech disorder	1%	3%
– Convulsion	0%	2%
– Hyperkinesia	0%	2%
– Amnesia	0%	2%
Respiratory System		
– Sinusitis	26%	36%
– Dyspnea*	2%	8%
– Laryngitis	2%	6%
Skin and Appendages		
– Sweating*	11%	23%
– Alopecia	2%	4%
Special Senses		
– Conjunctivitis	10%	12%
– Abnormal vision	4%	7%
Urogenital System		
– Dysmenorrhea	11%	18%
– Menstrual disorder*	8%	17%
– Metrorrhagia	8%	15%
– Cystitis	4%	8%
– Breast pain	3%	7%
– Menorrhagia	3%	6%
– Urinary urgency	2%	4%
– Fibrocystic breast	1%	3%
– Breast neoplasm	0%	2%
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 3 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 4. Adverse events significantly associated with BETASERON compared to placebo (p<0.05) are also indicated in Table 4.

Table 4: Incidence of Adverse Events ≥ 2% or > 2% Difference (BETASERON vs. Placebo) in the Secondary Progressive MS Study

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

*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.

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

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

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

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

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

Hemic and Lymphatic System: chronic lymphocytic leukemia, hemoglobin less than 9.4 g/100 mL, petechia, platelets less than 75,000/mm^3, and splenomegaly;

Metabolic and Nutritional Disorders: alcohol intolerance, alkaline phosphatase greater than 5 times baseline value, BUN greater than 40 mg/dL, calcium greater than 11.5 mg/dL, cyanosis, edema, glucose greater than 160 mg/dL, glycosuria, hypoglycemic reaction, hypoxia, ketosis, and thirst;

Musculoskeletal System: arthritis, arthrosis, bursitis, leg cramps, muscle atrophy, myopathy, myositis, ptosis, and tenosynovitis;

Nervous System: abnormal gait, acute brain syndrome, agitation, apathy, aphasia, ataxia, brain edema, chronic brain syndrome, coma, delirium, delusions, dementia, depersonalization, diplopia, dystonia, encephalopathy, euphoria, facial paralysis, foot drop, hallucinations, hemiplegia, hypalgesia, hyperesthesia, incoordination, intracranial hypertension, libido decreased, manic reaction, meningitis, neuralgia, neuropathy, neurosis, nystagmus, oculogyric crisis, ophthalmoplegia, papilledema, paralysis, paranoid reaction, psychosis, reflexes decreased, stupor, subdural hematoma, torticollis, tremor and urinary retention;

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

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

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

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

DOSAGE AND ADMINISTRATION FOR SUBCUTANEOUS USE ONLY

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

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

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

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

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

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

AVAILABILITY OF DOSAGE FORMS

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

References:

1. Product Monograph of ®BETASERON® (interferon beta-1b), Berlex Canada, June 1999.
2. 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.

Product Monograph available upon request.

Member PAAB R&D

See pages A-6, A-7, A-18, A-19

NEURONTIN*
(gabapentin)

(Gabapentin) 100 mg, 300 mg, 400 mg Capsules

600 mg and 800 mg Tablets

(Antiepileptic Agent)

INDICATIONS AND CLINICAL USE

Neurontin (gabapentin) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

CONTRAINDICATIONS

Neurontin (gabapentin) is contraindicated in patients who have demonstrated hypersensitivity to the drug or to any of the components of the formulation.

PRECAUTIONS

General Neurontin (gabapentin) is not considered effective in the treatment of absence seizures and should therefore be used with caution in patients who have mixed seizure disorders that include absence seizures.

Tumorigenic Potential Gabapentin produced an increased incidence of acinar cell adenomas and carcinomas in the pancreas of male rats, but not female rats or in mice, in oncogenic studies with doses of 2000 mg/kg which resulted in plasma concentrations 14 times higher than those occurring in humans at a dose of 2400 mg/day. The relevance of these pancreatic acinar cell tumours in male rats to humans is unknown, particularly since tumours of ductal rather than acinar cell origin are the predominant form of human pancreatic cancer.

Drug Discontinuation As with other anticonvulsant agents, abrupt withdrawal is not recommended because of the possibility of increased seizure frequency. When in the judgement of the clinician there is a need for dose reduction, discontinuation or substitution with alternative medication, this should be done gradually over a minimum of one week.

Occupational Hazards Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials, the most common adverse reactions observed were somnolence, ataxia, fatigue and nystagmus. Patients should be advised to refrain from activities requiring mental alertness or physical co-ordination until they are sure that Neurontin does not affect them adversely.

Drug Interactions

Antiepileptic Agents: There is no interaction between Neurontin and phenytoin, valproic acid, carbamazepine, or phenobarbital. Consequently, Neurontin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the plasma concentrations of gabapentin or the other antiepileptic drugs.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving antiepileptic agents.

Oral Contraceptives: Coadministration of Neurontin with the oral contraceptive Norlestrin does not influence the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Antacids: Coadministration of Neurontin with an aluminum and magnesium-based antacid reduces gabapentin bioavailability by up to 20%. Although the clinical significance of this decrease is not known, coadministration of similar antacids and gabapentin is not recommended.

Probenecid: Renal excretion of gabapentin is unaltered by probenecid.

Cimetidine: A slight decrease in renal excretion of gabapentin observed when it is coadministered with cimetidine is not expected to be of clinical importance.

Use in Pregnancy No evidence of impaired fertility or harm to the fetus due to gabapentin administration was revealed in reproduction studies in mice at doses up to 62 times, and in rats and rabbits at doses up to 31 times the human dose of 2400 mg/day.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus.

Use in Lactation Gabapentin is excreted in human milk. Because the effect on the nursing infant is unknown, caution should be exercised when gabapentin is administered to a nursing mother. Gabapentin should be used in nursing mothers only if the potential benefit outweighs the potential risks.

Use in Children Systematic studies to establish safety and efficacy in children have not been performed. Data in 39 patients between the ages of 12 and 18 years included in the double-blind, placebo-controlled trials showed that gabapentin was superior to placebo in reducing seizure frequency. Safety data showed that the incidence of adverse events in this group of patients were similar to those observed in older individuals.

Use in the Elderly Systematic studies in geriatric patients have not been conducted. Adverse clinical events reported among 59 patients over the age of 65 years treated with Neurontin did not differ from those reported for younger individuals. The small number of individuals evaluated and the limited duration of exposure limits the strength of any conclusions reached about the influence of age, if any, on the kind and incidence of adverse events associated with the use of Neurontin. As Neurontin is eliminated primarily by renal excretion, dosage adjustment may be required in elderly patients because of declining renal function (See Dosage and Administration).

Use in Renal Impairment Gabapentin clearance is markedly reduced in this patient population and dosage reduction is necessary (See Table 3 in Dosage and Administration).

Laboratory Tests Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin. Neurontin may be used in combination with other commonly used antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or other antiepileptic drugs. For urinary protein determination the sulfosalicylic acid precipitation procedure is recommended, as false positive readings were reported with the Ames N-Multistix SG® dipstick test, when gabapentin or placebo was added to other anticonvulsant drugs.

ADVERSE REACTIONS

Adverse Events in Controlled Trials The most commonly observed adverse events associated with the use of Neurontin in combination with other antiepileptic drugs, not seen at an equivalent frequency in placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, nystagmus and tremor. Among the treatment-emergent adverse events occurring in Neurontin-treated patients, somnolence and ataxia appeared to exhibit a positive dose-response relationship. Patients treated with 1800 mg/day (n=54, from one controlled study) experienced approximately a two-fold increase, as compared to patients on lower doses of 600 to 1200 mg/day (n=489, from several controlled studies), in the incidence of nystagmus (20.4%), tremor (14.8%), rhinitis (13%), peripheral edema (7.4%), abnormal co-ordination, depression and myalgia (all at 5.6%). Adverse events were usually mild to moderate in intensity, with a median time to resolution of 2 weeks. Since Neurontin was administered most often in combination with other antiepileptic agents, it was not possible to determine which agent(s) was associated with adverse events. Data from long-term, open, uncontrolled studies shows that Neurontin treatment does not result in any new or unusual adverse events.

Withdrawal From Treatment Due to Adverse Events Approximately 6.4% of the 543 patients who received Neurontin in the placebo-controlled studies withdrew due to adverse events. In comparison, approximately 4.5% of the 378 placebo-controlled participants withdrew due to adverse events during these studies. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue, nausea and/or vomiting and dizziness (all at 0.6%).

Treatment-Emergent Adverse Event Incidence In Placebo-Controlled Add-On Trials (Events in at Least 1% of Neurontin Patients and Numerically More Frequent Than in the Placebo Group)

Neurontin[a] (n=543), Placebo[a] (n = 378). **Body As Whole:** Fatigue (11.0% vs 5.0%), Weight Increase (2.9% vs 1.6%), Back Pain (1.8% vs 0.5%), Peripheral Edema (1.7% vs 0.5%). **Cardiovascular:** Vasodilatation (1.1% vs 0.3%). **Digestive System:** Dyspepsia (2.2% vs 0.5%), Mouth or Throat Dry (1.7% vs 0.5%), Constipation (1.5% vs 0.8%), Dental Abnormalities (1.5% vs 0.3%), Increased Appetite (1.1% vs 0.8%). **Hematologic and Lymphatic Systems:** Leukopenia (1.1% vs 0.5%). **Musculoskeletal System:** Myalgia (2.0% vs 1.9%), Fracture (1.1% vs 0.8%). **Nervous System:** Somnolence (19.3% vs 8.7%), Dizziness (17.1% vs 6.9%), Ataxia (12.5% vs 5.6%), Nystagmus (8.3% vs 4.0%), Tremor (6.8% vs 3.2%), Nervousness (2.4% vs 1.9%), Dysarthria (2.4% vs 0.5%), Amnesia (2.2% vs 0.0%), Depression (1.8% vs 1.8%), Thinking Abnormal (1.7% vs 1.3%), Twitching (1.3% vs 0.5%), Co-ordination Abnormal (1.1% vs 0.3%). **Respiratory System:** Rhinitis (4.1% vs 3.7%), Pharyngitis (2.8% vs 1.6%), Coughing (1.8 vs 1.3). **Skin and Appendages:** Abrasion (1.3% vs 0.0%), Pruritus (1.3% vs 0.5%). **Urogenital System:** Impotence (1.5% vs 1.1%). **Special Senses** : Diplopia (5.9% vs 1.9%), Amblyopia (4.2% vs 1.1%). **Laboratory Deviations:** WBC Decreased (1.1% vs 0.5%).[a]Plus background antiepileptic drug therapy.

POST MARKETING EXPERIENCE

Post-marketing adverse events that may have no causal relationship to gabapentin include sudden unexplained deaths, elevated liver function tests, blood glucose fluctuations in patients with diabetes, urinary incontinence, pancreatitis, erytheme multiforme and Stevens-Johnson syndrome.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute, life-threatening toxicity has not been observed with Neurontin (gabapentin) overdoses of up to 49 grams ingested at one time. In these cases, dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhea were observed. All patients recovered with supportive care.

Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, reduce toxicity from overdoses. An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

DOSAGE AND ADMINISTRATION

Adults: In clinical trials, the effective dosage range was 900 to 1800 mg/day. Therapy may be initiated by administering 300 mg three times a day (TID) on Day 1, or by titrating the dose as described below (see Table 1). Thereafter, the dose can be increased in three equally divided doses up to a clinically effective and tolerated dose. Dosages up to 2400 mg/day have been well tolerated in long-term, open-label clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration and have been tolerated. Neurontin is given orally with or without food.

TABLE 1. Titration Schedule

DOSE	Day 1	Day 2	Day 3
900 mg/day	300 mg OD	300 mg BID	300 mg TID
1200 mg/day	400 mg OD	400 mg BID	400 mg TID

Data from clinical trials suggest that doses higher than 1200 mg/day may have increased efficacy in some patients, however, higher doses may also increase the incidence of adverse events (See Adverse Reactions).

Daily maintenance doses should be given in three equally divided doses (See Table 2), and the maximum time between doses in a three times daily schedule should not exceed 12 hours. It is not necessary to monitor gabapentin plasma concentrations in order to optimize Neurontin therapy. Further, as there are no drug interactions with commonly used antiepileptic drugs, Neurontin may be used in combination with these drugs without concern for alteration of plasma concentrations of either gabapentin or other antiepileptic drugs.

TABLE 2. Maintenance Dosage Schedule

Total Daily Dose (mg/day)	Schedule
900	300 mg TID
1200	400 mg TID
1800	2x300 mg TID or 600 mg TID
2400	2x400 mg TID or 800 mg TID

Dosage adjustment in elderly patients due to declining renal function and in patients with renal impairment or undergoing hemodialysis is recommended as follows:

TABLE 3. Maintenance Dosage of Neurontin in Adults With Reduced Renal Function

Renal Function Creatinine Clearance (mL/min)	Total Daily Dose (mg/day)	Dose Regimen (mg)
>60	1200	400 Three Times a Day
30-60	600	300 Twice a Day
15-30	300	300 Once a Day
<15	150	300 Once Daily Every Other Day
Hemodialysis[a]	--	200-300[b]

[a] Loading dose of 300 to 400 mg

[b] Maintenance dose of 200 to 300 mg Neurontin following each 4 hours of hemodialysis

Children Over 12 Years of Age

The dosage used in a limited number of patients in this age group was 900-1200 mg/day. Doses above 1200 mg/day have not been investigated.

STABILITY AND STORAGE RECOMMENDATIONS

Capsules: Store at controlled room temperature, 15–30°C.

Tablets: Store at controlled room temperature, 20–25°C.

AVAILABILITY OF DOSAGE FORMS

Neurontin (gabapentin) capsules and tablets are supplied as follows:

100 mg capsules:
Hard gelatin CONI-SNAP® capsules with white opaque body and cap printed with "PD" on one side and "Neurontin/100 mg" on the other.
-bottles of 100 capsules

300 mg capsules:
Hard gelatin CONI-SNAP® capsules with yellow opaque body and cap printed with "PD" on one side and "Neurontin/300 mg" on the other.
-bottles of 100 capsules

400 mg capsules:
Hard gelatin CONI-SNAP® capsules with orange opaque body and cap printed with "PD" on one side and "Neurontin/400 mg" on the other.
-bottles of 100 capsules

600 mg tablets:
White, elliptical, film-coated tablets with "Neurontin 600" printed on one side.
-bottles of 100 tablets

800 mg tablets:
White, elliptical, film-coated tablets with "Neurontin 800" printed on one side.
-bottles of 100 tablets

Full Prescribing Information Available On Request

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See page A-27

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Zomig
zolmitriptan tablets 2.5 mg

Zomig*Rapimelt*
zolmitriptan orally dispersible tablets 2.5 mg

2.5 mg tablets and 2.5 mg orally dispersible tablets

PHARMACOLOGICAL CLASSIFICATION 5-HT_1 Receptor Agonist

THERAPEUTIC CLASSIFICATION Migraine Therapy

ACTIONS AND CLINICAL PHARMACOLOGY

ZOMIG® (zolmitriptan) is a selective 5-hydroxytryptamine$_1$ (5-$HT_{1B/1D}$) receptor agonist. It exhibits a high affinity at human recombinant 5-HT_{1B} and 5-HT_{1D} receptors and modest affinity for 5-HT_{1A} receptors. Zolmitriptan has no significant affinity (as measured by radioligand binding assays) or pharmacological activity at 5-HT_2, 5-HT_3, 5-HT_4, alpha$_1$, alpha$_2$, or beta$_1$, -adrenergic; H_1, H_2, histaminic; muscarinic; dopamine$_1$, or dopamine$_2$, receptors.
The N-desmethyl metabolite of zolmitriptan also has high affinity for 5-$HT_{1B/1D}$ and modest affinity for 5-HT_{1A} receptors.

It has been proposed that symptoms associated with migraine headaches arise from the activation of the trigemino-vascular system, which results in local cranial vasodilation and neurogenic inflammation involving the antidromic release of sensory neuropeptides [Vaso-active Intestinal Peptide (VIP), Substance P and calcitonin gene related peptide (CGRP)]. The therapeutic activity of zolmitriptan for the treatment of migraine headache is thought to be attributable to its agonist effects at 5-$HT_{1B/1D}$ receptors on the intracranial blood vessels, including the arterio-venous anastamoses, and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

Pharmacokinetics

Absorption and Bioavailability: In man, zolmitriptan is rapidly and well absorbed (at least 64%) after oral administration with peak plasma concentrations occurring in 2 hours. The mean absolute bioavailability of the parent compound is approximately 40%. Food has no significant effect on the bioavailability of zolmitriptan.

During a moderate to severe migraine attack in male and female patients, mean AUC_{0-4} and C_{max} for zolmitriptan were decreased by 40% and 25%, respectively and mean T_{max} was delayed by one-half hour compared to the same patients during a migraine free period.

Plasma Kinetics and Disposition: When given as a single dose to healthy volunteers, zolmitriptan displayed linear kinetics over the dose range of 2.5 to 50 mg.

The mean apparent volume of distribution is 7.0 L/kg. Plasma protein binding of zolmitriptan over the concentration range of 10 - 1000 ng/L is 25%.

There is no evidence of accumulation on multiple dosing with zolmitriptan up to doses of 10 mg.

Biotransformation and Elimination: Zolmitriptan is eliminated largely by hepatic biotransformation followed by urinary excretion of the metabolites. The enzymes responsible for the metabolism of zolmitriptan remain to be fully characterized. The mean elimination half-life of zolmitriptan is approximately 2.5 to 3 hours. Mean total plasma clearance of zolmitriptan is 31.5 mL/min/kg, of which one-sixth is renal clearance. The renal clearance is greater than the glomerular filtration rate suggesting renal tubular secretion.

In a study in which radiolabeled zolmitriptan was administered orally to healthy volunteers, 64% and 30% of the administered ^{14}C-zolmitriptan dose was excreted in the urine and feces, respectively. About 8% of the dose was recovered in the urine as unchanged zolmitriptan. The indole acetic acid and N-oxide metabolites, which are inactive, accounted for 31% and 7% of the dose, respectively, while the active N-desmethyl metabolite accounted for 4% of the dose.

Conversion of zolmitriptan to the active N-desmethyl metabolite occurs such that metabolite concentrations are approximately two thirds that of zolmitriptan. Because the 5-$HT_{1B/1D}$ potency of the N-desmethyl metabolite is 2 to 6 times that of the parent, the metabolite may contribute a substantial portion of the overall effect after zolmitriptan administration. The half-life of the active N-desmethyl metabolite is 3 hours and the T_{max} is approximately 2 to 3 hours.

Special Populations:

Adolescents (12 - 17 years of age) Elderly, Gender, Renal Impairment, Hepatic Impairment, Hypertension, Race: Please refer to product monograph for full prescribing information. Full product monograph available upon request at AstraZeneca Canada Inc. 1-800-668-6000.

Therapeutic Clinical Trials

The efficacy of ZOMIG® conventional tablets in the acute treatment of migraine attacks was evaluated in five randomized, double-blind, placebo-controlled studies, of which 2 utilized the 1 mg dose, 2 utilized the 2.5 mg dose and 4 utilized the 5 mg dose. In all studies, the effect of zolmitriptan was compared to placebo in the treatment of a single migraine attack. All studies used the marketed formulation. Study 1 was a single-center study in which patients treated their headaches in a clinic setting. In the other studies, patients treated their headaches as outpatients. In Study 4, patients who had previously used sumatriptan were excluded, whereas in the other studies no such exclusion was applied. Patients enrolled in these five studies were predominantly female (82%) and Caucasian (97%) with a mean age of 40 years (range 12-65). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed at 1, 2, and, in most studies, 4 hours after dosing. Associated symptoms such as nausea, photophobia and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours post dose. A second dose of ZOMIG® tablets or other medication was allowed 2 to 24 hours after the initial dose, to treat persistent and recurrent headache. The frequency and time to use of these additional treatments were also recorded.

Table 1 shows efficacy results for ZOMIG® in 5 placebo-controlled trials, 4 of which were multicenter. The percentage of patients with pain relief (grade 1/0) at 2 hours after treatment (the primary endpoint measure) was significantly greater among patients receiving ZOMIG® at all doses compared to those on placebo. In Study 3, which directly compared the 1 mg, 2.5 mg and 5 mg doses, there was a statistically significant greater proportion of patients with headache response at 2 and 4 hours in the higher dose groups (2.5 mg or 5 mg) than in the 1 mg group. There was no statistically significant difference between the 2.5 mg and 5 mg dose groups for the primary endpoint measure of pain relief (1/0) at 2 hours, or at any other time point measured.

Table 1: Percentage of Patients with Pain Relief (1/0)* at 1, 2 and 4 hours - Intent to Treat Population

Study	Hour Post-dose	Placebo	Zomig® Dose (mg) 1	2.5	5
		%	%	%	%
1	1	15	9	-	24
	2	15	27	-	62†
	4	70	68	-	71
		(N=20)	(N=22)	-	(N=21)
2	1	18	-	-	42†
	2	21	-	-	61†
		(N=99)	-	-	(N=213)
3	1	24	33	43†	44†
	2	32	50†	63†**	65†**
	4	31	58†	74†	75†
		(N=140)	(N=141)	(N=298)	(N=280)
4	1	21	-	-	34†
	2	44	-	-	59†
	4	60	-	-	80†
		(N=56)	-	-	(N=498)
5	1	26	-	35	-
	2	36	-	62†	-
	4	35	-	71†	-
		(N=101)	-	(N=200)	-

*p≤0.05 in comparison with placebo. **p≤0.01 in comparison with 1 mg
†p≤0.01 in comparison with placebo - = Not studied

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

The proportion of patients pain free at 2 hours was statistically significantly greater for patients receiving ZOMIG® tablets at doses of 1, 2.5 and 5 mg compared with placebo in Study 3.

For patients with migraine associated photophobia, phonophobia, and nausea at baseline, there was a decreased incidence of these symptoms following administration of ZOMIG® as compared to placebo (see Table 2).

Table 2. Improvement in Non-Headache Symptoms*

Symptom	Patients free of non-headache symptoms at 2 hours, % (Percentage improvement over baseline)			
	Placebo	Zomig® Dose (mg) 1	2.5	5
Nausea	61 (16)	70 (23)	72 (20)	73 (26)
Photophobia	36 (18)	48 (23)	57 (39)	63 (43)
Phonophobia	46 (16)	61 (34)	67 (40)	67 (40)

*combined data from Studies 1,2,3 and 5

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The probability of taking a second ZOMIG® dose or other medication for migraine over 24 hours following the initial dose of study treatment was lower for ZOMIG® treated groups as compared to placebo. For the 1 mg dose, the probability of taking a second dose was similar to placebo and greater than with either the 2.5 or 5 mg dose.

The efficacy of ZOMIG® was not affected by the presence of aura and was independent of headache duration pre-treatment, relationship to menses, gender, age or weight of the patient, pre-treatment nausea and concomitant use of common migraine prophylactic drugs.

In an open label study conducted to evaluate long-term safety, patients treated multiple migraine headaches with 5 mg doses of zolmitriptan for up to 1 year. A total of 31,579 migraine attacks were treated during the course of the study (mean number of headaches treated per patient was 15). An analysis of patients who treated at least 30 migraine attacks of moderate or severe intensity (n = 233) suggests that the 2 hour headache response rate is maintained with repeated use of zolmitriptan.

Zomig Rapimelt

The ZOMIG RAPIMELT orally dispersible formulation was found to be bioequivalent with the conventional tablet in terms of AUC and C_{max} for zolmitriptan and its active metabolite (183C91). The time to maximum plasma concentration following administration of ZOMIG RAPIMELT is similar for the active metabolite (183C91) but can be prolonged for zolmitriptan with this formulation relative to the conventional tablet. In a clinical pharmacology study to compare the two formulations, for the active metabolite 183C91, the T_{max} ranged from 0.75 to 5 hours (median 3.0 hours) for the conventional tablet, and 1 to 6 hours (median 3.0 hours) for the orally dispersible tablet, whereas for zolmitriptan the ranges were 0.5 to 3 hours (median 1.5 hours) and 0.6 to 5 hours (median 3.0 hours), respectively. However, plasma concentrations of zolmitriptan for the orally dispersible and conventional tablet formulations are similar up to 45 minutes post dose.

Indications and Clinical Use

ZOMIG® (zolmitriptan) is indicated for the acute treatment of migraine attacks with or without aura.

ZOMIG® is not intended for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine (see CONTRAINDICATIONS). Safety and efficacy have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS

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

Because ZOMIG® can give rise to increases in blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension (see WARNINGS).

ZOMIG® should not be used within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide.

ZOMIG® is contraindicated in patients with hemiplegic, basilar or ophthalmoplegic migraine.

Concurrent administration of MAO inhibitors or use of zolmitriptan within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see PRECAUTIONS, Drug Interactions).

ZOMIG® is contraindicated in patients with hypersensitivity to zolmitriptan or any component of the formulation.

WARNINGS

ZOMIG® (zolmitriptan) should only be used where a clear diagnosis of migraine has been established.

***Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:* ZOMIG® has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. Following the use of other 5-HT_1 agonists, in rare cases these symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of 5-HT_1 agonists, including ZOMIG®. ZOMIG® should not be given to patients who have documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS).**

It is strongly recommended that ZOMIG® not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female who is surgically or physiologically postmenopausal, or male who is over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, ZOMIG® should not be administered (see CONTRAINDICATIONS).

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

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

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

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to ZOMIG®.

Cardiac Events and Fatalities Associated With 5-HT_1 Agonists: In special cardiovascular studies (see below), another 5-HT_1 agonist has been shown to cause coronary vasospasm. ZOMIG® has not been tested under similar conditions, however, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described below should be considered for all agents of this class. Serious adverse cardiac events, including acute myocardial infarction, life threatening disturbance of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low.

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

Premarketing Experience with ZOMIG Tablets: Among the more than 2,500 patients with migraine who participated in premarketing controlled clinical trials of ZOMIG® tablets, no deaths or serious cardiac events were reported.

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

Special Cardiovascular Pharmacology Studies With Another 5-HT_1 Agonist: In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT_1 agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.

In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperaemic myocardial blood flow (~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT_1 agonist is not known.

Similar studies have not been done with ZOMIG®. However, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.

Hypersensitivity: Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as ZOMIG®. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Owing to the possibility of cross-reactive hypersensitivity reactions, ZOMIG® should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists.

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

Increases in Blood Pressure: In pharmacodynamic studies, an increase of 1 and 5 mmHg in the systolic and diastolic blood pressure, respectively, was seen in volunteers with 5 mg ZOMIG®. In the headache trials, vital signs were measured only in a small, single-center inpatient study, and no effect on blood pressure was seen. In a study of patients with moderate to severe liver disease, 7 of 27 patients experienced 20 to 80 mmHg elevations in systolic or diastolic blood pressure after a 10 mg ZOMIG® dose. Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension who received 5-HT_1 agonists. ZOMIG® is contraindicated in patients with uncontrolled or severe hypertension.

PRECAUTIONS

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

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

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

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

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

Drug Interactions:

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

Other 5-HT_1 Agonists: The administration of ZOMIG® with other 5-HT_1 agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with coadministration of 5-HT_1 agonists, use of these drugs within 24 hours of each other is contraindicated.

All drug interaction studies with drugs listed below were performed in healthy volunteers using a single 10 mg dose of ZOMIG® and a single dose of the other drug, except where otherwise noted.

MAO Inhibitors: In a limited number of subjects, following one week administration of 150 mg b.i.d moclobemide, a specific MAO-A inhibitor, there was an increase of approximately 26% in both AUC and C_{max} for zolmitriptan and a 3-fold increase in the AUC and C_{max} of the active N-desmethyl metabolite. Administration of selegiline, a selective MAO-B inhibitor, at a dose of 10 mg/day for one week, had no effect on the pharmacokinetic parameters of zolmitriptan and the active N-desmethyl metabolite. The specificity of selegiline diminishes with higher doses and varies between patients. Therefore, coadministration of zolmitriptan in patients taking MAO inhibitors is contraindicated (see CONTRAINDICATIONS).

Cimetidine and other 1A2 Inhibitors: Following administration of cimetidine, a general P450 inhibitor, the half life and AUC of zolmitriptan and its active metabolite were approximately doubled. Patients taking cimetidine should not exceed a dose of 5 mg ZOMIG® in any 24 hour period. Based on the overall interaction profile, an interaction with specific inhibitors of CYP 1A2 cannot be excluded. Therefore, the same dose reduction is recommended with compounds of this type, such as fluvoxamine and the quinolones (e.g., ciprofloxacin). Following the administration of rifampicin, no clinically relevant differences in the pharmacokinetics of zolmitriptan or its active metabolite were observed.

Oral Contraceptives: Retrospective analysis of pharmacokinetic data across studies indicated that mean plasma concentrations of zolmitriptan were generally greater in females taking oral contraceptives compared to those not taking oral contraceptives. Mean C_{max} and AUC of zolmitriptan were found to be higher by 30% and 50%, respectively, and t_{max} was delayed by 30 minutes in females taking oral contraceptives. The effect of ZOMIG® on the pharmacokinetics of oral contraceptives has not been studied.

Propranolol: Propranolol, at a dose of 160 mg/day for 1 week increased the C_{max} and AUC of zolmitriptan by 1.5-fold. C_{max} and AUC of the N-desmethyl metabolite were reduced by 30% and 15%, respectively. There were no interactive effects on blood pressure or pulse rate following administration of propranolol with zolmitriptan.

Selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, paroxetine,fluvoxamine, sertraline): SSRIs have been reported, rarely, to cause weakness, hyper-reflexia, and incoordination when co-administered with 5-HT_1 agonists. If concomitant treatment with ZOMIG® and an SSRI is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised.

The pharmacokinetics and effects of ZOMIG® on blood pressure were unaffected by 4-week pre-treatment with oral fluoxetine (20 mg/day). The effects of zolmitriptan on fluoxetine metabolism were not assessed.

Acetaminophen: After concurrent administration of single 10 mg doses of ZOMIG® and 1 g acetaminophen, there was no significant effect on the pharmacokinetics of ZOMIG®. ZOMIG® reduced the AUC and C_{max} of acetaminophen by 11% and 31% respectively and delayed the t_{max} of acetaminophen by 1 hour.

Metoclopramide: Metoclopramide (single 10 mg dose) had no effect on the pharmacokinetics of ZOMIG® or its metabolites.

Use in Pregnancy: The safety of ZOMIG® for use during human pregnancy has not been established. ZOMIG® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers: It is not known whether zolmitriptan and/or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when considering the administration of ZOMIG® to nursing women. Lactating rats dosed with zolmitriptan had milk levels equivalent to maternal plasma levels at 1 hour and 4 times higher than plasma levels at 4 hours.

Use in Pediatrics: Safety and efficacy of ZOMIG® have not been studied in children under 12 years of age. Use of the drug in this age group is, therefore, not recommended.

Use in Adolescents (12-17 years of age): Systemic exposure to the parent compound does not differ significantly between adolescents and adults, however exposure to the active metabolite is greater in adolescents (see ACTIONS AND CLINICAL PHARMACOLOGY). Safety and efficacy of ZOMIG® have not been established in patients 12-17 years of age. The use of ZOMIG® in adolescents is, therefore, not recommended.

Use in the Elderly: The safety and effectiveness of ZOMIG® have not been studied in individuals over 65 years of age. The risk of adverse reactions to this drug may be greater in elderly patients as they are more likely to have decreased hepatic function, be at higher risk for CAD, and experience blood pressure increases that may be more pronounced. Clinical studies did not include patients over 65 years of age. Its use in this age group is, therefore, not recommended.

Drug/Laboratory Test Interactions: Zolmitriptan is not known to interfere with commonly employed clinical laboratory tests.

Dependence Liability: The abuse potential of ZOMIG® has not been assessed in clinical trials.

Binding to Melanin-Containing Tissues: When pigmented rats were given a single oral dose of 10 mg/kg of radiolabeled zolmitriptan, the radioactivity in the eye after 7 days, the latest time point examined, was still 75% of the values measured after 4 hours. This suggests that zolmitriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that zolmitriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with zolmitriptan were noted in any of the toxicity studies. No systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, however, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Phenylketonuria: Patients with phenylketonuria should be informed that ZOMIG RAPIMELT orally dispersible tablets contain phenylalanine (a component of aspartame). Each orally dispersible tablet contains 2.81 mg of phenylalanine.

ADVERSE EVENTS

Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

Experience in Controlled Clinical Trials with ZOMIG® (zolmitriptan)

Typical 5-HT_1 Agonist Adverse Reactions: As with other 5-HT_1 agonists, ZOMIG® has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb. In very rare cases, as with other 5-HT_1 agonists, angina pectoris and myocardial infarction have been reported.

Acute Safety: In placebo-controlled migraine trials, 1,673 patients received at least one dose of ZOMIG®. The following table (Table 3) lists adverse events that occurred in placebo-controlled clinical trials in migraine patients. Events that occurred at an incidence of 1% or more in any one of the ZOMIG® 1 mg, 2.5 mg or 5 mg dose groups and that occurred at a higher incidence than in the placebo group are included. The events cited reflect experience gained under closely monitored conditions in clinical trials, in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Several of the adverse events appear dose related, notably paresthesia, sensation of heaviness or tightness in chest, neck, jaw and throat, dizziness, somnolence, and possibly asthenia and nausea.

Table 3: Treatment Emergent Adverse Events in Five Single-Attack Placebo-Controlled Migraine Trials, Reported by ≥ 1% Patients Treated With ZOMIG®

Number of patients	Placebo 401	Zomig® 1 mg 163	Zomig® 2.5 mg 498	Zomig® 5 mg 1012
	% incidence			
Symptoms of potential cardiac origin:				
neck/throat/jaw sensations*	3.0	6.1	7.0	10.9
chest/thorax sensations*	1.2	1.8	3.4	3.8
upper limb sensations*	0.5	2.4	4.2	4.1
palpitations	0.7	0	0.2	2.2
Other Body Systems:				
Neurological:				
dizziness	4.0	5.5	8.4	9.5
nervousness	0.2	0	1.4	0.7
somnolence	3.0	4.9	6.0	7.7
thinking abnormal	0.5	0	1.2	0.3
tremor	0.7	0.6	1.0	0.7
vertigo	0	0	0	1.5
hyperesthesia	0	0	0.6	1.1
Digestive:				
diarrhea	0.5	0.6	1.0	0.6
dry mouth	1.7	4.9	3.2	3.2
dyspepsia	0.5	3.1	1.6	1.0
dysphagia	0	0	0	1.8
nausea	3.7	3.7	9.0	6.2
vomit	2.5	0.6	1.4	1.5
Miscellaneous:				
asthenia	3.2	4.9	3.2	8.8
limb sensations (upper & lower)*	0.7	0.6	0.4	1.6
limb sensations (lower)*	0.7	1.2	0.4	1.8
sensations - location unspecified*	5.2	4.9	5.8	9.2
abdominal pain	1.7	1.2	0.6	1.3
reaction aggravated	1.0	1.2	1.0	0.7
head/face sensations*	1.7	6.7	8.6	10.9
myalgia	0.2	0	0.2	1.3
myasthenia	0.2	0	0.6	1.9
dyspnea	0.2	0.6	0.2	1.2
rhinitis	0.2	1.2	1.2	0.9
sweating	1.2	0	1.6	2.5
taste perversion	0.5	2.5	0.6	0.7

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

ZOMIG® is generally well tolerated. Across all doses, most adverse events were mild to moderate in severity as well as transient and self-limiting. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age of patients; use of prophylactic medications; or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse events.

Long-Term Safety: In a long-term open label study in which patients were allowed to treat multiple migraine attacks for up to one year, 8% (167 of 2,058) of patients withdrew from the study due to an adverse experience. In this study, migraine headaches could be treated with either a single 5 mg dose of ZOMIG®, or an initial 5 mg dose followed by a second 5 mg dose if necessary (5+5 mg). The most common adverse events (defined as occurring at an incidence of at least 5%) recorded for the 5 mg and 5+5 mg doses, respectively, were little different and comprised, in descending order of frequency: neck/throat sensations* (16%, 15%), head/face sensations* (15%, 14%), asthenia (14%, 14%), sensations* location unspecified (12%, 11%), limb sensations* (11%, 11%), nausea (12%, 8%), dizziness (11%, 9%), somnolence (10%, 10%), chest/thorax sensations* (7%, 7%), dry mouth (4%, 5%), and hyperesthesia (5%, 4%). Due to the lack of a placebo arm in this study, the role of ZOMIG® in causation cannot be reliably determined. (*See footnote for Table 3.) The long-term safety of a 2.5 mg dose was not assessed in this study. Long-term safety information on the 2.5 mg dose is not yet available.

Other Events: In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of ZOMIG® in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used ZOMIG® (n=4,027) and reported an event divided by the total number of patients exposed to ZOMIG®.
All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: infrequent adverse events are those occurring in 1/100 to 1/1,000 patients and rare adverse events are those occurring in fewer than 1/1,000 patients.

Atypical sensation: Infrequent was hyperesthesia.

General: Infrequent were allergy reaction, chills, facial edema, fever, malaise and photosensitivity.

Cardiovascular: Infrequent were arrhythmias, hypertension and syncope. Rare were bradycardia, extrasystoles, postural hypotension, QT prolongation, tachycardia and thrombophlebitis.

Digestive: Infrequent were increased appetite, tongue edema, esophagitis, gastroenteritis, liver function abnormality and thirst. Rare were anorexia, constipation, gastritis, hematemesis, pancreatitis, melena and ulcer.

Hemic: Infrequent was ecchymosis. Rare were cyanosis, thrombocytopenia, eosinophilia and leukopenia.

Metabolic: Infrequent was edema. Rare were hyperglycemia and alkaline phosphatase increased.

Musculoskeletal: Infrequent were back pain, leg cramps and tenosynovitis. Rare were arthritis, tetany and twitching.

Neurological: Infrequent were agitation, anxiety, depression, emotional lability and insomnia. Rare were akathesia, amnesia, apathy, ataxia, dystonia, euphoria, hallucinations, cerebral ischemia, hyperkinesia, hypotonia, hypertonia and irritability.

Respiratory: Infrequent were bronchitis, bronchospasm, epistaxis, hiccup, laryngitis and yawn. Rare were apnea and voice alteration.

Skin: Infrequent were pruritus, rash and urticaria.

Special Senses: Infrequent were dry eye, eye pain, hyperacusis, ear pain, parosmia, and tinnitus. Rare were diplopia and lacrimation.

Urogenital: Infrequent were hematuria, cystitis, polyuria, urinary frequency, urinary urgency. Rare were miscarriage and dysmenorrhea.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no experience with clinical overdose. Volunteers receiving single 50 mg oral doses of ZOMIG® (zolmitriptan) commonly experienced sedation.

The elimination half-life of zolmitriptan is 2.5 - 3 hours (see ACTIONS & CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with ZOMIG® should continue for at least 15 hours or while symptoms or signs persist.

There is no specific antidote to zolmitriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of zolmitriptan.

DOSAGE AND ADMINISTRATION

ZOMIG® (zolmitriptan) is recommended only for the acute treatment of migraine attacks. ZOMIG® should not be used prophylactically.

Adults: The minimal effective single adult dose of ZOMIG® is 1 mg. The recommended single dose is 2.5 mg. The 1 mg dose can be approximated by manually breaking a 2.5 mg tablet in half. **The ZOMIG RAPIMELT 2.5 mg orally dispersible tablet cannot be broken in half.**

In controlled clinical trials, single doses of 1 mg, 2.5 mg or 5 mg ZOMIG® were shown to be effective in the acute treatment of migraine headaches. In the only direct comparison of the 2.5 and 5 mg doses, there was little added benefit from the higher dose, while side effects increased with 5 mg ZOMIG® (see Therapeutic Clinical Trials, Table 1, and ADVERSE EVENTS, Table 3).

If the headache returns, the dose may be repeated after 2 hours. A total cumulative dose of 10 mg should not be exceeded in any 24 hour period. Controlled trials have not established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating more than 3 migraine headaches with ZOMIG® in a one month period remains to be established.

ZOMIG RAPIMELT: The ZOMIG RAPIMELT orally dispersible tablet rapidly dissolves when placed on the tongue and is swallowed with the patient's saliva. ZOMIG RAPIMELT orally dispersible tablets can be taken when water is not available thus allowing early administration of treatment for a migraine attack. This formulation may also be beneficial for patients who suffer from nausea and are unable to drink during a migraine attack, or for patients who do not like swallowing conventional tablets.

Hepatic Impairment: Patients with moderate to severe hepatic impairment have decreased clearance of zolmitriptan and significant elevation in blood pressure was observed in some patients. Use of a low dose (<2.5 mg) with blood pressure monitoring is recommended (see ACTIONS AND CLINICAL PHARMACOLOGY, and WARNINGS).

Hypertension: ZOMIG® should not be used in patients with uncontrolled or severe hypertension. In patients with mild to moderate controlled hypertension, patients should be treated cautiously at the lowest effective dose.

Cimetidine and other 1A2 inhibitors: Patients taking cimetidine and other 1A2 inhibitors should not exceed a dose of 5 mg ZOMIG® in any 24 hour period (see PRECAUTIONS, Drug Interactions).

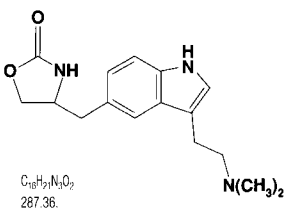
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Zolmitriptan

Chemical name: (S)-4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone

Structural Formula:



Molecular Formula: $C_{16}H_{21}N_3O_2$

Molecular Weight: 287.36.

Physical Form: White to almost white powder

Solubility: slightly soluble in water (1.3 mg/mL at 25°C), 0.1M hydrochloric acid (33 mg/mL at 25°C).

pKa : 9.64 ± 0.01

Partition co-efficient: octanol-1-ol/water partition log K_D=-1.0.

Melting point: 136°C.

Composition Inactive ingredients: anhydrous lactose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400 and 8000, sodium starch glycolate, titanium dioxide, yellow iron oxide (2.5 mg).

ZOMIG RAPIMELT: Inactive ingredients: aspartame, citric acid, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, microcrystaline cellulose, orange flavour SN027512, sodium bicarbonate.

Stability and Storage Recommendations Store at room temperature between 15 and 30°C.

AVAILABILITY OF DOSAGE FORMS

ZOMIG® (zolmitriptan) 2.5 mg tablets are yellow, round biconvex film-coated tablets intagliated "Z" on one side. Available in blister packs of 3 and 6 tablets.

ZOMIG RAPIMELT™ orally dispersible 2.5 mg tablets are white, round, uncoated tablets intagliated "Z" on one side with a bevelled edge. Available in blister packs of 2 and 6 tablets.

Product Monograph available on request.

References:
1. Purdy A et al. Zolmitriptan 2.5 mg orally disintegrating tablet for the acute treatment of migraine. Poster. 42nd Annual Scientific Meeting of the American Headache Society, June 23-25, 2000.
2. Zomig, and Zomig RapimeltTM (zolmitriptan) Product Monograph, AstraZeneca Canada Inc.

See pages A-9, A-21

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P COPAXONE®
(glatiramer acetate for injection)

20 mg, single use vials for Subcutaneous Injection

Therapeutic Classification: Immunomodulator

PHARMACOLOGY – COPAXONE® [glatiramer acetate (formerly known as copolymer-1) for injection] 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) unknown. Pre-clinical study results suggest that glatiramer acetate may modulate immune processes that are currently thought involved in the pathogenesis of MS. In particular, glatiramer acetate has been shown to reduce the incidence and severity of experimental allergic encephalomyelitis (EAE), a condition which may be induced in several animal species through immunization against CNS derived material containing myelin and an often used experimental animal model of MS. 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 – There is no information regarding the absorption, distribution, metabolism or excretion profile of COPAXONE® (glatiramer acetate for injection) in humans as appropriate pharmacokinetic studies have not been done. Based on preclinical studies it is assumed that a large fraction of a subcutaneously administered dose of glatiramer acetate would be hydrolyzed locally. Some fraction of injected material 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 similarly designed placebo-controlled trials in patients with relapsing-remitting MS (RR-MS). In both these studies, a dose of 20 mg/day was used. No other dose of glatiramer acetate has been evaluated in this patient population. The first trial was a pilot study (Trial I) which was conducted at a single-centre and was a double-blind, randomized, matched-pair, parallel group placebo-controlled trial. Fifty patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n = 25) or placebo (n = 25) subcutaneously. The protocol-specified primary outcome measure was the proportion of patients who were relapse free during the 2 year duration of the trial, but two additional relevant outcomes were also specified as endpoints: frequency of attacks during the trial, and the change in the number of attacks compared to the rate of attacks in the 2 years prior to study entry. Results from this study (see Table 1) provided preliminary evidence of effectiveness.

Table 1

Outcome	Trial I*		
	Glatiramer acetate n=25	Placebo n=25	p-Value
Mean relapse rate (2 years)	0.6	2.4	0.005
% Relapse free	56%	28%	0.085
Change in Relapse rate	3.2	1.6	0.025
Median Time to first Relapse (days)	>700	150	0.03
% of patients progression free*	80%	52%	0.07

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

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

Trial II was a multicentre double-blind, randomized, placebo-controlled trial. Two hundred and fifty-one patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n = 125) or placebo (n = 126) subcutaneously. Patients were diagnosed with RR-MS by standard criteria, and had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients had a score of no more than 5 on the Kurtzke Expanded Disability Scale Score (EDSS), a standard scale ranging from 0 (normal) to 10 (death due to MS). A score of 5 is defined as one at which a patient is still ambulatory but for whom full daily activities are impaired due to disability, a score of 6 is defined as one at which the patient is still ambulatory but requires assistance and a score of 7 on this scale means that the patient requires a wheelchair. Patients were seen every 3 months for 2 years, as well as within several days of a presumed exacerbation. In order for an exacerbation to be confirmed, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the lesion for at least 48 hours). The protocol specified primary outcome measure was the mean two-year relapse rate. Table 2 shows results of the analysis of primary and secondary outcome measures from Trial II based on the intent-to-treat population.

Table 2

Outcome	Trial II*		
	Glatiramer acetate n=125	Placebo n=126	p-Value
Mean relapse rate (2 years)	1.19	1.68	0.055
% Relapse free	34%	27%	0.25
Median Time to first Relapse (days)	287	198	0.23
% of patients progression free*	78%	75%	0.48
Mean change in EDSS	-0.05	+0.21	0.023

* The primary efficacy measure for Trial II was the mean two-year relapse rate [Mean relapse rate (2 years)]. Analyses were based on the intent-to-treat population.

* 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.

INDICATIONS – For use in ambulatory patients with Relapsing-Remitting Multiple Sclerosis to reduce the frequency of relapses. A correlation between a reduction in attack frequency alone and a decreased risk of future disability remains to be established. The safety and efficacy of COPAXONE® (glatiramer acetate for injection) beyond 2 years have not been adequately studied in placebo-controlled trials. The safety and efficacy of COPAXONE® in chronic progressive MS have not been evaluated. COPAXONE® should only be prescribed by clinicians who are experienced in the diagnosis and management of Multiple Sclerosis.

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 multicentre 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. ECG monitoring was not performed during any of these episodes and the pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New 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 – Patients should be instructed in aseptic reconstitution and self-injection techniques to assure the safe administration of COPAXONE® (glatiramer acetate for injection). The first injection should be performed under the supervision of an appropriately qualified healthcare 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. There is also no information on whether COPAXONE® can alter normal human immune responses, such as the recognition of foreign antigens. 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. Studies in both the rat and monkey have shown that immune complexes are deposited in renal glomeruli. Furthermore, in a controlled trial of 125 patients with relapsing-remitting MS treated for 2 years with 20 mg/day COPAXONE®, serum IgG levels reached approximately 3 times baseline values in 80% of patients within 3 to 6 months of treatment. These values returned to about 50% greater than baseline during the remainder of treatment.

Although COPAXONE® is intended to attenuate the autoimmune response to myelin, whether chronic treatment with COPAXONE®, and in consequence, continued alteration of cellular immunity can result in detrimental effects is unknown. 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. 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, 10 patients who switched from therapy with Interferon beta to COPAXONE® have not reported any serious and 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. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During three 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 – Approximately 850 MS patients and 50 healthy volunteers 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 5 years (28 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 after 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.

Chest Pain – Approximately 26% of glatiramer acetate patients in the multicentre 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. ECG monitoring was not performed during any of these episodes. 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. 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.

Table 3 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 multicentre 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 3 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.

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.

Musculoskeletal – 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 all 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. The frequencies presented represent the proportion of the 860 individuals exposed to COPAXONE® who had data available for this determination. 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 those not reasonably related to drug. Additional adverse reactions reported during the post-marketing period are included. 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, and abscess. ***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.

Table 3. Adverse Experiences ≥ 2% Incidence and ≥ 2% Above Placebo

Adverse Experience	COPAXONE (n=125) n	COPAXONE (n=125) %	Placebo (n=126) n	Placebo (n=126) %
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	6.3
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

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 discoloration 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:*** Ataxia, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, paranoid reaction, paraplegia, psychotic depression and transient stupor.
Respiratory - *Frequent:* Hyperventilation. ***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 - *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, 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) 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, arrythmia, 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 clinicians who have experience in the diagnosis and management of Multiple Sclerosis.* The recommended dose of COPAXONE® (glatiramer acetate for 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, abdomen, hips, and thighs. A vial is suitable for single use only; unused portions should be discarded. (See **COPAXONE® PATIENT INFORMATION** sheet for **SELF-INJECTION PROCEDURE**.)

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 1.0 mL of Sterile Water for Injection plus a 0.2 mL overage to allow for losses in reconstitution and transfer.

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° to 30°C) for up to 14 days. The vials of diluent should be stored at room temperature.

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	2 mL
Volume of Diluent to be Added	1.1 mL
Volume to be Injected	1.0 mL
Nominal Concentration per 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 vials. A separate vial, containing 1.1 mL of diluent (Sterile Water for Injection) plus 0.1 mL of overage of diluent is included in the Self Injection Administration Package for each vial of drug. COPAXONE® 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.

Product Monograph available upon request.

References:
1. COPAXONE® (glatiramer acetate) Product Monograph, Teva Marion Partners Canada™.
2. 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. *Neurology* 1995;45:1268-1276. 3. 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. 4. Khan O, Tselis A, Garbern J et al. ANA 124th Annual Meeting Program. *Annals of Neurology* 1999:46(6):938. 5. Comi G, Filippi M. The effect of glatiramer acetate (Copaxone®) on disease activity as measured by cerebral MRI in patients with relapsing-remitting multiple sclerosis (RRMS): A multi-center, randomized, double-blind, placebo-controlled study extended by open-label treatment. *Neurology* 1999;52(6)Suppl 2. 6. Mancardi GL, Sardanelli F, Parodi RC et al. Effect of copolymer-1 on serial gadolinium-enhanced MRI in relapsing remitting multiple sclerosis. *Neurology* 1998;50:1127-1133. 7. 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. 8. Data on file, Teva Marion Partners Canada™.

℗COPAXONE®
(glatiramer acetate for injection)

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Pr Zanaflex®
(tizanidine hydrochloride)

Zanaflex®
(tizanidine HCl)
equivalent to 4 mg tizanidine
Antispastic Agent

PRODUCT MONOGRAPH

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION[1,2,3]

Tizanidine is an agonist at α_2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

The imidazoline chemical structure of tizanidine is related to that of the anti-hypertensive drug clonidine and other α_2-adrenergic agonists. Pharmacological studies in animals show similarities between the two compounds, but tizanidine was found to have one-tenth to one-fiftieth (1/50) of the potency of clonidine in lowering blood pressure.

PHARMACOKINETICS

Following oral administration, tizanidine is essentially completely absorbed and has a half-life of approximately 2.5 hours (coefficient of variation [CV] = 33%). Following administration of tizanidine peak plasma concentrations occurred at 1.5 hours (CV = 40%) after dosing. Food increases C_{max} by approximately one-third and shortens time to peak concentration by approximately 40 minutes, but the extent of tizanidine absorption is not affected. Tizanidine has linear pharmacokinetics over a dose of 1 to 20 mg. The absolute oral bioavailability of tizanidine is approximately 40% (CV = 24%), due to extensive first-pass metabolism in the liver; approximately 95% of an administered dose is metabolized. Tizanidine metabolites are not known to be active; their half-lives range from 20 to 40 hours. Tizanidine is widely distributed throughout the body; mean steady state volume of distribution is 2.4 L/kg (CV = 21%) following intravenous administration in healthy adult volunteers.

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

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

SPECIAL POPULATIONS

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

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

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

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

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

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

CLINICAL STUDIES

The capacity of Zanaflex (tizanidine HCl) to reduce increased muscle tone associated with spasticity was demonstrated in two adequate and well controlled studies in patients with multiple sclerosis or spinal injury.

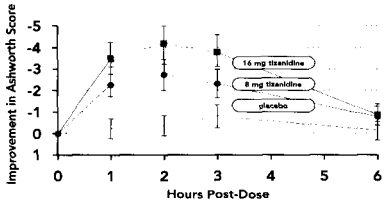
In one study, patients with multiple sclerosis were randomized to receive single oral doses of drug or placebo.[4] Patients and assessors were blind to treatment assignment and efforts were made to reduce the likelihood that assessors would become aware indirectly of treatment assignment (e.g., they did not provide direct care to patients and were prohibited from asking questions about side effects). In all, 140 patients received either placebo, 8 mg or 16 mg of Zanaflex.

Response was assessed by physical examination; muscle tone was rated on a 5 point scale (Ashworth score), with a score of 0 used to describe normal muscle tone. A score of 1 indicated a slight spastic catch while a score of 2 indicated more marked muscle resistance. A score of 3 was used to describe considerable increase in tone, making passive movement difficult. A muscle immobilized by spasticity was given a score of 4. Spasm counts were also collected.

Assessments were made at 1, 2, 3 and 6 hours after treatment. A statistically significant reduction of the Ashworth score for Zanaflex compared to placebo was detected at 1, 2 and 3 hours after treatment. Figure 1 below shows a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale. The greatest reduction in muscle tone was 1 to 2 hours after treatment. By 6 hours after treatment, muscle tone in the 8 and 16 mg tizanidine groups was indistinguishable from muscle tone in placebo treated patients. Within a given patient, improvement in muscle tone was correlated with plasma concentration. Plasma concentrations were variable from patient to patient at a given dose. Although 16 mg produced a larger effect, adverse events including hypotension were more common and more severe than in the 8 mg group. There were no differences in the number of spasms occurring in each group.

In a multiple dose study, 118 patients with spasticity secondary to spinal cord injury were randomized to either placebo or Zanaflex.[5] Steps similar to those taken in the first study were employed to ensure the integrity of blinding.

FIGURE 1: Single Dose Study - Mean Change in Muscle Tone from Baseline as Measured by the Ashworth Scale ± 95% Confidence Interval
(A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)



Patients were titrated over 3 weeks up to a maximum tolerated dose or 36 mg daily given in three unequal doses (e.g., 10 mg given in the morning and afternoon and 16 mg given at night). Patients were then maintained on their maximally tolerated dose for 4 additional weeks (i.e., maintenance phase). Throughout the maintenance phase, muscle tone was assessed on the Ashworth scale within a period of 2.5 hours following either the morning or afternoon dose and counts of spasms were collected by patient diary.

At endpoint (the protocol-specified time of outcome assessment), there were statistically significant reductions in muscle tone and spasms in the Zanaflex treated group compared to placebo. The reduction in muscle tone was not associated with a reduction in muscle strength (a desirable outcome) but also did not lead to any consistent advantage of Zanaflex treated patients on measures of activities of daily living. Figures 2 and 3 below show a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale and a comparison of the mean change in daytime spasms as recorded in patient diaries, respectively.

FIGURE 2: Multiple Dose Study - Mean Change in Muscle Tone 0.5-2.5 Hours after Dosing as Measured by the Ashworth Scale ± 95% Confidence Interval
(A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)

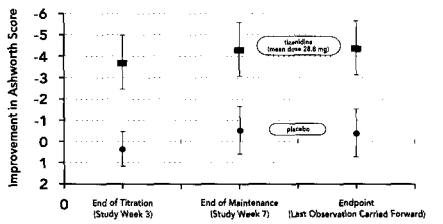
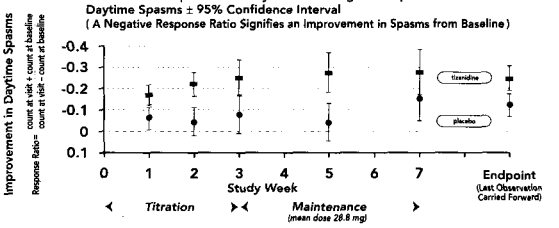


FIGURE 3: Multiple Dose Study - Mean Change in Response Ratio of Daytime Spasms ± 95% Confidence Interval
(A Negative Response Ratio Signifies an Improvement in Spasms from Baseline)



In a second multiple dose study, 187 patients with spasticity secondary to multiple sclerosis were randomized to either placebo or Zanaflex.[6] Patients were titrated over 3 weeks up to a maximum tolerated dose or 36 mg daily given in three equal doses. Patients were then maintained on their maximally tolerated dose for 9 additional weeks (i.e., maintenance phase). Throughout the maintenance phase, muscle tone was assessed on the Ashworth scale and global efficacy was assessed by both patient and investigator.

There was a statistically significant reduction in muscle tone in the Zanaflex treated group as compared to placebo at the last maintenance phase measurement of muscle tone (the protocol-specified time of outcome assessment) and throughout the maintenance phase. The reduction in muscle tone was not associated with a reduction in muscle strength.

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

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

WARNINGS

HYPOTENSION

Tizanidine HCl is an α_2-adrenergic agonist (like clonidine) and can produce hypotension. In a single dose study where blood pressure was monitored closely after dosing, two-thirds of patients treated with 8 mg of Zanaflex had a 20% reduction in either the diastolic or systolic BP. The reduction was seen within 1 hour after dosing, peaked 2 to 3 hours after dosing and was associated, at times, with bradycardia, orthostatic hypotension, lightheadedness/dizziness and rarely syncope. The hypotensive effect is dose related and has been measured following single doses of ≥ 2 mg.

The chance of significant hypotension may possibly be minimized by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to a fixed upright position may be at increased risk for hypotensive and orthostatic effects.

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

RISK OF LIVER INJURY

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

Monitoring of aminotransferase levels is recommended during the first 6 months of treatment (e.g., baseline, 1, 3 and 6 months) and periodically thereafter, based on clinical status. Because of the potential toxic hepatic effect of tizanidine, the drug should be used only with extreme caution in patients with impaired hepatic function.

SEDATION

In the multiple dose, controlled clinical studies, 48% of patients receiving any dose of Zanaflex reported sedation as an adverse event. In 10% of these cases, the sedation was rated as severe compared to <1% in the placebo treated patients. Sedation may interfere with every day activity.

The effect appears to be dose related. In a single dose study, 92% of the patients receiving 16 mg, when asked, reported that they were drowsy during the 6 hour study. This compares to 76% of the patients on 8 mg and 35% of the patients on placebo. Patients began noting this effect 30 minutes following dosing. The effect peaked 1.5 hours following dosing. Of the patients who received a single dose of 16 mg, 51% continued to report drowsiness 6 hours following dosing compared to 13% in the patients receiving placebo or 8 mg of Zanaflex.

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

HALLUCINATIONS

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

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

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

PRECAUTIONS

GENERAL

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

CARDIOVASCULAR

Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses equal to the maximum human dose on a mg/m^2 basis. ECG evaluation was not performed in the controlled clinical studies. Reduction in pulse rate has been noted in association with decreases in blood pressure in the single dose controlled study (see WARNINGS).

OPHTHALMIC

Dose-related retinal degeneration and corneal opacities have been found in animal studies at doses equivalent to approximately the maximum recommended dose on a mg/m^2 basis. There have been no reports of corneal opacities or retinal degeneration in the clinical studies.

USE IN ELDERLY

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

USE IN CHILDREN

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

USE IN OBSTETRICS

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

Reproduction studies performed in rats at a dose of 3 mg/kg, equal to the maximum recommended human dose on a mg/m^2 basis and in rabbits at 30 mg/kg, 16 times the maximum recommended human dose on a mg/m^2 basis did not show evidence of teratogenicity. Tizanidine at doses that are equal to and up to 8 times the maximum recommended human dose on a mg/m^2 basis increased gestation duration in rats. Prenatal and postnatal pup loss was increased and developmental retardation occurred. Postimplantation loss was increased in rabbits at doses of 1 mg/kg or greater, equal to or greater than 0.5 times the maximum recommended human dose on a mg/m^2 basis. Zanaflex has not been studied in pregnant women. Zanaflex should be given to pregnant women only if clearly needed.

NURSING MOTHERS

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

PATIENTS WITH SPECIAL DISEASES AND CONDITIONS

USE IN RENALLY IMPAIRED PATIENTS

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

USE IN WOMEN TAKING ORAL CONTRACEPTIVES

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

DEPENDENCE LIABILITY

Monkeys were shown to self-administer tizanidine in a dose-dependent manner, and abrupt cessation of tizanidine produced transient signs of withdrawal at doses > 35 times the maximum recommended human dose on a mg/m^2 basis. These transient withdrawal signs (increased locomotion, body twitching, and aversive behavior toward the observer) were not reversed by naloxone administration.

DRUG INTERACTIONS

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

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

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

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

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

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

INFORMATION TO BE PROVIDED TO THE PATIENTS

Patients should be advised of the limited clinical experience with Zanaflex both in regard to duration of use and the higher doses required to reduce muscle tone (see WARNINGS).

Because of the possibility of Zanaflex lowering blood pressure, patients should be warned about the risk of clinically significant orthostatic hypotension (see WARNINGS).

Because of the possibility of sedation, patients should be warned about performing activities requiring alertness, such as driving a vehicle or operating machinery (see WARNINGS). Patients should also be instructed that the sedation may be additive when Zanaflex is taken in conjunction with drugs (baclofen, benzodiazepines) or substances (e.g., alcohol) that act as CNS depressants.

ADVERSE REACTIONS

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

COMMON ADVERSE EVENTS LEADING TO DISCONTINUATION

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

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF TIZANIDINE

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

ADVERSE EVENTS REPORTED IN CONTROLLED STUDIES

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

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

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

* weakness, fatigue and/or tiredness

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

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

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

* weakness, fatigue and/or tiredness

OTHER ADVERSE EVENTS OBSERVED DURING THE EVALUATION OF TIZANIDINE

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

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

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

BODY AS A WHOLE: *Frequent:* fever; *Infrequent:* allergic reaction, moniliasis, malaise, abscess, neck pain, sepsis, cellulitis, death, overdose; *Rare:* carcinoma, congenital anomaly, suicide attempt.

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

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

HEMIC AND LYMPHATIC SYSTEM: *Infrequent:* ecchymosis, hypercholesteremia, anemia, hyperlipemia, leukopenia, leukocytosis, sepsis; *Rare:* petechia, purpura, thrombocythemia, thrombocytopenia.

METABOLIC AND NUTRITIONAL SYSTEM: *Infrequent:* edema, hypothyroidism, weight loss; *Rare:* adrenal cortex insufficiency, hyperglycemia, hypokalemia, hyponatremia, hypoproteinemia, respiratory acidosis.

MUSCULOSKELETAL SYSTEM: *Frequent:* myasthenia, back pain; *Infrequent:* pathological fracture, arthralgia, arthritis, bursitis.

Continued on page A-63

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EXELON*

(rivastigmine)

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

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

Clinical Pharmacokinetics

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

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

Metabolism: Rivastigmine is subject to first pass clearance and is rapidly and extensively metabolised, primarily via esterase-, including acetylcholinesterase-, mediated hydrolysis to a decarbamylated phenolic metabolite. *In vitro* preclinical studies suggest that the decarbamylated phenolic metabolite has approximately 10% the activity of the parent compound. The plasma half-life of the decarbamylated phenolic metabolite ranges from 2.5 to 4 hours. Additional metabolites include a sulphate conjugate, a demethylated sulfate conjugate and several unidentified minor metabolites. The pharmacokinetics of rivastigmine in patients with butyrylcholinesterase enzyme deficiency are unknown (see **PRECAUTIONS: Genetic Polymorphism**). Evidence from *in vitro* studies suggest that the major cytochrome P450 isozymes are minimally involved in rivastigmine metabolism (see **PRECAUTIONS: Drug-Drug Interactions**). Rivastigmine inhibits acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activity. In patients with Alzheimer Disease significant dose-dependent inhibition of AChE and BChE activity were noted in cerebrospinal fluid, with comparable maximum mean inhibition (62%). In plasma, significant inhibition of BChE activity is generally observed from 1.5 hours post-dose up to 6 hours post-dose, with a maximum observed inhibition of 51% at 5 mg b.i.d. Rivastigmine may therefore inhibit the butyrylcholinesterase mediated metabolism of other drugs (see **PRECAUTIONS: Drug-Drug Interactions**).

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

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

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

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

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

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

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

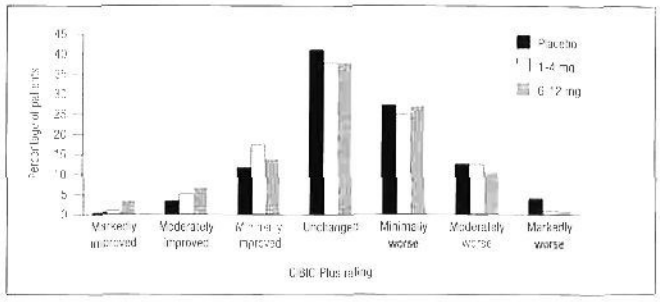
Study I (B352, USA, 26 week trial)

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

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

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

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



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

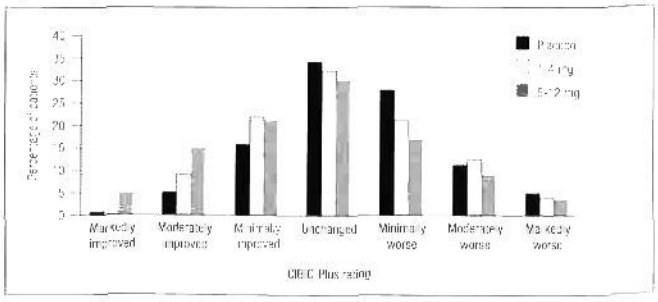
Study II (B303, Multinational, 26 week trial)

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

Effects on ADAS-cog: At baseline, mean ADAS-cog scores (mean ± SE) were for the placebo group: 23.28 ± 0.75 units; for the 1-4 mg/day group: 23.87 ± 0.76 units and for the 6-12 mg/day group: 23.57 ± 0.77 units. At the first measurement of efficacy (Week 12) the difference in mean ADAS-cog change scores (mean ± standard error) for rivastigmine treated patients compared to placebo treated patients for the intent-to-treat (ITT) population were for the 1-4 mg/day group: 0.19 ± 0.55 units and for the 6-12 mg/day group: 1.71 ± 0.57 units. Only the difference between the 6-12 mg/day group and placebo was significant at this time point. At Weeks 18 and 26 mean ADAS-cog change scores from placebo were: for the 1-4 mg/day group: 0.57 ± 0.59 (Week 18); 0.22 ± 0.67 units (Week 26) and for the 6-12 mg/day group: 1.77 ± 0.60 units (Week 18); 2.29 ± 0.69 units (Week 26). As for Week 12, only the difference between the 6-12 mg/day group and placebo was statistically significant. At the end of the 26 week treatment period, either no evidence of deterioration or an improvement was observed in 40% of the placebo group (45% (1-4 mg/day) and 52% (6-12 mg/day)) in the rivastigmine groups. A 4-point improvement in ADAS-cog score from baseline was observed in 18% of patients who received placebo, 18% (1-4 mg/day) and 27% (6-12 mg/day) of rivastigmine treated patients at Week 26. Differences between rivastigmine (6-12 mg/day) and placebo treated groups were significant for both categorical measures.

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

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



Effects on PDS: The progressive deterioration scale was used as a secondary efficacy measure. At baseline, mean PDS scores (mean ± SE) were for the placebo group: 54.8 ± 1.3 units; for the 1-4 mg/day group: 53.8 ± 1.3 units; for the 6-12 mg/day group: 55.2 ± 1.2 units. At Week 26, while the placebo group declined an average of 2.2 ± 0.9 units and the 1-4 mg/day group deteriorated by 3.3 ± 0.9 units, the 6-12 mg/day group improved by 0.5 ± 1.0 units, which was a statistically significant difference. The 6-12 mg/day group was statistically significantly superior to placebo as well as the lower dose range.
Data from these controlled clinical trials suggest that rivastigmine doses between 6-12 mg/day are more likely to result in beneficial symptomatic effects.

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

Cardiovascular Conditions: Because of their pharmacological action, cholinomimetics may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials patients with serious cardiovascular disease were excluded. Caution should therefore be exercised in treating patients with active coronary artery disease or congestive heart failure. Syncopal episodes have been reported in association with the use of EXELON. It is recommended that EXELON not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes.

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

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

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

PRECAUTIONS

Concomitant use with other drugs:

Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. **Use with Cholinomimetics and Other Cholinesterase Inhibitors:** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. **Use with other Psychoactive Drugs:** In controlled clinical trials with EXELON few patients received neuroleptics, antidepressants or anticonvulsants, there is thus limited information concerning the interaction of EXELON with these drugs.

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

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

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

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

Drug-Drug Interactions

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

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

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

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

Pregnancy

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

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

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

Adverse Events Leading to Discontinuation

Overall, 18% (340/1923) of patients treated with EXELON discontinued from Phase III controlled clinical trials due to adverse events compared to 9% (75/868) in the placebo group. During the titration phases of controlled clinical trials the incidence of discontinuations due to adverse events was 5% for placebo, 5% for EXELON 1-4 mg/day and 21% for EXELON 6-12 mg/day. During the maintenance phases, 3% of patients who received placebo, 3% of patients who received 1-4 mg/day EXELON and 6% of patients who received EXELON 6-12 mg/day withdrew from studies due to adverse events. Female patients treated with EXELON were approximately twice as likely to discontinue study participation due to adverse events than were male patients (Females: 21%; Males: 12%). The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most frequent adverse events (≥2% and twice the rate in the placebo group) leading to withdrawal from randomized placebo controlled clinical trials B351, B352, and B303 during titration and maintenance phases*

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

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

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

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

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

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

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

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

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

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

Adverse Events Reported in Controlled Trials

The events cited reflect experience gained under closely monitored condition of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in Phase 3 placebo-controlled trials for which the rate of occurrence was greater for EXELON assigned than placebo assigned patients. There were too few non Caucasian patients enrolled to assess the effect of race on the incidence of adverse events in the Phase III controlled studies. Similarly, there were too few patients aged more than 85 years to systematically assess the effect of advanced age. Female patients were more susceptible to nausea, vomiting, loss of appetite and weight loss.

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

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

Other Adverse Events Observed During Clinical Trials

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

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

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

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

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

Collagen Disorders:
Frequent: None.
Infrequent: Rheumatoid arthritis

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

Continued on page A-59

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Lamotrigine

Lamictal® Antiepileptic

Do not exceed the recommended initial dose and subsequent dose escalations of LAMICTAL. More rapid initial titration has been associated with an increased incidence of serious dermatological reactions (see WARNINGS).

Lamotrigine Tablets (25, 100, and 150 mg Tablets; 5 mg Chewable/Dispersible Tablets)

ACTION AND CLINICAL PHARMACOLOGY

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

Clinical trials

In adult placebo-controlled clinical studies, LAMICTAL has been shown to be effective in reducing seizure frequency and the number of days with seizures when added to existing antiepileptic drug therapy in adult patients with partial seizures, with or without generalized tonic-clonic seizures, that are not satisfactorily controlled.

The effectiveness of lamotrigine adjunctive therapy has also been shown in pediatric and adult patients with Lennox-Gastaut syndrome. A significant reduction in major motor seizures, drop attacks, and tonic-clonic seizures was seen following lamotrigine treatment compared with placebo treated patients. Improvements in cognitive skills (speech, nonverbal communication, alertness, attention, intellectual capacity), behaviour, and fine coordination have been seen with lamotrigine treatment in these patients.

Studies have also been conducted using lamotrigine monotherapy in adult patients (n=443) newly diagnosed with epilepsy (partial seizures, with or without secondary generalization or primary generalized tonic-clonic). Results have shown comparable efficacy (time to first seizure, seizure frequency, percentage of patients seizure-free) with fewer side effects than currently approved therapies.

Clinical trials have also demonstrated that adult patients (any seizure type) can be converted to lamotrigine monotherapy from polytherapy with significant numbers of patients maintaining or improving seizure control. Efficacy was maintained during long-term treatment (up to 152 weeks).

Pharmacokinetics

Adults: LAMICTAL is rapidly and completely absorbed following oral administration, reaching peak plasma concentrations 1.4 to 4.8 hours (T_{max}) post-dosing. When administered with food, the rate of absorption is slightly reduced, but the extent remains unchanged. Following single LAMICTAL doses of 50-400 mg, peak plasma concentration (C_{max}=0.6-4.6 µg/mL) and the area under the plasma concentration-versus-time curve (AUC=29.9-211 h•µg/mL) increase linearly with dose. The time-to-peak concentration, elimination half-life ($t_{½}$), and volume of distribution (Vd/F) are independent of dose. The $t_{½}$ averages 33 hours after single doses and Vd/F ranges from 0.9 to 1.4 L/kg. Following repeated dosing in healthy volunteers for 14 days, the $t_{½}$ decreased by an average of 26% (mean steady state $t_{½}$ of 26.4 hours) and plasma clearance increased by an average of 33%. In a single-dose study where healthy volunteers were administered both oral and intravenous doses of lamotrigine, the absolute bioavailability of oral lamotrigine was 98%.

Lamotrigine is approximately 55% bound to human plasma proteins. This binding is unaffected by therapeutic concentrations of phenytoin, phenobarbital or valproic acid. Lamotrigine does not displace other antiepileptic drugs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

Lamotrigine is metabolized predominantly in the liver by glucuronic acid conjugation. The major metabolite is an inactive 2-N-glucuronide conjugate that can be hydrolyzed by β-glucuronidase. Approximately 70% of an oral LAMICTAL dose is recovered in urine as this metabolite.

Table 1 Mean pharmacokinetic parameters in adult patients with epilepsy or healthy volunteers

		Healthy young volunteers		Patients with epilepsy		
	LAMICTAL administered	LAMICTAL	LAMICTAL +Valproic acid*	LAMICTAL +Enzyme-inducing AEDs	LAMICTAL +Valproic acid	LAMICTAL +Valproic acid +Enzyme-inducing AEDs
T_{max} (hrs)	Single dose	2.2 (0.25-12.0)†	1.8 (1.0-4.0)	2.3 (0.5-5.0)	4.8 (1.8-8.4)	3.8 (1.0-10.0)
	Multiple dose	1.7 (0.5-4.0)	1.9 (0.5-3.5)	2.0 (0.75-5.93)	ND	ND
$t_{½}$	Single dose	32.8 (14.0-103.0)	48.3 (31.5-88.6)	14.4 (6.4-30.4)	58.8 (30.5-88.8)	27.2 (11.2-51.6)
	Multiple dose	25.4 (11.6-61.6)	70.3 (41.9-113.5)	12.6 (7.5-23.1)	ND	ND
Plasma clearance (mL/min/kg)	Single dose	0.44 (0.12-1.10)	0.30 (0.14-0.42)	1.10 (0.51-2.22)	0.28 (0.16-0.40)	0.53 (0.27-1.04)
	Multiple dose	0.58 (0.24-1.15)	0.18 (0.12-0.33)	1.21 (0.66-1.82)	ND	ND

*Valproic acid administered chronically (Multiple-dose study) or for 2 days (Single-dose study). ND=Not done
†Range of individual values across studies.

Pediatrics: Lamotrigine was rapidly absorbed in children, with a T_{max} ranging from 1 to 6 hours. The mean Vd/F of lamotrigine in children aged 5 to 11 years (1.3 to 1.4 L/kg) was similar to that seen in adults (0.9 to 1.4 L/kg) but was larger in younger children (1.8 to 2.3 L/kg). As with adults, the elimination of lamotrigine in pediatric patients was similarly affected by concomitant AEDs. While the CL/F was higher and $t_{½}$ was shorter in younger children than in older children, the mean CL/F was higher and mean $t_{½}$ was shorter in both pediatric groups than in adults. Population analysis results showed that the estimated apparent plasma clearances in patients aged 13 to 18 years were similar to those found in adult patients.

Table 2 Mean pharmacokinetic parameters in pediatric patients with epilepsy

Pediatric study population	Number of subjects	T_{max} (h)	$t_{½}$ (h)	CL/F (mL/min/kg)
10 months to 5.3 years of age				
Patients taking EIAEDs	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking AEDs with no known effect on drug-metabolizing enzymes	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking VPA only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
5 to 11 years of age				
Patients taking EIAEDs	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking EIAEDs plus VPA	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking VPA only*	3	4.5 (3.0-6.0)	55.4 (24.3-73.7)	0.31 (0.20-0.54)
13 to 18 years of age				
Patients taking EIAEDs	11	†	†	1.3
Patients taking EIAEDs plus VPA	8	†	†	0.5
Patients taking VPA only	4	†	†	0.3

*Two subjects were included in the calculation for mean T_{max}. EIAEDs=Enzyme-inducing antiepileptic drugs; VPA=Valproic acid
†Parameter not estimated.

Elderly: The pharmacokinetics of lamotrigine in 12 healthy elderly volunteers (≥65 years) who each received a single oral dose of LAMICTAL (150 mg) was not different from the one in healthy young volunteers. (However, see PRECAUTIONS, **Use in the elderly** and DOSAGE AND ADMINISTRATION.)

Renal impairment: The pharmacokinetics of a single oral dose of LAMICTAL (100 mg) was evaluated in 12 individuals with chronic renal failure (with mean creatinine clearance of 13 mL/min) who were not receiving other antiepileptic drugs. In this study, the elimination half-life of unchanged lamotrigine was prolonged (by an average of 63%) relative to individuals with normal renal function (see PRECAUTIONS, **Renal failure** and DOSAGE AND ADMINISTRATION).

Hemodialysis: In six hemodialysis patients, the elimination half-life of unchanged lamotrigine was doubled off dialysis, and reduced by 50% on dialysis, relative to individuals with normal renal function.

Hepatic impairment: The pharmacokinetics of lamotrigine in patients with impaired liver function has not been evaluated.

Gilbert's syndrome: Gilbert's syndrome (idiopathic unconjugated hyperbilirubinemia) does not appear to affect the pharmacokinetic profile of lamotrigine.

Concomitant antiepileptic drugs: In patients with epilepsy, concomitant administration of LAMICTAL with enzyme-inducing AEDs (phenytoin, carbamazepine, primidone, or phenobarbital) decreases the mean lamotrigine $t_{½}$ to 13 hours. Concomitant administration of LAMICTAL with valproic acid significantly increases $t_{½}$ and decreases the clearance of lamotrigine, whereas concomitant administration of LAMICTAL with valproic acid plus enzyme-inducing AEDs can prolong $t_{½}$ up to approximately 27 hours. Chronic administration of acetaminophen was shown to slightly decrease the $t_{½}$ and increase the clearance of a single dose of lamotrigine. The key lamotrigine parameters for adult patients and healthy volunteers are summarized in Table 1, and for pediatric patients in Table 2.

INDICATIONS AND CLINICAL USE

LAMICTAL (lamotrigine) is indicated: as adjunctive therapy for the management of adult patients with epilepsy who are not satisfactorily controlled by conventional therapy; for use as monotherapy in adults following withdrawal of concomitant antiepileptic drugs; as adjunctive therapy for the management of the seizures associated with Lennox-Gastaut syndrome in pediatric and adult patients.

CONTRAINDICATIONS

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

WARNINGS

SERIOUS RASHES ASSOCIATED WITH HOSPITALIZATION HAVE OCCURRED WITH THE USE OF LAMICTAL (lamotrigine). THE INCIDENCE OF THESE RASHES IN CLINICAL TRIALS WAS 1% (1/100) IN PEDIATRIC PATIENTS (AGE <16 YEARS) AND 0.3% (3/1000) IN ADULTS. THE INCIDENCE OF SERIOUS RASH REPORTED AS STEVENS-JOHNSON SYNDROME (SJS) IN CLINICAL TRIALS WAS 0.5% (1/200) IN PEDIATRIC PATIENTS AND 0.1% (1/1000) IN ADULTS. IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR DEATH ASSOCIATED WITH RASH HAVE BEEN REPORTED, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.

A HIGHER INCIDENCE OF SERIOUS DERMATOLOGIC EVENTS (see PRECAUTIONS, **Skin-related events**, Tables 3 and 4; see also DOSAGE AND ADMINISTRATION) HAS BEEN ASSOCIATED WITH MORE RAPID INITIAL TITRATION (EXCEEDING THE RECOMMENDED INITIAL DOSE OR EXCEEDING THE RECOMMENDED DOSE ESCALATION) AND USE OF CONCOMITANT VALPROIC ACID. NEARLY ALL CASES OF RASH ASSOCIATED WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (e.g., 6 MONTHS). ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE POTENTIAL RISK SIGNALLED BY THE FIRST APPEARANCE OF A RASH.

ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE LIFE-THREATENING. ACCORDINGLY, ALL PATIENTS WHO DEVELOP RASH SHOULD BE PROMPTLY EVALUATED AND LAMICTAL WITHDRAWN IMMEDIATELY, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED.

Table 3 Effect of concomitant AEDs on rash associated with LAMICTAL in all adult controlled and uncontrolled clinical trials regardless of dosing escalation scheme

AED group	Total patient number	All rashes	Withdrawal due to rash	Hospitalization in association with rash
Enzyme-inducing AEDs*	1788	9.2%	1.8%	0.1%
Enzyme-inducing AEDs + VPA	318	8.8%	3.5%	0.9%
VPA±Non-enzyme-inducing AEDs†	159	20.8%	11.9%	2.5%
Non-enzyme-inducing AEDs	27	18.5%	0.0%	0.0%

*Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.
†Non-enzyme-inducing AEDs include clonazepam, clobazam, ethosuximide, methsuximide, vigabatrin, and gabapentin.

Table 4 Effect of the initial daily dose* of LAMICTAL, in the presence of concomitant AEDs, on the incidence of rash leading to withdrawal of treatment in adult add-on clinical trials

AED group	Enzyme-inducing AEDs†		Enzyme-inducing AEDs+VPA		VPA±Non-enzyme-inducing AEDs‡	
LAMICTAL average daily dose (mg)	Total patient number	Percentage of patients withdrawn	Total patient number	Percentage of patients withdrawn	Total patient number	Percentage of patients withdrawn
12.5	9	0.0	10	0.0	51	7.8
25	3	0.0	7	0.0	58	12.1
50	182	1.1	111	0.9	35	5.7
100	993	1.4	179	4.5	15	40.0
≥125	601	2.8	11	18.2	0	0.0

*Average daily dose in week 1.
†Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.
‡Non-enzyme-inducing AEDs include clonazepam, clobazam, ethosuximide, methsuximide, vigabatrin, and gabapentin.

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

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

PRECAUTIONS

Drug discontinuation

Abrupt discontinuation of any antiepileptic drug (AED) in a responsive patient with epilepsy may provoke rebound seizures. In general, withdrawal of an AED should be gradual to minimize this risk. Unless safety concerns (i.e., rash) require a more rapid withdrawal, the dose of LAMICTAL (lamotrigine) should be tapered over a period of at least two weeks (see DOSAGE AND ADMINISTRATION).

Occupational hazards

Patients with uncontrolled epilepsy should not drive or handle potentially dangerous machinery. During clinical trials, common adverse effects included dizziness, ataxia, drowsiness, diplopia, and blurred vision. Patients should be advised to refrain from activities requiring mental alertness or physical coordination until they are sure that LAMICTAL does not affect them adversely.

Skin-related events

In adult controlled studies of adjunctive lamotrigine therapy, the incidence of rash (usually maculopapular and/or erythematous) in patients receiving LAMICTAL was 10% compared with 5% in placebo patients. The rash usually

occurred within the first six weeks of therapy and resolved during continued administration of LAMICTAL. LAMICTAL was discontinued because of rash in 1.1% of adult patients in controlled studies and 3.8% of all patients in all studies. The rate of rash-related withdrawal in clinical studies was higher with more rapid initial titration dosing and in patients receiving concomitant valproic acid (VPA), particularly in the absence of enzyme-inducing AEDs (see Tables 3 and 4; see also WARNINGS and DOSAGE AND ADMINISTRATION).

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

Drug interactions

Antiepileptic drugs (AEDs): Lamotrigine does not affect the plasma concentrations of concomitantly administered enzyme-inducing AEDs. Antiepileptic drugs that induce hepatic drug-metabolizing enzymes (phenytoin, carbamazepine, phenobarbital, primidone) increase the plasma clearance and reduce the elimination half-life of lamotrigine (see ACTION AND CLINICAL PHARMACOLOGY).

Valproic acid reduces the plasma clearance and prolongs the elimination half-life of lamotrigine (see ACTION AND CLINICAL PHARMACOLOGY). When LAMICTAL was administered to 18 healthy volunteers already receiving valproic acid, a modest decrease (25% on average) in the trough steady-state valproic acid plasma concentrations was observed over a 3-week period, followed by stabilization. However, the addition of LAMICTAL did not affect the plasma concentration of valproic acid in patients receiving enzyme-inducing AEDs in combination with valproic acid. *See also* PRECAUTIONS, ***Skin-related events***.

The net effects of co-administration of LAMICTAL with phenytoin, carbamazepine or valproic acid are summarized in Table 5.

Table 5 Summary of AED interactions with LAMICTAL

AED	AED plasma concentration with adjunctive LAMICTAL*	Lamotrigine plasma concentration with adjunctive AEDs†
Phenytoin (PHT)	No significant effect	↓50%
Carbamazepine (CBZ)	No significant effect	↓40%
CBZ epoxide‡	Conflicting data	
Valproic acid (VPA)	Decreased	↑200%
VPA + PHT and/or CBZ	Not evaluated	No significant effect

*From adjunctive clinical trials and volunteer studies.

†Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteer studies.

‡Not administered, but an active metabolite of carbamazepine.

Oral contraceptives: In a study of 12 female volunteers, LAMICTAL did not affect plasma concentrations of ethinyloestradiol and levonorgestrel following administration of the oral contraceptive pill. However, as with the introduction of other chronic therapy in patients taking oral contraceptives, the patient should be asked to report any change in the menstrual bleeding pattern.

Drugs depressing cardiac conduction: (see **Patients with special diseases and conditions and Cardiac conduction abnormalities**).

Drug/laboratory test interactions: LAMICTAL has not been associated with any assay interferences in clinical laboratory tests.

Use in pediatrics

Safety and efficacy in patients below the age of 16 years, other than those with Lennox-Gastaut syndrome, have not been established.

Use in the elderly

The safety and efficacy of LAMICTAL in elderly patients with epilepsy have not been systematically evaluated in clinical trials. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal, and cardiac dysfunctions and limited experience with LAMICTAL in this population.

Use in obstetrics

Pregnancy: Studies in mice, rats and rabbits given lamotrigine orally or intravenously revealed no evidence of teratogenicity; however, maternal and secondary fetal toxicity were observed. Studies in rats and rabbits indicate that lamotrigine crosses the placenta; placental and fetal levels of lamotrigine were low and comparable to levels in maternal plasma. Because animal reproduction studies are not always predictive of human response, LAMICTAL should only be used during pregnancy if the benefits of therapy outweigh the risks associated with it.

Clinical trial data indicate that lamotrigine has no effect on blood folate concentrations in adults; however, its effects during human fetal development are unknown.

To facilitate monitoring fetal outcomes of pregnant women exposed to lamotrigine, physicians are encouraged to register patients, before fetal outcome (e.g., ultrasound, results of amniocentesis, birth, etc.) is known, in the Antiepilpetic Drug Pregnancy Registry by calling 1 800 336-2176 (toll free).

Labor and delivery: The effect of LAMICTAL on labor and delivery in humans is unknown.

Nursing mothers: LAMICTAL is excreted in human milk. Because of the potential for adverse reactions from LAMICTAL in nursing infants, breast-feeding while taking this medication is not recommended.

Patients with special diseases and conditions

Clinical experience with LAMICTAL in patients with concomitant illness is limited. Caution is advised when using LAMICTAL in patients with diseases or conditions that could affect the metabolism or elimination of the drug.

Renal failure: A study in individuals with chronic renal failure (not receiving other AEDs) indicated that the elimination half-life of unchanged lamotrigine is prolonged relative to individuals with normal renal function (see ACTION AND CLINICAL PHARMACOLOGY). Use of LAMICTAL in patients with severe renal impairment should proceed with caution.

Impaired liver function: There is no experience with the use of LAMICTAL in patients with impaired liver function. Caution should be exercised in dose selection for patients with this condition.

Cardiac conduction abnormalities: One placebo-controlled trial that compared electrocardiograms at baseline and during treatment demonstrated a mild prolongation of the P-R interval associated with LAMICTAL administration. The prolongation was statistically significant but clinically insignificant. Patients with significant cardiovascular disease or electrocardiographic abnormalities were, however, systematically excluded from clinical trials. Thus, LAMICTAL should be used with caution in patients with cardiac conduction abnormalities, and in patients taking concomitant medications which depress AV conduction.

Dependence liability

No evidence of abuse potential has been associated with LAMICTAL, nor is there evidence of psychological or physical dependence in humans.

Laboratory tests

The use of LAMICTAL does not require routine monitoring of any clinical laboratory parameters or plasma levels of concomitant AEDs.

ADVERSE REACTIONS

RARELY, SERIOUS SKIN RASHES, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS (LYELL SYNDROME) HAVE BEEN REPORTED. ALTHOUGH THE MAJORITY RECOVER FOLLOWING DRUG WITHDRAWAL, SOME PATIENTS EXPERIENCE IRREVERSIBLE SCARRING AND THERE HAVE BEEN RARE CASES OF ASSOCIATED DEATH (see WARNINGS).

Adverse experiences in patients receiving LAMICTAL (lamotrigine) were generally mild, occurred within the first two weeks of therapy, and resolved without discontinuation of the drug.

Commonly observed

The most commonly observed adverse experiences associated with the use of adjunctive therapy with LAMICTAL (incidence of at least 10%) were dizziness, headache, diplopia, somnolence, ataxia, nausea, and asthenia.

Dizziness, diplopia, ataxia, and blurred vision were dose-related and occurred more commonly in patients receiving carbamazepine in combination with LAMICTAL than in patients receiving other enzyme-inducing AEDs with LAMICTAL. Reduction of the daily dose and/or alteration of the timing of doses of concomitant antiepileptic drugs and/or LAMICTAL may reduce or eliminate these symptoms. Clinical data suggest a higher incidence of rash in patients who are receiving concomitant valproic acid, or non-inducing AEDs (see WARNINGS; see also PRECAUTIONS, **Skin-related events**, Table 3).

Adverse events associated with discontinuation of treatment

Across all adult add-on studies, the most common adverse experiences associated with discontinuation of LAMICTAL were rash, dizziness, headache, ataxia, nausea, diplopia, somnolence, seizure exacerbation, asthenia, and blurred vision. In controlled clinical trials, 6.9% of the 711 patients receiving LAMICTAL discontinued therapy due to an adverse experience, versus 2.9% of the 419 patients receiving placebo. Of 3501 patients and volunteers who received LAMICTAL in premarketing clinical studies, 358 (10.2%) discontinued therapy due to an adverse experience.

Serious adverse events associated with discontinuation of treatment

Discontinuation due to an adverse experience classified as serious occurred in 2.3% of adult patients and volunteers who received LAMICTAL in the premarketing studies. Rash accounted for almost half of the discontinuations due to serious adverse experiences. More rapid initial titration of LAMICTAL and concomitant use of valproic acid were associated with higher incidences of rash-related withdrawal in clinical studies (see WARNINGS; see also PRECAUTIONS, **Skin-related events**, Table 4).

Adult controlled add-on clinical studies

Table 6 enumerates adverse experiences that occurred with an incidence of 2% or greater among refractory patients with epilepsy treated with LAMICTAL.

Table 6 Treatment-emergent adverse experience incidence in adult placebo-controlled clinical studies*

Body system/ Adverse experience†		Percent of patients receiving LAMICTAL (and other AEDs) (n=711)	Percent of patients receiving placebo (and other AEDs) (n=419)
BODY AS A WHOLE	Headache	29.1	19.1
	Accidental injury	9.1	8.6
	Asthenia	8.6	8.8
	Flu syndrome	7.0	5.5
	Pain	6.2	2.9
	Back pain	5.8	6.2
	Fever	5.5	3.6
	Abdominal pain	5.2	3.6
	Infection	4.4	4.1
	Neck pain	2.4	1.2
	Malaise	2.3	1.9
	Seizure exacerbation	2.3	0.5
DIGESTIVE	Nausea	18.6	9.5
	Vomiting	9.4	4.3
	Diarrhea	6.3	4.1
	Dyspepsia	5.3	2.1
	Constipation	4.1	3.1
	Tooth disorder	3.2	1.7
MUSCULOSKELETAL	Myalgia	2.8	3.1
	Arthralgia	2.0	0.2
NERVOUS	Dizziness	38.4	13.4
	Ataxia	21.7	5.5
	Somnolence	14.2	6.9
	Incoordination	6.0	2.1
	Insomnia	5.6	1.9
	Tremor	4.4	1.4
	Depression	4.2	2.6
	Anxiety	3.8	2.6
	Convulsion	3.2	1.2
	Irritability	3.0	1.9
	Speech disorder	2.5	0.2
	Memory decreased	2.4	1.9
RESPIRATORY	Rhinitis	13.6	9.3
	Pharyngitis	9.8	8.8
	Cough increased	7.5	5.7
	Respiratory disorder	5.3	5.5
SKIN AND APPENDAGES	Rash	10.0	5.0
	Pruritus	3.1	1.7
SPECIAL SENSES	Diplopia	27.6	6.7
	Blurred vision	15.5	4.5
	Vision abnormality	3.4	1.0
UROGENITAL (Female patients)		**(n=365)**	**(n=207)**
	Dysmenorrhea	6.6	6.3
	Menstrual disorder	5.2	5.8
	Vaginitis	4.1	0.5

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

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

Other events observed during clinical studies

During clinical testing, multiple doses of LAMICTAL were administered to 3501 patients and volunteers. The conditions and duration of exposure to LAMICTAL during these clinical studies varied greatly. Studies included monotherapy and pediatric trials. A substantial proportion of the exposure was gained in open, uncontrolled clinical studies. Adverse experiences associated with exposure to LAMICTAL were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of adverse experiences into a smaller number of standardized event categories.

Since the reported adverse experiences occurred during treatment with LAMICTAL in combination with other antiepileptic drugs, they were not necessarily caused by LAMICTAL.

The following adverse events have been reported on one or more occasions by at least 1% of patients and volunteers exposed to LAMICTAL: anorexia, weight gain, amnesia, concentration disturbance, confusion, emotional lability, nervousness, nystagmus, paresthesia, thinking abnormality, and vertigo. (All types of events are included except those already listed in Table 6.)

Adult monotherapy clinical studies

Withdrawals due to adverse events were reported in 42 (9.5%) of newly diagnosed patients treated with LAMICTAL monotherapy. The most common adverse experiences associated with discontinuation of LAMICTAL were rash (6.1%), asthenia (1.1%), headache (1.1%), nausea (0.7%), and vomiting (0.7%).

Adjunctive therapy in Lennox-Gastaut syndrome

In 169 adult and pediatric patients with Lennox-Gastaut syndrome, 3.8% of patients on LAMICTAL and 7.8% of patients on placebo discontinued due to adverse experiences. The most commonly reported adverse experiences that led to discontinuation were rash for patients treated with LAMICTAL, and deterioration of seizure control for patients treated with placebo. Fever and infection occurred at least 10% more frequently in patients ≤12 years of age than in patients >12 years of age on LAMICTAL. Rash occurred at least 10% more frequently in female patients than male patients on LAMICTAL. Table 7 lists adverse events that occurred in at least 1% of 79 adult and pediatric patients who received LAMICTAL up to 15 mg/kg per day or a maximum of 400 mg per day.

Other events observed during clinical practice and from "compassionate plea" patients

In addition to the adverse experiences reported during clinical testing of LAMICTAL, the following adverse experiences have been reported in patients receiving LAMICTAL marketed in other countries and from worldwide "compassionate plea" patients. These adverse experiences have not been listed in Tables 6 and 7 and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: apnea, erythema multiforme, esophagitis, hematemesis, hemolytic anemia, pancreatitis, pancytopenia and progressive immunosuppression.

Table 7 Treatment-emergent adverse experience incidence in placebo-controlled add-on trial in adult and pediatric patients with Lennox-Gastaut syndrome*

Body system/ Adverse experience		Percent of patients receiving LAMICTAL (n=79)	Percent of patients receiving placebo (n=90)
BODY AS A WHOLE	Infection	13	8
	Accidental injury	9	7
	Flu syndrome	5	0
	Asthenia	3	1
	Abdominal pain	3	0
	Back pain	1	0
	Edema of the face	1	0
	Lab test abnormal	1	0
	Pain	1	0
CARDIOVASCULAR	Hemorrhage	3	0
DIGESTIVE	Vomiting	9	7
	Constipation	5	2
	Diarrhea	4	2
	Nausea	4	1
	Anorexia	3	1
	Stomatitis aphthosa	1	0
	Tooth disorder	1	0
ENDOCRINE	Cushing's syndrome	1	0
	Hypothyroidism	1	0
HEMIC AND LYMPHATIC	Lymphadenopathy (enlarged cervical nodes)	1	0
NERVOUS SYSTEM	Ataxia	4	1
	Convulsions	4	1
	Tremor	3	0
	Agitation	1	0
	Coordination	1	0
	Dizziness	1	0
	Emotional lability	1	0
	Nervousness	1	0
	Vertigo	1	0
RESPIRATORY	Pharyngitis	14	10
	Bronchitis	9	7
	Pneumonia	3	0
	Dyspnea	1	0
SKIN	Rash	9	7
	Eczema	4	0
	Nail disorder	1	0
SPECIAL SENSES	Blepharitis	1	0
	Conjunctivitis	1	0
	Keratitis	1	0
	Ear pain	1	0
	Eye pain	1	0
UROGENITAL	Urinary tract infection	3	0
	Balanitis	2	0
	Penis disorder	2	0

* The most frequently reported adverse reactions in children ≤12 years of age in both treatment groups were pharyngitis, fever, and infection.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

During the clinical development program, the highest known overdose of LAMICTAL (lamotrigine) occurred in a 33-year old female who ingested between 4000 and 5000 mg LAMICTAL that corresponded to a plasma level of 52 µg/mL four hours after the ingestion. The patient presented to the emergency room comatose and remained comatose for 8 to 12 hours, returned to almost normal over the next 24 hours, and completely recovered by the third day. Among patients ≤16 years of age, the two highest known single doses of LAMICTAL have been 3000 mg by a 14-year old female and approximately 1000 mg by a 4-year old male. The 14-year old female was taking marketed LAMICTAL; after the dose, she lost consciousness and was admitted to the hospital for supportive therapy, where she recovered fully (time to recovery not reported). The 4-year old male was drowsy and agitated when found, and his condition worsened to coma level II after hospitalization. He was given supportive therapy, and his condition improved rapidly with full recovery in 3 days.

There are no specific antidotes for LAMICTAL. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced or gastric lavage should be performed. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In six renal failure patients, about 20% of the amount of lamotrigine in the body was removed during 4 hours of hemodialysis.

DOSAGE AND ADMINISTRATION

General

LAMICTAL (lamotrigine) is intended for oral administration and may be taken with or without food. LAMICTAL should be added to the patient's current antiepileptic therapy.

Valproic acid more than doubles the elimination half-life of lamotrigine and reduces the plasma clearance by 50%; conversely, hepatic enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, and primidone reduce the elimination half-life of lamotrigine by 50% and double the plasma clearance (see ACTION AND CLINICAL PHARMACOLOGY). These clinically important interactions require dosage schedules of LAMICTAL as summarized in Tables 8 through 11.

LAMICTAL does not alter plasma concentrations of concomitantly administered enzyme-inducing AEDs, and therefore, they do not usually require dose adjustment to maintain therapeutic plasma concentrations. For patients receiving LAMICTAL in combination with other AEDs, an evaluation of all AEDs in the regimen should be considered if a change in seizure control or an appearance or worsening of adverse experiences is observed. If there is a need to discontinue therapy with LAMICTAL, a step-wise reduction of dose over at least two weeks (approximately 50% per week) is recommended unless safety concerns (i.e., rash) require a more rapid withdrawal (see WARNINGS and PRECAUTIONS).

The relationship of plasma concentration to clinical response has not been established for lamotrigine. Dosing of LAMICTAL should be based on therapeutic response. In controlled clinical studies, doses of LAMICTAL that were efficacious generally produced steady-state trough plasma lamotrigine concentrations of 1 to 4 µg/mL in patients receiving one or more concomitant AEDs. Doses of LAMICTAL producing this plasma concentration range were well tolerated. As with any antiepileptic drug, the oral dose of LAMICTAL should be adjusted to the needs of the individual patient, taking into consideration the concomitant AED therapy the patient is receiving.

Adults and children over 12 years of age

Do not exceed the recommended initial dose and subsequent dose escalations of LAMICTAL. More rapid initial titration has been associated with an increased incidence of serious dermatological reactions (see WARNINGS). For patients taking AEDs whose pharmacokinetic interactions with LAMICTAL are currently unknown, follow the titration schedule for concomitant VPA and non-enzyme-inducing AEDs.

There have been no controlled studies to establish the effectiveness or optimal dosing regimen of add-on LAMICTAL therapy in patients receiving only non-enzyme-inducing AEDs or valproic acid. However, available data from open clinical trials indicate that the addition of LAMICTAL under these conditions is associated with a higher incidence of serious rash or rash-related withdrawal, even at an initial titration dose of 12.5 mg daily (see PRECAUTIONS, Skin-related events, Tables 3 and 4; see also WARNINGS). The potential medical benefits of the addition of LAMICTAL under these conditions must be weighed against the increased risk of serious rash. If use of LAMICTAL under these conditions is considered clinically indicated, titration should proceed with extreme caution, especially during the first six weeks of treatment.

Table 8 LAMICTAL added to VPA with enzyme-inducing AEDs* in patients over 12 years of age

		For information† Patients taking valproic acid *only* or VPA and non-EIAEDs
Weeks 1 + 2	25 mg once a day	*25 mg every other day*
Weeks 3 + 4	25 mg twice a day	*25 mg once a day*
Usual maintenance	To achieve maintenance, doses may be increased by 25-50 mg every 1 to 2 weeks. Usual dose is between 50-100 mg twice a day.	To achieve maintenance, doses may be increased by 25-50 mg every 1 to 2 weeks. *Usual dose is between 50-100 mg twice a day.*

*Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.
†*Column reflects dosage recommendations in the U.K. and is provided for information.*

Table 9 LAMICTAL added to enzyme-inducing AEDs* (without VPA) in patients over 12 years of age

Weeks 1 + 2	50 mg once a day
Weeks 3 + 4	50 mg twice a day
Usual maintenance	To achieve maintenance, doses may be increased by 100 mg every 1 to 2 weeks. Usual dose is between 150-250 mg twice a day.

*Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.

Withdrawal of concomitant AEDs in adults

Concomitant AEDs may be decreased over a 5-week period, by approximately 20% of the original dose every week. However, a slower taper may be used if clinically indicated. During this period, the dose of LAMICTAL administered will be dependent upon the effect of the drug being withdrawn on the pharmacokinetics of lamotrigine, together with the overall clinical response of the patient. The withdrawal of enzyme-inducing AEDs (i.e., phenytoin, phenobarbital, primidone, and carbamazepine) will result in an approximate doubling of the $t_{1/2}$ of lamotrigine. Under these conditions, it may be necessary to reduce the dose of LAMICTAL. In contrast, the withdrawal of enzyme inhibiting AEDs (i.e., valproic acid) will result in a decrease in the $t_{1/2}$ of lamotrigine and may require an increase in the dose of LAMICTAL.

Pediatric dosing

Do not exceed the recommended initial dose and subsequent dose escalations of LAMICTAL. More rapid initial titration has been associated with an increased incidence of serious dermatological reactions (see WARNINGS). Safety and efficacy in patients below the age of 16 years, other than those with Lennox-Gastaut syndrome, have not been established.

Table 10 Pediatric dosing with LAMICTAL for patients receiving valproic acid with or without enzyme-inducing AEDs*

Weight range		Weeks 1 + 2 0.15 mg/kg once a day	Weeks 3 + 4 0.3 mg/kg once a day	Weeks 5 and onwards to usual maintenance dose† To achieve maintenance, doses may be increased by 0.3 mg/kg every 1-2 weeks, to a maximum of 200 mg/day. Usual dose is between 1-5 mg/kg once a day.‡
<17 kg	<37 lbs	Do not take LAMICTAL because therapy cannot be initiated with currently available tablet strengths.		
17-33 kg	37-73 lbs	5 mg every other day	5 mg/day	Increase dose by no more than 5 mg/day every 1-2 weeks.
34-49 kg	75-108 lbs	5 mg /day	10 mg/day	Increase dose by no more than 10 mg/day every 1-2 weeks.
≥50 kg§	≥110 lbs	5 mg/day	15 mg/day	Increase dose by no more than 15 mg/day every 1-2 weeks.

*Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.
†It may take several weeks to months to achieve an individualized maintenance dose.
‡Can be given as two divided doses.
§Insufficient data are available to be able to support the mg/kg dosing in patients weighing more than 50 kg.

Table 11 Pediatric dosing with LAMICTAL for patients receiving enzyme-inducing AEDs*,†,‡ without valproic acid

Weight range		Weeks 1 + 2 0.3 mg/kg twice a day	Weeks 3 + 4 0.6 mg/kg twice a day	Weeks 5 and onwards to usual maintenance dose§ To achieve maintenance, doses may be increased by 1.2 mg/kg every 1-2 weeks, to a maximum of 400 mg/day. Usual dose is between 2.5-7.5 mg/kg twice a day.
<9 kg	<20 lbs	Do not take LAMICTAL because therapy cannot be initiated with currently available tablet strengths		
9-12 kg	20-26 lbs	5 mg/day	10 mg/day	Increase dose by no more than 10 mg/day every 1-2 weeks.
13-16 kg	29-35 lbs	5 mg/day	15 mg/day	Increase dose by no more than 15 mg/day every 1-2 weeks.
17-20 kg	37-44 lbs	10 mg/day	20 mg/day	Increase dose by no more than 20 mg/day every 1-2 weeks.
21-24 kg	46-53 lbs	10 mg/day	25 mg/day	Increase dose by no more than 25 mg/day every 1-2 weeks.
25-29 kg	55-64 lbs	15 mg/day	30 mg/day	Increase dose by no more than 30 mg/day every 1-2 weeks.
30-33 kg	66-73 lbs	15 mg/day	35 mg/day	Increase dose by no more than 35 mg/day every 1-2 weeks.
34-37 kg	75-81 lbs	20 mg/day	40 mg/day	Increase dose by no more than 40 mg/day every 1-2 weeks.
38-41 kg	84-90 lbs	20 mg/day	45 mg/day	Increase dose by no more than 45 mg/day every 1-2 weeks.
42-45 kg	92-99 lbs	25 mg/day	50 mg/day	Increase dose by no more than 50 mg/day every 1-2 weeks.
46-49 kg	101-108 lbs	25 mg/day	55 mg/day	Increase dose by no more than 55 mg/day every 1-2 weeks.
50-54 kg	110-119 lbs	30 mg/day	60 mg/day	Increase dose by no more than 60 mg/day every 1-2 weeks.
55-58 kg	121-128 lbs	30 mg/day	65 mg/day	Increase dose by no more than 65 mg/day every 1-2 weeks.
≥59 kg¶	≥130 lbs	35 mg/day	70 mg/day	Increase dose by no more than 70 mg/day every 1-2 weeks.

*Enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone.
†Can be given as two divided doses.
‡Total daily dose can be divided.
§It may take several weeks to months to achieve an individualized maintenance dose.
¶Insufficient data are available to be able to support the mg/kg dosing in patients weighing more than 59 kg.

The starting doses and dose escalations listed above are different than those used in clinical trials, however, the maintenance doses are the same as those used in clinical trials. Smaller starting doses and slower dose escalations than those used in clinical trials are recommended because of concern that the risk of serious rash may be greater with higher initial doses and more rapid dose escalation. Consequently, it may take several weeks to months to

achieve an individualized maintenance dose.
The smallest available strength of LAMICTAL Chewable/Dispersible Tablets is 5 mg, and only whole tablets should be administered (scoreline on the 5 mg tablet is not intended for tablet splitting). Therefore, recommended doses have been determined based on the individual, or combination of, tablet strengths which most closely approximate, but do NOT exceed, the target dose calculated on the basis of patient weight. LAMICTAL should not be administered if the calculated daily dose is less than 2.5 mg (e.g., patients weighing less than 17 kg [37 lbs] and on concomitant VPA, or patients weighing less than 9 kg [20 lbs] and on concomitant EIAEDs without VPA). If the initial calculated daily dose of LAMICTAL is 2.5 to 5 mg, then 5 mg of LAMICTAL should be taken on alternative days for the first 2 weeks.
For patients taking AEDs whose pharmacokinetic interactions with LAMICTAL are currently unknown, follow the titration schedule for concomitant VPA.

Elderly patients

There is little experience with the use of LAMICTAL in elderly patients. Caution should thus be exercised in dose selection for an elderly patient, recognizing the more frequent hepatic, renal and cardiac dysfunctions.

Patients with impaired renal function

The elimination half-life of lamotrigine is prolonged in patients with impaired renal function (see ACTION AND CLINICAL PHARMACOLOGY). Caution should be exercised in dose selection for patients with impaired renal function.

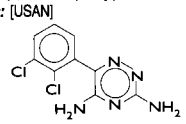
Patients with impaired hepatic function

There is no experience with the use of LAMICTAL in patients with impaired liver function. Because lamotrigine is metabolized by the liver, caution should be exercised in dose selection for patients with this condition.

PHARMACEUTICAL INFORMATION

Drug substance

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



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

Composition

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

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

LAMICTAL Chewable/Dispersible Tablets (5 mg) contain lamotrigine and the following non-medicinal ingredients: aluminum magnesium silicate, blackcurrant flavour, calcium carbonate, hydroxypropylcellulose, magnesium stearate, povidone, saccharin sodium and sodium starch glycollate.

Administration of LAMICTAL Chewable/Dispersible Tablets

LAMICTAL Chewable/Dispersible Tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit juice. The scoreline on the 5 mg tablet is not intended for tablet splitting. If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in swallowing. To disperse the tablets, add the tablets to a small amount of liquid (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the tablets are completely dispersed, swirl the solution and consume the entire quantity immediately. No attempt should be made to administer partial quantities of the dispersed tablets.

Stability and storage recommendations

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

AVAILABILITY OF DOSAGE FORMS

LAMICTAL Tablets (scored, shield-shaped, engraved "LAMICTAL") are available in three different strengths in the following pack formats:

- 25 mg tablets (white) in bottles of 100;
- 100 mg tablets (peach) in bottles of 100;
- 150 mg tablets (cream) in bottles of 60.

LAMICTAL Chewable/Dispersible Tablets (white, scored and biconvex, engraved "LAMICTAL") are available in the following pack format:

- 5 mg (initiation dose only) in blisters of 28.

Product Monograph available to healthcare professionals upon request.

References:

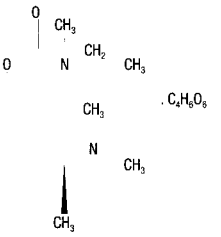
1. Motte J, Trevathan E, Arvidsson JFV, et al. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. *N Engl J Med* 1997;337:1807-1812. **2.** Product Monograph of PrLamictal® (lamotrigine), Glaxo Wellcome Inc. May 1999. **3.** Mullens L, Gallagher J, and Manasco P. Improved neurological function accompanies effective control of the Lennox-Gastaut syndrome with Lamictal®: results of a multinational, placebo-controlled trial. *Epilepsia* 1996;37(Suppl. 5):163.

Continued from page A-55

Increases to 4.5 mg bid (9 mg/day) and then 6 mg bid (12 mg/day) should also be based on good tolerability of the current dose and should only be considered after a minimum of two weeks treatment at that dose level. The maximum dose should not exceed 6 mg bid (12 mg/day). Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects. If adverse effects (e.g. nausea, vomiting, abdominal pain, loss of appetite) are observed during treatment, the patient should be instructed to stop treatment for a few days and then restart at the same dose level, or lower, as clinically indicated. If side effects persist, the drug should be discontinued.
Special Populations: For elderly patients (>85 years old) with low body weight (especially females) or serious comorbid diseases (see **WARNINGS** and **PRECAUTIONS**), it is recommended to start treatment with less frequent dosing (1.5 mg once a day) and to escalate dosage at a slower rate than for adults.
Renally or hepatically impaired: For patients with renal or hepatic impairment (see **PRECAUTIONS**) it is recommended that treatment be started with less frequent dosing (1.5 mg once a day) and that dose escalation be slower than that recommended for adults. EXELON should be taken with food in divided doses in the morning and evening. In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

PHARMACEUTICAL INFORMATION

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



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

AVAILABILITY OF DOSAGE FORM

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

Product Monograph available on request.

*Registered trademark

EXE-00-06-4980E

Once-a-day

P Aricept*

donepezil HCl 5 & 10 mg tablets

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

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

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

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

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

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

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

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

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

Other Adverse Events Observed During Clinical Trials: During the pre-marketing phase, **ARICEPT** has been administered to over 1700 individuals for various lengths of time during clinical trials worldwide. Approximately 1,200 patients have been treated for at least 3 months, and more than 1,000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 115 patients treated for over 1 year. The range of patient exposure is from 1 to 1,214 days. Treatment-emergent signs and symptoms that occurred during three placebo-controlled clinical trials and two open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the studies were integrated and the events were grouped into a smaller number of standardized categories using a modified *COSTART* dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving **ARICEPT**. All adverse events occurring at least twice are included. Adverse events already listed in Tables 2 and 3 are not repeated here (i.e., events occurring at an incidence >2%). Also excluded are *COSTART* terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed as occurring in ≥1% and <2% of patients (i.e., in 1/100 to 2/100 patients: *frequent*) or in <1% of patients (i.e., in 1/100 to 1/1,000 patients: *infrequent*). These adverse events are not necessarily related to **ARICEPT** treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. **Adverse Events Occurring in ≥1% and <2% or <1% of Patients Receiving ARICEPT:** ***Body as a Whole:*** (≥1% and <2%) influenza, chest pain, toothache; (<1%) fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, head pressure, listlessness. ***Cardiovascular System:*** (≥1% and <2%) hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; (<1%) angina pectoris, postural hypotension, myocardial infarction, premature ventricular contraction, arrhythmia, AV Block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thromboses. ***Digestive System:*** (≥1% and <2%) faecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; (<1%) eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, haemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. ***Endocrine System:*** (<1%) diabetes mellitus, goiter. ***Hemic & Lymphatic System:*** (<1%) anaemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. ***Metabolic and Nutritional Disorders:*** (≥1% and <2%) dehydration; (<1%) gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. ***Musculoskeletal System:*** (≥1% and <2%) bone fracture; (<1%) muscle weakness, muscle fasciculation. ***Nervous System:*** (≥1% and <2%) delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, libido increased, restlessness, abnormal crying, nervousness, aphasia; (<1%) cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing, seizures. ***Respiratory System:*** (≥1% and <2%) dyspnea, sore throat, bronchitis; (<1%) epistaxis, postnasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. ***Skin and Appendages:*** (≥1% and <2%) abrasion, pruritus, diaphoresis, urticaria; (<1%) dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. ***Special Senses:*** (≥1% and <2%) cataract, eye irritation, blurred vision; (<1%) dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. ***Urogenital System:*** (≥1% and <2%) urinary incontinence, nocturia; (<1%) dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. ***Long-Term Safety:*** Patients were exposed to **ARICEPT** in two open-label extension studies (n=885) of over two years. In one of the studies, 763 patients who previously completed one of two placebo-controlled studies of 15 or 30 weeks duration continued to receive **ARICEPT** and were evaluated for safety and neuropsychological evaluations for up to 152 weeks; the safety profile of **ARICEPT** in this extension study remained consistent with that observed in placebo-controlled trials. Following one and two years of treatment, 76% (n=580) and 49% (n=374) of these patients, respectively, were still receiving therapy (cumulative weeks 48 and 108). ***Postmarketing Reports:*** Voluntary reports of adverse events temporally associated with **ARICEPT** that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash. **DOSAGE AND ADMINISTRATION *ARICEPT*** (donepezil hydrochloride) tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. The recommended initial dose of **ARICEPT** is 5 mg taken once daily. Therapy with the 5 mg dose should be maintained for 4-6 weeks before considering a dose increase, in order to avoid or decrease the incidence of the most common adverse reactions to the drug (see **ADVERSE REACTIONS** Section) and to allow plasma levels to reach steady state. For those patients who do not respond adequately to the 5 mg daily dose after 4 -to- 6 weeks of treatment, the 10 mg daily dose may then be considered. The maximum recommended dose is 10 mg taken once daily. Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects. Adverse events are more common in individuals of low body weight, in patients ≥ 85 years old and in females. It is recommended that **ARICEPT** be used with caution in elderly women of low body weight and that the dose should not exceed 5 mg/day. **ARICEPT** should be taken once daily in the evening, before retiring. For patients experiencing insomnia, **ARICEPT** may be taken in the morning. It may be taken with or without food. In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision. **AVAILABILITY OF DOSAGE FORMS ARICEPT** is supplied as film-coated tablets containing 5 mg (white tablets) or 10 mg (yellow tablets) of donepezil hydrochloride. The name **ARICEPT** and the strength are embossed on each tablet. **ARICEPT** is available in high density polyethylene (HDPE) bottles of 30 tablets and in blister strips boxed as 28 tablets (combination of 2 strips of 14 tablets). **REFERENCES:** 1. Aricept® Product Monograph. Pfizer Canada Inc. May 2000. 2. Patterson C, et al. The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia. *CMAJ* 1999;160(suppl 12). 3. Waldemar G, et al. Donepezil benefits patients with both mild and moderate Alzheimer's disease over one year. 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PAAB

See pages A-28, A-29

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

IM Injection

PRESCRIBING INFORMATION

THERAPEUTIC CLASSIFICATION

Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

Description

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

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

General

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

Biologic Activities

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

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

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

CLINICAL TRIALS: EFFECTS IN MULTIPLE SCLEROSIS

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

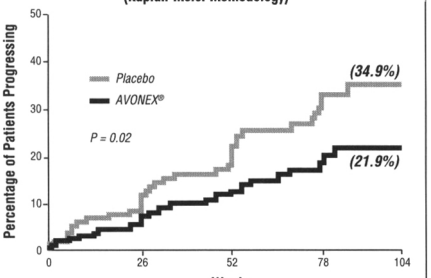
All patients had a definite diagnosis of MS of at least 1 year duration and had at least 2 exacerbations in the 3 years prior to study entry (or 1 per year if the duration of disease was less than 3 years). At entry, study participants were without exacerbation during the prior 2 months and had Kurtzke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

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

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

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

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



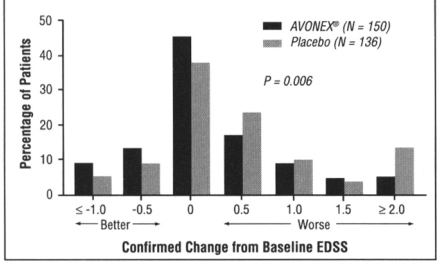
Note: Disability progression represents at least a 1.0 point increase in EDSS score sustained for at least 6 months. The value p=0.02 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given timepoint (e.g., 34.9% vs. 21.9%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

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

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

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

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



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

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

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

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

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

Table 1
MAJOR CLINICAL ENDPOINTS

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

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

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

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

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

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

[5] Analyzed by likelihood ratio test.

[6] Analyzed by Wilcoxon rank-sum test.

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General

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

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

Laboratory Tests

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

Drug Interactions

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

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

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

Use in Pregnancy

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

Nursing Mothers

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

Pediatric Use

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

Information to Patients

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

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

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

ADVERSE EVENTS

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

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

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

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

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

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

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

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

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

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

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

Serum Neutralizing Antibodies

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

PHARMACEUTICAL INFORMATION

Composition:

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

Reconstitution:

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

Stability and Storage:

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

AVAILABILITY OF DOSAGE FORMS

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

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

REFERENCES:

1 AVONEX® Product Monograph, April 6, 1998.
2 Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol.* 1996;39:285-294.
3 Data on file, PRB#8154-1, Biogen, Inc., November 20, 1997.
4 Data on file, Biogen, Inc.
5 Herndon RM, et al. Ongoing efficacy and safety analysis of interferon beta-1a (AVONEX®) in patients with Multiple Sclerosis. 122nd Annual Meeting ANA, San Diego, CA. 1997.

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PAAB

See page A-12, A-13

Continued from page A-52

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

RESPIRATORY SYSTEM: *Infrequent:* sinusitis, pneumonia, bronchitis; *Rare:* asthma.

SKIN AND APPENDAGES: *Frequent:* rash, sweating, skin ulcer; *Infrequent:* pruritus, dry skin, acne, alopecia, urticaria; *Rare:* exfoliative dermatitis, herpes simplex, herpes zoster, skin carcinoma.

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

PHARMACEUTICAL INFORMATION

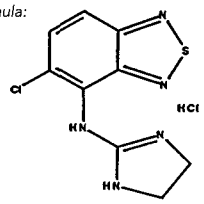
DRUG SUBSTANCE

Proper name: tizanidine HCl (USAN)

Chemical name: 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiodiazole hydrochloride

Molecular formula: $C_9H_9Cl_2N_5S$

Structural formula:



Molecular weight: 290.2

Appearance: white to off-white, fine crystalline powder, odorless or faint characteristic odor

Solubility: approximately 5% soluble in water and methanol; solubility in water decreases as the pH increases

pK_a value: 7.35 determined potentiometrically

pH: 4.3 - 5.3

Partition coefficient: 3.6:1

Melting point: 288 - 290°C

COMPOSITION

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

STABILITY AND STORAGE RECOMMENDATIONS

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

AVAILABILITY OF DOSAGE FORMS

Zanaflex is supplied as 4 mg white tablets for oral administration, embossed with the Athena logo and "594" on one side and cross-scored on the other. Zanaflex is available in 75 cc white, square, wide mouth high density polyethylene (HDPE) bottles of 150 tablets.

REFERENCES: 1. Nance PW, Bugaresti J, Shellenberger K, *et al.* Efficacy and safety of tizanidine in the treatment of spasticity in patients with spinal cord injury. *Neurology.* 1994;44(Suppl 9):S44-S52. 2. Wagstaff AJ. And Bryson HM. Tizanidine – A Review of its Pharmacology, Clinical Efficacy and Tolerability in the Management of Spasticity Associated with Cerebral and Spinal Disorders. *Drugs* 1997; 53(3):435-452. 3. Lataste X, Emre M, Davis C, Groves L. Comparative profile of tizanidine in the management of spasticity. *Neurology* 1994;44(Suppl 9):S53-S59. 4. Coward DM. Tizanidine: Neuropharmacology and Mechanism of Action. *Neurology* 1994;44(Suppl 9):S6-S11. 5. Zanaflex Product Monograph.

Full Product Monograph available upon request.

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Zanaflex (tizanidine hydrochloride)

Relief. Strength. Flexibility.

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See page A-15

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FUNCTIONAL MRI NEUROLOGIST UNIVERSITY OF TORONTO

The Division of Neurology of the University of Toronto seeks to recruit a neurologist with expertise in functional imaging to the Toronto Western Research Institute and the University Health Network, at an Assistant, Associate or full Professor academic rank. The candidate is expected to provide leadership in fMRI research related to neurodegenerative, vascular or behavioral disorders. PET, SPECT and MEG technology are also available at this university. The successful applicant will be eligible for certification in Neurology by the Royal College of Physicians and Surgeons of Canada.

The University of Toronto and the University Health Network are strongly committed to diversity within their community. The University especially welcomes applications from visible minority group members, women, aboriginal persons, persons with disabilities, and others who may contribute to further diversification of ideas. Canadian citizens and permanent residents will be considered first for this position.

Interested candidates should submit a letter of application, together with a curriculum vitae and addresses of three (3) referees by August 30, 2001 to:

Dr. James A. Sharpe,
Professor and Head,
Division of Neurology,
University of Toronto
University Health Network,
399 Bathurst St. EC 5042, TWH,
Toronto, ON M5T 2S8, Canada

Neuro-oncologist, University of Toronto

The Division of Neurology of the University Health Network in the University of Toronto is seeking to recruit a Neuro-oncologist to the Princess Margaret Hospital, at the Academic rank of Assistant, Associate or full Professor. The candidate's research should focus on either clinical trials or basic bench research applied to brain tumors. The successful neurologist must have fellowship training in Neuro-oncology and be eligible for certification in Neurology by the Royal College of Physicians and Surgeons of Canada.

The University of Toronto and the University Health network are strongly committed to diversity within their community. The University especially welcomes applications from visible minority group members, women, aboriginal persons, persons with disabilities, and others who may contribute to further diversification of ideas. Canadian citizens and permanent residents will be considered first for this position.

Interested candidates should submit a letter of application, together with a curriculum vitae and names and addresses of three (3) referees before September 1, 2001 to:

Dr. James A. Sharpe
Professor and Head,
Division of Neurology,
University of Toronto
University Health Network,
399 Bathurst St. EC 5042 TWH
Toronto ON M5T 2S8 Canada

NEUROLOGY – ST. MICHAEL'S HOSPITAL UNIVERSITY OF TORONTO

The Division of Neurology at St. Michael's Hospital is seeking to recruit a clinician scientist. The successful candidate's research should focus on basic mechanisms of cellular injury as applied to demyelinating disease. St. Michael's Hospital has identified multiple sclerosis as one of its primary foci of academic development within the Neuromusculoskeletal Program. The Division of Neurology currently consists of nine neurologists. The successful candidate must hold an MD degree, be eligible for certification in Neurology by the Royal College of Physicians and Surgeons of Canada, and have, or be eligible for, licensure in Ontario.

The University of Toronto and St. Michael's Hospital are strongly committed to diversity within their community. The University especially welcomes applications from visible minority group members, women, aboriginal persons, persons with disability and others who may contribute to further diversification of ideas. Canadian citizens and permanent residents will be considered first for this position.

Interested candidates should submit a letter of application together with a curriculum vitae and the names and addresses of three referees by May 15th, 2001 to:

Dr. P. O'Connor,
Head, Division of Neurology
St. Michael's Hospital
Room 3-007, Shuter Wing
Toronto, Ontario M5B 1W8

Queen Elizabeth II
Health Sciences Centre

CLINICAL STROKE RESEARCH FELLOW

The Acute Stroke Program at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia is seeking an individual who is interested gaining training and experience in clinical stroke research. The successful applicant will have completed a neurology residency in Canada in the previous two years. The educational component will be formalized by enrolling in the MSc Program offered by Dalhousie University's Department of Community Health and Epidemiology.

Interested applicants should make inquiries or send curriculum vitae to:

Dr. Stephen J. Phillips,
Director, Acute Stroke Program, Division of Neurology
Queen Elizabeth II Health Sciences Centre
1796 Summer Street
Halifax, Nova Scotia, B3H 3A7,
Phone:(902)473-5423 Fax:(902)473-4438
Email: stephill@is.dal.ca

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Neurosurgeon Vacancy

Queen's University at Kingston, Ontario, has a vacancy as of April 30, 2001, for a geographic full time clinical Neurosurgeon. The successful candidate will be a participant in our Alternative Funding Plan, which provides a competitive income recognizing the marketplace within Neurosurgery.

All neurosurgeons will be considered, from the postgraduate trainee completing their residency to an established academic who could be considered to lead the Division.

The successful applicant will share the call and clinical practice with two other academic neurosurgeons. This position offers protected time for academic pursuits; however, a surgeon whose main interest is high quality clinical care and teaching would find this an attractive position.

Kingston offers an unsurpassed lifestyle on Lake Ontario and the St. Lawrence River in close proximity to Ottawa, Toronto, Montreal and New York State.

Applications for this position should be directed to Dr. Peter M. Brown, Head, Department of Surgery, Queen's University, Kingston, ON K7L 3N6.

Canadian citizens and permanent residents will be considered first for this position. Queen's University is committed to employment equity and welcomes applications from all qualified men and women, including visible minorities, aboriginal people, persons with a disability, gay men and lesbians.

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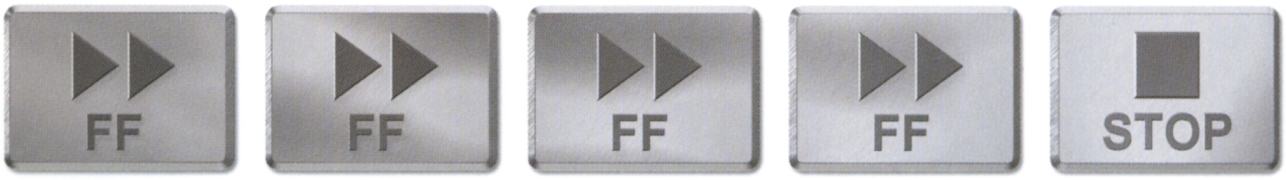

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  * Onset of action: 10–15 min. subcutaneous, 15 min. nasal spray, 30 min. tablet.
- Fast relief – Up to 86% efficacy was shown at 2 hours[3]†
- Established tolerability profile[2]‡
- Flexible formats for fast relief[2]

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

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

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

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

Product Monograph available to health care professionals upon request.

GlaxoWellcome

For brief prescribing information see pages A-37, A-38

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Exelon can make a difference in patients with Alzheimer Disease

Now on Formulary in Alberta, Saskatchewan Ontario and Quebec

The only dual-acting cholinesterase inhibitor†

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

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

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

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

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

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

1. Rösler M, Anand R, Cicin-Sain A, et al. BMJ 1999;318:633-40.
2. Schneider LS, Anand R, Farlow MR. Intl J Ger Psychopharm 1998;Suppl(1):S1-S34.
3. Corey-Bloom J, Anand R, Veach J. Intl J Ger Psychopharm 1998;1:55-65.
4. Exelon Product Monograph, April 13, 2000, Novartis Pharmaceuticals Canada Inc.

Product Monograph available upon request.

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EXE-01-05-7041E

NOVARTIS

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Dorval, Québec H9S 1A9

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Individualized Dosing

Dosing can be individualized to help optimize the therapeutic response. The suggested starting dose is 1.5 mg b.i.d. (3 mg/day), with the daily dose increased in 3 mg increments every 4 weeks.‡‡ Usual maintenance therapy is administered as 3-6 mg b.i.d. (6-12 mg/day) with morning and evening meals.

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

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

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

‡‡ Dose increases can be considered after a minimum of two weeks, as tolerated. Dose increases above 6 mg/day should proceed cautiously. The maximum dose should not exceed 6 mg b.i.d. For elderly patients (> 85 years old) with low body weight (especially females) or serious comorbid diseases, 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 younger adults.

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

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To Help Preserve Independence

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For brief prescribing information see pages A-53, A-54, A-55, A-59