PDR®

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PHYSICIANS' DESK REFERENCE®

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CONTENTS

Treatment—Standard symptomatic treatment may be undertaken if overdosage occurs. If the patient develops a dramatic increase in blood pressure, 5 to 10 mg of phentolamine mesylate has been shown to be effective in lowering blood pressure for the short time that control would be needed. It is unknown whether GlucaGen® is dialyzable, but such a procedure is unlikely to provide any benefit given the short half-life and nature of the symptoms of overdose.

DOSAGE AND ADMINISTRATION

GlucaGen® should be reconstituted with 1 ml of Sterile Water for Reconstitution (if supplied) or with 1 mL Sterile Water for Injection, USP.

Using the syringe, withdraw all of the Sterile Water for Reconstitution (if supplied) or 1 mL Sterile Water for Injection, USP and inject into the GlucaGen® vial. Roll the vial gently until powder is completely dissolved and no particles remain in the fluid. The reconstituted fluid should be clear and of water-like consistency. The reconstituted GlucaGen® gives a concentration of approximately 1 mg/ml Glucagon. The reconstituted GlucaGen® should be used immediately after reconstitution. Discard any unused portion.

For the treatment of hypoglycemia: For adults and for pediatric patients weighing 55 lb (25 kg) or more, administer 1 mg by subcutaneous, intramuscular, or intravenous injection.[1,6] According to the literature, ½ adult dose (0.5 mg) is recommended for pediatric patients weighing less than 55 lb (25 kg) or younger than 6–8 years old.[2,3,4,5,6] Emergency assistance should be sought if the patient fails to respond within 15 minutes after subcutaneous or intramuscular injection of glucagon. The glucagon injection may be repeated while waiting for emergency assistance.[1] Intravenous glucose MUST be administered if the patient fails to respond to glucagon. When the patient has responded to the treatment, give oral carbohydrate to restore the liver glycogen and prevent recurrence of hypoglycemia.

Directions for Use as a Diagnostic Aid: Reconstitute as indicated above. Discard any unused portion. When the diagnostic procedure is over, give oral carbohydrate to restore the liver glycogen and prevent occurrence of secondary hypoglycemia.

Time of maximal glucose concentration
Intravenous: 5 to 20 minutes
Intramuscular: 30 minutes
Subcutaneous: 30 to 45 minutes

Time for GI smooth muscle relaxation[1]
Intravenous: 0.25 to 2 mg (IU)—45 seconds.
Intramuscular:
1 mg (IU)—8 to 10 minutes
2 mg (IU)—4 to 7 minutes

Duration of action—
Hyperglycemic action—60 to 90 minutes
Smooth muscle relaxation—[1]
Intravenous:
0.25 to 0.5 mg (IU)—9 to 17 minutes
1 mg (IU)—22 to 25 minutes
Intramuscular:
1 mg (IU)—12 to 27 minutes
2 mg (IU)—21 to 32 minutes

Stability and storage
Before Reconstitution: The GlucaGen® package may be stored up to 24 months at controlled room temperature 20° to 25°C (68° to 77°F) prior to reconstitution. Avoid freezing and protect from light. GlucaGen® should not be used after the expiry date on the vials.

After Reconstitution: Reconstituted GlucaGen® should be used immediately. Discard any unused portion. If the solution shows any sign of gel formation or particles, it should be discarded.

HOW SUPPLIED

The GlucaGen® Diagnostic Kit includes:
1 vial containing 1 mg (1 IU) GlucaGen® [glucagon (rDNA origin) for injection]
1 vial containing 1 ml Sterile Water for Reconstitution
NDC 55390-004-01

or

The GlucaGen® 10-pack includes:
10×1 vial containing 1 mg (1 IU) GlucaGen® [glucagon (rDNA origin) for injection]
NDC 55390-004-10

Edition March 2001

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BETASERON®

[*bay-ta-seer-on*]
Interferon beta-1b

DESCRIPTION

Betaseron® (Interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques. 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 cystine residue found at position 17. Interferon beta-1b 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.

The specific activity of Betaseron is approximately 32 million international units (IU)/mg Interferon beta-1b. Each vial contains 0.3 mg of Interferon beta-1b. The unit measurement is derived by comparing the antiviral activity of the product to the World Health Organization (WHO) reference standard of recombinant human interferon beta. Mannitol, USP and Albumin (Human), USP (15 mg each/vial) are added as stabilizers.

Lyophilized Betaseron is a sterile, white to off-white powder, for subcutaneous injection after reconstitution with the diluent supplied (Sodium Chloride, 0.54% Solution).

CLINICAL PHARMACOLOGY

General

Interferons (IFNs) are a family of naturally occurring proteins, produced by eukaryotic cells in response to viral infection and other biologic agents. Three major groups of interferons have been distinguished: alpha, beta, and gamma. Interferons alpha and beta comprise the Type I interferons and interferon gamma is a Type II interferon. Type I interferons have considerably overlapping but also distinct biologic activities. The bioactivities of IFNs are mediated by their interactions with specific receptors found on the surfaces of human cells. Differences in bioactivites induced by IFNs likely reflect divergences in the signal transduction process induced by IFN-receptor binding.

Biologic Activities

The mechanism of action of Interferon beta-1b in patients with multiple sclerosis is unknown. Interferon beta-1b receptor binding induces the expression of proteins that are responsible for the pleiotropic bioactivities of Interferon beta-1b. A number of these proteins (including neopterin, β_2-microglobulin, MxA protein, and IL-10) have been measured in blood fractions from Betaseron-treated patients and Betaseron-treated healthy volunteers. Immunomodulatory effects of Interferon beta-1b include the enhancement of suppressor T cell activity, reduction of pro-inflammatory cytokine production, down-regulation of antigen presentation, and inhibition of lymphocyte trafficking into the central nervous system. It is not known if these effects play an important role in the observed clinical activity of Betaseron in multiple sclerosis (MS).

Pharmacokinetics

Because serum concentrations of Interferon beta-1b are low or not detectable following subcutaneous administration of 0.25 mg or less of Betaseron, pharmacokinetic information in patients with MS receiving the recommended dose of Betaseron is not available. Following single and multiple daily subcutaneous administrations of 0.5 mg Betaseron to healthy volunteers (N=12), serum Interferon beta-1b concentrations were generally below 100 IU/mL. Peak serum Interferon beta-1b concentrations occurred between one to eight hours, with a mean peak serum interferon concentration of 40 IU/mL. Bioavailability, based on a total dose of 0.5 mg Betaseron given as two subcutaneous injections at different sites, was approximately 50%.

After intravenous administration of Betaseron (0.006 mg to 2.0 mg), similar pharmacokinetic profiles were obtained from healthy volunteers (N=12) and from patients with diseases other than MS (N=142). In patients receiving single intravenous doses up to 2.0 mg, increases in serum concentrations were dose proportional. Mean serum clearance values ranged from 9.4 mL/min•kg^{-1} to 25.5 mL/min•kg^{-1} and were independent of dose. Mean terminal elimination half-life values ranged from 8.0 minutes to 4.3 hours and mean steady-state volume of distribution values ranged from 0.25 L/kg to 2.88 L/kg. Three-times-a-week intravenous dosing for two weeks resulted in no accumulation of Interferon beta-1b in sera of patients. Pharmacokinetic parameters after single and multiple intravenous doses of Betaseron were comparable.

Following every other day subcutaneous administration of 0.25 mg Betaseron in healthy volunteers, biologic response marker levels (neopterin, β_2-microglobulin, MxA protein, and the immunosuppressive cytokine, IL-10) increased significantly above baseline six-twelve hours after the first Betaseron dose. Biologic response marker levels peaked between 40 and 124 hours and remained elevated above baseline throughout the seven-day (168-hour) study. The relationship between serum Interferon beta-1b levels or induced biologic response marker levels and the clinical effects of Interferon beta-1b in multiple sclerosis is unknown.

CLINICAL STUDIES

The safety and efficacy of Betaseron have been assessed in three multicenter trials. Study 1 evaluated Betaseron in relapsing-remitting MS (RRMS) patients and Studies 2 and 3 assessed Betaseron in secondary progressive MS (SPMS) patients.

The effectiveness of Betaseron in relapsing-remitting MS (Study 1) was evaluated in a double blind, multiclinic, randomized, parallel, placebo controlled clinical investigation of two years duration. The study enrolled MS patients, aged 18 to 50, who were ambulatory (EDSS of ≤ 5.5), exhibited a relapsing-remitting clinical course, met Poser's criteria[1] for clinically definite and/or laboratory supported definite MS and had experienced at least two exacerbations over two years preceding the trial without exacerbation in the preceding month. Patients who had received prior immunosuppressant therapy were excluded.

An exacerbation was defined 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 of Betaseron (N=125), or 0.25 mg of Betaseron (N=124) self-administered subcutaneously every other day. Outcome based on the 372 randomized patients was evaluated after two years.

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

The primary protocol-defined outcome measures were 1) frequency of exacerbations per patient and 2) proportion of exacerbation free patients. A number of secondary clinical and magnetic resonance imaging (MRI) measures were also employed. All patients underwent annual T2 MRI imaging and a subset of 52 patients at one site had MRIs performed every six weeks for assessment of new or expanding lesions.

The study results are shown in **Table 1.**

[See table 1 at top of next page]

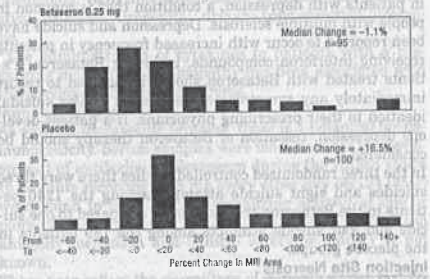
Of the 372 RRMS patients randomized, 72 (19%) failed to complete two full years on their assigned treatments.

Over the two-year period, there were 25 MS-related hospitalizations in the 0.25 mg Betaseron-treated group compared to 48 hospitalizations in the placebo group. In comparison, non-MS hospitalizations were evenly distributed among the groups, with 16 in the 0.25 mg 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 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 two years was obtained by grouping the percentages in successive intervals of equal width. Figure 1 displays a histogram of the proportions of patients, which fell into each of these intervals. The median percent change in MRI area for the 0.25 mg group was -1.1%, which was significantly smaller than the 16.5% observed for the placebo group (p=0.0001).

Distribution of Change in MRI Area

Figure 1



In an evaluation of frequent MRI scans (every six weeks) on 52 patients at one site, the percent of scans with new or expanding lesions was 29% in the placebo group and 6% in the 0.25 mg treatment group (p=0.006).

The exact relationship between MRI findings and clinical status of patients is unknown. Changes in lesion area often do not correlate with changes in disability progression. The prognostic significance of the MRI findings in this study has not been evaluated.

Continued on next page

Betaseron—Cont.

Studies 2 and 3 were multicenter, randomized, double-blind, placebo controlled trials conducted to assess the effect of Betaseron in patients with SPMS. Study 2 was conducted in Europe and Study 3 was conducted in North America. Both studies enrolled patients with clinically definite or laboratory-supported MS in the secondary progressive phase, and who had evidence of disability progression (both Study 2 and 3) or two relapses (Study 2 only) within the previous two years. Baseline Kurtzke expanded disability status scale (EDSS) scores ranged from 3.0 to 6.5.[2] Patients in Study 2 were randomized to receive Betaseron 0.25 mg (n=360) or placebo (n=358). Patients in Study 3 were randomized to Betaseron 0.25 mg (n=317), Betaseron 0.16 mg/m^2 of body surface area (n=314, mean assigned dose 0.30 mg), or placebo (n=308). Test agents were administered subcutaneously, every other day for three years.

The primary outcome measure was progression of disability, defined as a 1.0 point increase in the EDSS score, or a 0.5 point increase for patients with baseline EDSS ≥ 6.0. In Study 2, time to progression in EDSS was longer in the Betaseron treatment group (p=0.005), with estimated annualized rates of progression of 16% and 19% in the Betaseron and placebo groups, respectively. In Study 3, the rates of progression did not differ significantly between treatment groups, with estimated annualized rates of progression of 12%, 14%, and 12% in the Betaseron fixed dose, surface area-adjusted dose, and placebo groups, respectively.

Multiple analyses, including covariate and subset analyses based on sex, age, disease duration, clinical disease activity prior to study enrollment, MRI measures at baseline and early changes in MRI following treatment were evaluated in order to interpret the discordant study results. No demographic or disease-related factors enabled identification of a patient subset where Betaseron treatment was predictably associated with delayed progression of disability.

In Studies 2 and 3, like Study 1, a statistically significant decrease in the incidence of relapses associated with Betaseron treatment was demonstrated. In Study 2, the mean annual relapse rates were 0.42 and 0.63 in the Betaseron and placebo groups, respectively (p<0.001). In Study 3, the mean annual relapse rates were 0.16, 0.20, and 0.28, for the fixed dose, surface area-adjusted dose, and placebo groups, respectively (p<0.02).

MRI endpoints in both Study 2 and Study 3 showed lesser increases in T2 MRI lesion area and decreased number of active MRI lesions in patients in the Betaseron groups. The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in MRI findings often do not correlate with changes in disability progression. The prognostic significance of the MRI findings in these studies is not known.

Safety and efficacy of treatment with Betaseron beyond three years are not known.

INDICATIONS AND USAGE

Betaseron (Interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.

CONTRAINDICATIONS

Betaseron 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

Depression and Suicide

Betaseron (Interferon beta-1b) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression and suicide have been reported to occur with increased frequency in patients receiving interferon compounds, including Betaseron. Patients treated with Betaseron should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, cessation of Betaseron therapy should be considered.

In the three randomized controlled studies there were three suicides and eight suicide attempts among the 1240 patients in the Betaseron treated groups compared to one suicide and four suicide attempts among the 789 patients in the placebo groups.

Injection Site Necrosis

Injection site necrosis (ISN) has been reported in 5% of patients in controlled clinical trials (see **ADVERSE REACTIONS**). Typically, injection site necrosis occurs within the first four months of therapy, although post-marketing reports have been received of ISN occurring over one year after initiation of therapy. Necrosis may occur at a single or multiple injection sites. The necrotic lesions are typically three cm or less in diameter, but larger areas have been reported. Generally the necrosis has extended only to subcutaneous fat. However, there are also reports of necrosis extending to and including fascia overlying muscle. In some lesions where biopsy results are available, vasculitis has been reported. For some lesions debridement and, infrequently, skin grafting have been required.

As with any open lesion, it is important to avoid infection and, if it occurs, to treat the infection. Time to healing was varied depending on the severity of the necrosis at the time treatment was begun. In most cases healing was associated with scarring.

TABLE 1
Two Year RRMS Study Results
Primary and Secondary Clinical Outcomes

Efficacy Parameters		Treatment Groups			Statistical Comparisons p-value		
Primary End Points		Placebo (N=123)	0.05 mg (N=125)	0.25 mg (N=124)	Placebo vs 0.05 mg	0.05 mg vs 0.25 mg	Placebo vs 0.25 mg
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	0.288	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	0.995	0.108	0.144
Mean change in Scripps score‡‡ at endpoint		-0.53	-0.50	0.66	0.641	0.051	0.128
Median duration in days per exacerbation		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, six from 0.05 mg, and eight from 0.25 mg) dropped out of the study before completing six 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 1-10, with higher scores reflecting greater disability.
‡‡ Scripps neurologic rating scores range from 0-100, with smaller scores reflecting greater disability.

Some patients have experienced healing of necrotic skin lesions while Betaseron therapy continued; others have not. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis. For patients who continue therapy with Betaseron after injection site necrosis has occurred, Betaseron should not be administered into the affected area until it is fully healed. If multiple lesions occur, therapy should be discontinued until healing occurs.

Patient understanding and use of aseptic self-injection techniques and procedures should be periodically reevaluated, particularly if injection site necrosis has occurred.

Anaphylaxis

Anaphylaxis has been reported as a rare complication of Betaseron use. Other allergic reactions have included dyspnea, bronchospasm, tongue edema, skin rash and urticaria (see **ADVERSE REACTIONS**).

Albumin (Human), USP

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

Information for Patients

All patients should be instructed to carefully read the supplied Betaseron Medication Guide. Patients should be cautioned not to change the dose or schedule of administration without medical consultation.

Patients should be made aware that serious adverse reactions during the use of Betaseron have been reported, including depression and suicidal ideation, injection site necrosis, and anaphylaxis (see **WARNINGS**). Patients should be advised of the symptoms of depression or suicidal ideation and be told to report them immediately to their physician. Patients should also be advised of the symptoms of allergic reactions and anaphylaxis.

Patients should be advised to promptly report any break in the skin, which may be associated with blue-black discoloration, swelling, or drainage of fluid from the injection site, prior to continuing their Betaseron therapy.

Patients should be informed that flu-like symptoms are common following initiation of therapy with Betaseron. In the controlled clinical trials, antipyretics and analgesics were permitted for relief of these symptoms. In addition, gradual dose titration during initiation of Betaseron treatment may reduce flu-like symptoms (see **DOSAGE AND ADMINISTRATION**).

Female patients should be cautioned about the abortifacient potential of Betaseron (see **PRECAUTIONS, Pregnancy: Teratogenic Effects**).

Instruction on Self-injection Technique and Procedures

Patients should be instructed in the use of aseptic technique when administering Betaseron. Appropriate instruction for reconstitution of Betaseron and self-injection should be provided, including careful review of the Betaseron Medication Guide. The first injection should be performed under the supervision of an appropriately qualified health care professional.

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.

Patients should be advised of the importance of rotating areas of injection with each dose, to minimize the likelihood of severe injection site reactions, including necrosis or localized infection, (see **Picking an Injection Site** section of the **Medication Guide**).

Laboratory Tests

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts and blood chemistries, including liver function tests, are recommended at regular intervals (one, three, and six months) following introduction of Betaseron therapy, and then periodically thereafter in the absence of clinical symptoms. Thyroid function tests are recommended every six months in patients with a history of thyroid dysfunction or as clinically indicated. 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 Betaseron. In the placebo controlled studies in MS, corticosteroids or ACTH were administered for treatment of relapses for periods of up to 28 days in patients (N=664) receiving Betaseron.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: Interferon beta-1b has not been tested for its carcinogenic potential in animals.

Mutagenesis: Betaseron was not mutagenic when assayed for genotoxicity in the Ames bacterial test in the presence or absence of metabolic activation. Interferon beta-1b was not mutagenic to human peripheral blood lymphocytes *in vitro*, in the presence or absence of metabolic inactivation. Betaseron treatment of mouse BALBc-3T3 cells did not re-

sult in increased transformation frequency in an *in vitro* model of tumor transformation.

Impairment of fertility: Studies in normally cycling, female rhesus monkeys at doses up to 0.33 mg/kg/day (32 times the recommended human dose based on body surface area, body surface dose based on 70 kg female) had no apparent adverse effects on either menstrual cycle duration or associated hormonal profiles (progesterone and estradiol) when administered over three consecutive menstrual cycles. The validity of extrapolating doses used in animal studies to human doses is not known. Effects of Betaseron on normally cycling human females are not known.

Pregnancy - Teratogenic Effects

Pregnancy Category C: Betaseron was not teratogenic at doses up to 0.42 mg/kg/day when given to pregnant female rhesus monkeys on gestation days 20 to 70. However, a dose related abortifacient activity was observed in these monkeys when Interferon beta-1b was administered at doses ranging from 0.028 mg/kg/day to 0.42 mg/kg/day (2.8 to 40 times the recommended human dose based on body surface area comparison). The validity of extrapolating doses used in animal studies to human doses is not known. Lower doses were not studied in monkeys. Spontaneous abortions while on treatment were reported in patients (n=4) who participated in the Betaseron RRMS clinical 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. If the patient becomes pregnant or plans to become pregnant while taking Betaseron, the patient should be apprised of the potential hazard to the fetus and it should be recommended that the patient discontinue therapy.

Nursing Mothers

It is not known whether Betaseron is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Betaseron, a decision should be made to either discontinue nursing or discontinue the drug, taking into account the importance of drug to the mother.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Clinical studies of Betaseron did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

ADVERSE REACTIONS

In all studies, the most serious adverse reactions with Betaseron were depression, suicidal ideation and injection site necrosis (see **WARNINGS**). The incidence of depression of any severity was approximately 34% in both Betaseron-treated patients and placebo-treated patients. Anaphylaxis and other allergic reactions have been reported in patients using Betaseron (see **WARNINGS**). The most commonly reported adverse reactions were lymphopenia (lymphocytes $<1500/mm^3$), injection site reaction, asthenia, flu-like symptom complex, headache, and pain. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Betaseron, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were depression, flu-like symptom complex, injection site reactions, leukopenia, increased liver enzymes, asthenia, hypertonia, and myasthenia.

Because clinical trials are conducted under widely varying conditions and over varying lengths of time, adverse reaction rates observed in the clinical trials of Betaseron cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to Betaseron in the three placebo controlled trials of 1115 patients with MS treated with 0.25 mg or 0.16 mg/m^2, including 1041 exposed for greater than one year. The population encompassed an age range from 18-65 years. Sixty-five percent (65%) of the patients were female. The percentages of Caucasian, Black, Asian, and Hispanic patients were 94.0%, 4.3%, 0.2%, and 0.8%, respectively.

The safety profiles for Betaseron-treated patients with SPMS and RRMS were similar. Clinical experience with Betaseron in other populations (patients with cancer, HIV positive patients, etc.) provides additional data regarding adverse reactions; however, experience in non-MS populations may not be fully applicable to the MS population.

Injection Site Reactions

In three controlled clinical trials, injection site reactions occurred in 86% of patients receiving Betaseron with injection site necrosis in 5%. Inflammation (53%), pain (18%), hypersensitivity (3%), necrosis (5%), mass (2%), edema (3%) and non-specific reactions were significantly associated with Betaseron treatment (see **WARNINGS** and **PRECAUTIONS**). The incidence of injection site reactions tended to decrease over time, with approximately 76% of patients experiencing the event during the first three months of treatment, compared to approximately 45% at the end of the studies.

Flu-Like Symptom Complex

The rate of flu-like symptom complex was approximately 60% in the three controlled clinical trials. The incidence decreased over time, with only 10% of patients reporting flu-like symptom complex at the end of the studies. For patients who experienced a flu-like symptom complex in Study 1, the median duration was 7.5 days.

Laboratory Abnormalities

In the three clinical trials, leukopenia was reported in 18% and 5% of patients in Betaseron- and placebo-treated groups, respectively. No patients were withdrawn or dose reduced for neutropenia in Study 1. Three percent (3%) of patients in Studies 2 and 3 experienced leukopenia and were dose-reduced. Other laboratory abnormalities included SGPT greater than five times baseline value (10%), and SGOT greater than five times baseline value (3%). In Study 1, two patients were dose reduced for increased liver enzymes; one continued on treatment and one was ultimately withdrawn. In Studies 2 and 3, 1.5% of Betaseron patients were dose-reduced or interrupted treatment for increased liver enzymes. Three (0.3%) patients were withdrawn from treatment with Betaseron for any laboratory abnormality including two (0.2%) patients following dose reduction (see **PRECAUTIONS, Laboratory Tests**).

Menstrual Irregularities

In the three clinical trials, 82 (14%) of the 577 pre-menopausal females treated with Betaseron and 74 (18%) of the 405 pre-menopausal females treated with placebo reported menstrual disorders. One event was reported as severe, all other reports were mild to moderate severity. No patients withdrew from the studies due to menstrual irregularities.

Table 2 enumerates adverse events and laboratory abnormalities that occurred among all patients treated with 0.25 mg or 0.16 mg/m^2 Betaseron every other day for periods of up to three years in the controlled trials at an incidence that was at least 2% more than that observed in the placebo patients.

TABLE 2
Adverse Reactions and Laboratory Abnormalities

Adverse Reaction	Placebo (n=789)	Betaseron (n=1115)
Body as a Whole		
Injection site reaction	29%	85%
Asthenia	54%	61%
Flu-like symptom complex	41%	60%
Headache	48%	57%
Pain	42%	51%
Fever	22%	36%
Chills	11%	25%
Abdominal pain	13%	19%
Chest pain	7%	11%
Malaise	4%	8%
Injection site necrosis	0%	5%
Cardiovascular System		
Peripheral edema	12%	15%
Vasodilation	6%	8%
Hypertension	4%	7%
Peripheral vascular disorder	4%	6%
Palpitation	2%	4%
Tachycardia	2%	4%
Digestive System		
Nausea	25%	27%
Constipation	18%	20%
Diarrhea	16%	19%
Dyspepsia	12%	14%
Hemic and Lymphatic System		
Lymphocytes $< 1500/mm^3$	70%	88%
ANC $< 1500/mm^3$	5%	14%
WBC $< 3000/mm^3$	4%	14%
Lymphadenopathy	4%	8%
Metabolic and Nutritional Disorders		
SGPT > 5 times baseline	4%	10%
SGOT > 5 times baseline	1%	3%
Weight gain	5%	7%
Musculoskeletal System		
Myasthenia	43%	46%
Arthralgia	29%	31%
Myalgia	16%	27%
Leg cramps	2%	4%
Nervous System		
Hypertonia	40%	50%
Dizziness	21%	24%
Insomnia	19%	24%
Incoordination	18%	21%
Anxiety	8%	10%
Nervousness	5%	7%
Respiratory System		
Dyspnea	4%	7%
Skin and Appendages		
Rash	18%	24%
Skin disorder	10%	12%
Sweating	6%	8%
Alopecia	2%	4%
Urogential System		
Urinary urgency	10%	13%
Metrorrhagia*	8%	11%
Menorrhagia*	6%	8%
Impotence**	7%	9%
Urinary frequency	5%	7%
Dysmenorrhea*	5%	7%
Prostatic disorder**	1%	3%

* pre-menopausal women
** male patients

The following adverse events have been observed during postmarketing experience with Betaseron and are classified within body system categories:

Body General: *fatal capillary leak syndrome; Cardiovascular: cardiomyopathy, deep vein thrombosis, pulmonary embolism; Digestive: hepatitis, pancreatitis, vomiting; Endocrine: hypothyroidism, hyperthyroidism, thyroid dysfunction; Hemic and Lymphatic System: anemia, thrombocytopenia; Metabolic and Nutritional: Gamma GT increase, hypocalcemia, hyperuricemia, triglyceride increase; Nervous: ataxia, confusion, convulsion, depersonalization, emotional lability, paresthesia; Respiratory: bronchospasm, pneumonia; Skin and Appendages: pruritus, skin discoloration, urticaria; Urogenital: urinary tract infection, urosepsis.

*The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of this syndrome.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Serum samples were monitored for the development of antibodies to Betaseron during the RRMS study. In patients receiving 0.25 mg every other day 56/124 (45%) were found to have serum neutralizing activity at one or more of the time points tested. The relationship between antibody formation and clinical safety or efficacy is not known.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Betaseron using a biological neutralization assay that measures the ability of immune sera to inhibit the production of the interferon-inducible protein, MxA. Neutralization assays are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, timing of sample collection,

Continued on next page

Betaseron—Cont.

concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Betaseron with the incidence of antibodies to other products may be misleading.

Anaphylactic reactions have rarely been reported with the use of Betaseron.

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

Safety of doses higher than 0.25 mg every other day has not been adequately evaluated. The maximum amount of Betaseron that can be safely administered has not been determined.

DOSAGE AND ADMINISTRATION

The recommended dose of Betaseron is 0.25 mg injected subcutaneously every other day. Generally, patients should be started at 0.0625 mg (0.25 mL) subcutaneously every other day, and increased over a six-week period to 0.25 mg (1.0 mL) every other day (see **Table 3**).

Table 3. Schedule for Dose Titration

	Recommended Titration	Betaseron Dose	Volume
Weeks 1-2	25%	0.0625 mg	0.25 mL
Weeks 3-4	50%	0.125 mg	0.50 mL
Weeks 5-6	75%	0.1875 mg	0.75 mL
Week 7+	100%	0.25 mg	1.0 mL

To reconstitute lyophilized Betaseron for injection, attach the prefilled syringe containing the diluent (Sodium Chloride, 0.54% Solution) to the Betaseron vial using the vial adapter. Slowly inject 1.2 mL of diluent into the Betaseron vial. Gently swirl the vial to dissolve the drug completely; do not shake. Foaming may occur during reconstitution or if the vial is swirled or shaken too vigorously. If foaming occurs, allow the vial to sit undisturbed until the foam settles. Visually inspect the reconstituted product before use; discard the product if it contains particulate matter or is discolored. Keeping the syringe and vial adapter in place, turn the assembly over so that the vial is on top. Withdraw the appropriate dose of Betaseron solution. Remove the vial from the vial adapter before injecting Betaseron. One mL of reconstituted Betaseron solution contains 0.25 mg of Interferon beta-1b/mL.

Betaseron is intended for use under the guidance and supervision of a physician. It is recommended that physicians or qualified medical personnel train patients in the proper technique for self-administering subcutaneous injections. Patients should be advised to rotate sites for subcutaneous injections (see **PRECAUTIONS, Instruction on Self-injection Technique and Procedures**). Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days. Betaseron should be visually inspected for particulate matter and discoloration prior to administration.

Stability and Storage

The reconstituted product contains no preservative. Before reconstitution with diluent, store Betaseron at room temperature 25°C (77°F). Excursions of 15° to 30°C (59° to 86°F) are permitted. After reconstitution, if not used immediately, the product should be refrigerated and used within three hours. Avoid freezing.

HOW SUPPLIED

Betaseron is supplied as a lyophilized powder containing 0.3 mg of Interferon beta-1b, 15 mg Albumin (Human), USP, and 15 mg Mannitol, USP. Drug is packaged in a clear glass, single-use vial (3 mL capacity). A pre-filled single-use syringe containing 1.2 mL of diluent (Sodium Chloride, 0.54% solution), two alcohol prep pads, and one vial adapter with attached 27 gauge needle are included for each vial of drug. Betaseron and the diluent are for single-use only. Unused portions should be discarded. Store at room temperature.

NDC 50419-523-25 . . . . . 15 blister units, 0.3 mg/vial

Rx only

REFERENCES

1. Poser CM, et al. Ann Neurol 1983; 13(3): 227–231. 2. Kurtzke JF. Neurology 1983; 33(11): 1444–1452.

U.S. Patent No. 4,588,585; 4,959,314; 4,737,462; 4,530,787

Medication Guide

Betaseron® (bav-ta-seer-on)

Interferon beta-1b

(in-ter-feer-on beta-one-be)

Please read this leaflet carefully before you start to use Betaseron® and each time your prescription is refilled since there may be new information. The information in this medication guide does not take the place of talking with your doctor or healthcare professional.

What is the most important information I should know about Betaseron?

Betaseron will not cure multiple sclerosis (MS) but it has been shown to decrease the number of flare-ups of the disease. Betaseron can cause serious side effects, so before you start taking Betaseron, you should talk to your doctor about the possible benefits of Betaseron and its possible side effects to decide if Betaseron is right for you. Potential serious side effects include:

- **Depression.** Some patients treated with interferons, including Betaseron, have become seriously depressed (feeling sad). Some patients have thought about or have attempted to kill themselves. Depression (a sinking of spirits or sadness) is not uncommon in people with multiple sclerosis. However, if you are feeling noticeably sadder or helpless, or feel like hurting yourself or others, you should tell a family member or friend right away and call your doctor or health care provider as soon as possible. Your doctor may ask that you stop using Betaseron. Before starting Betaseron, you should also tell your doctor if you have ever had any mental illness, including depression, and if you take any medications for depression.
- **Risk to pregnancy.** If you become pregnant while taking Betaseron you should stop using Betaseron immediately and call your doctor. Betaseron may cause you to lose your baby (miscarry) or may cause harm to your unborn child. You and your doctor will need to decide whether the potential benefit of taking Betaseron is greater than the potential risks to your unborn child.
- **Allergic reactions.** Some patients taking Betaseron have had severe allergic reactions leading to difficulty breathing and swallowing; these reactions can happen quickly. Allergic reactions can happen after your first dose or may not happen until after you have taken Betaseron many times. Less severe allergic reactions such as rash, itching, skin bumps or swelling of the mouth and tongue can also happen. If you think you are having an allergic reaction, stop using Betaseron immediately and call your doctor.
- **Injection site problems.** Betaseron may cause redness, pain or swelling at the place where an injection was given. A few patients have developed skin infections or areas of severe skin damage (necrosis). If one of your injection sites becomes swollen and painful or the area looks infected and it doesn't heal within a few days, you should call your doctor.

What is Betaseron?

Betaseron is a type of protein called beta interferon that occurs naturally in the body. It is used to treat relapsing forms of multiple sclerosis. It will not cure your MS but may decrease the number of flare-ups of the disease. MS is a lifelong disease that affects your nervous system by destroying the protective covering (myelin) that surrounds your nerve fibers. The way Betaseron works in MS is not known.

Who should not take Betaseron?

Do not take Betaseron if you:

- Have had allergic reactions such as difficulty breathing, flushing or hives to another interferon beta or to human albumin.

If you have any of the following conditions or serious medical problems, you should tell your doctor *before* taking Betaseron:

- Depression (a sinking feeling or sadness), anxiety (feeling uneasy, nervous, or fearful for no reason), or trouble sleeping
- Liver diseases
- Problems with your thyroid gland
- Blood problems such as bleeding or bruising easily and anemia (low red blood cells) or low white blood cells
- Epilepsy
- Are pregnant, breast feeding, or planning to become pregnant

You should tell your doctor if you are taking any other prescription or non-prescription medicines. This includes any vitamin or mineral supplements, or herbal products.

How should I take Betaseron?

Betaseron is given by injection under the skin (subcutaneous injection) every other day. Your injections should be approximately 48 hours (two days) apart, so it is best to take them at the same time each day, preferably in the evening just before bedtime.

You may be started on a lower dose when you first start taking Betaseron. Your doctor will tell you what dose of Betaseron to use, and that dose may change based on how your body responds. You should not change your dose without talking with your doctor.

If you miss a dose, you should take your next dose as soon as you remember or are able to take it. Your next injection should be taken about 48 hours (two days) after that dose.

Do not take Betaseron® on two consecutive days. If you accidentally take more than your prescribed dose, or take it on two consecutive days, call your doctor right away.

You should always follow your doctor's instructions and advice about how to take this medication. If your doctor feels that you, or a family member or friend may give you the injections, then you and/or the other person should be trained by your doctor or healthcare provider in how to give an injection. Do not try to give yourself (or have another person give you) injections at home until you (or both of you) understand and are comfortable with how to prepare your dose and give the injection.

Always use a new, unopened, vial of Betaseron and syringe for each injection. Never reuse vials or syringes.

It is important that you change your injection site each time Betaseron is injected. This will lessen the chance of your having a serious skin reaction at the spot where you inject Betaseron. You should always avoid injecting Betaseron into an area of skin that is sore, reddened, infected or otherwise damaged.

At the end of this leaflet there are detailed instructions on how to prepare and give an injection of Betaseron. You should become familiar with these instructions and follow your doctor's orders before injecting Betaseron.

What should I avoid while taking Betaseron?

- **Pregnancy.** You should avoid becoming pregnant while taking Betaseron until you have talked with your doctor. Betaseron can cause you to lose your baby (miscarry).
- **Breast feeding.** You should talk to your doctor if you are breast feeding an infant. It is not known if the interferon in Betaseron can be passed to an infant in mother's milk, and it is not known whether the drug could harm the infant if it is passed to an infant.

What are the possible side effects of Betaseron?

- **Flu-like symptoms.** Most patients have flu-like symptoms (fever, chills, sweating, muscle aches and tiredness). For many patients, these symptoms will lessen or go away over time. You should talk to your doctor about whether you should take an over the counter medication for pain or fever reduction before or after taking your dose of Betaseron.
- **Skin reactions.** Soreness, redness, pain, bruising or swelling may occur at the place of injection. (***see "What is the most important information I should know about Betaseron?"***).
- **Depression and anxiety.** Some patients taking interferons have become very depressed and/or anxious. There have been patients taking interferons who have had thoughts about killing themselves. If you feel sad or hopeless you should tell a friend or family member right away and call your doctor immediately. (***see "What is the most important information I should know about Betaseron?"***).
- **Liver problems.** Your liver function may be affected. Symptoms of changes in your liver include yellowing of the skin and whites of the eyes and easy bruising.
- **Blood problems.** You may have a drop in the levels of infection-fighting white blood cells, red blood cells, or cells that help you form blood clots. If drops in levels are severe, they can lessen your ability to fight infections, make you feel tired or sluggish or cause you to bruise or bleed easily.
- **Thyroid problems.** Your thyroid function may change. Symptoms of changes in the function of your thyroid include feeling cold or hot much of the time or change in your weight (gain or loss) without a change in your diet or amount of exercise you are getting.
- **Allergic reaction.** Some patients have had hives, rash, skin bumps or itching while they were taking Betaseron. There is also a rare possibility that you can have a life-threatening allergic reaction. (***see "What is the most important information I should know about Betaseron?"***).

Whether you experience any of these side effects or not, you and your doctor should periodically talk about your general health. Your doctor may want to monitor you more closely and ask you to have blood tests done more frequently.

General Information About Prescription Medicines

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This medication has been prescribed for your particular medical condition. Do not use it for another condition or give this drug to anyone else. If you have any questions you should speak with your doctor or health care professional. You may also ask your doctor or pharmacist for a copy of the information provided to them with the product. Keep this and all drugs out of the reach of children.

Instructions for Preparing and Giving Yourself an Injection of Betaseron

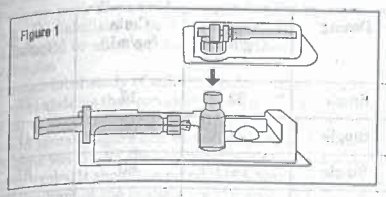
1. Find a clean, flat working surface that is well-lit and collect all the supplies you will need to give yourself an injection. You will need:
   - One tray containing Betaseron. Make sure the tray contains: A pre-filled diluent syringe
   - A vial of Betaseron
   - Two (2) alcohol prep pads
   - A vial adapter with a 27 gauge needle attached (in the blister pack)
   - A puncture-resistant sealable container to dispose of used syringes/needles
2. Check the expiration date on the tray label to make sure that it has not expired. **Do not use it if the medication has expired.**
3. Wash your hands thoroughly with soap and water.
4. Open the tray by peeling off the label and take out all the contents. Make sure the blister pack containing the vial adapter is sealed. Check to make sure the rubber cap on the diluent syringe is firmly attached.
5. Turn the tray over, place the Betaseron vial in the well (vial holder) and place the prefilled diluent syringe in the U-shaped trough.

Reconstituting Betaseron

1. Remove the Betaseron vial from the well and take the cap off the vial.
2. Place the vial back into the vial holder. Use an alcohol prep pad to clean the top of the vial. Move the prep pad in one direction. Leave the alcohol prep pad on top of the vial until step 5.
3. Peel the label off the blister pack with the vial adapter in it, but do not remove vial adapter. The vial adapter is sterile; avoid touching the vial adapter.
4. Remove the alcohol prep pad from the top of the Betaseron vial. Keeping the vial adapter in the blister pack, place the adapter on top of the Betaseron vial and push down on the adapter until it pierces the rubber top

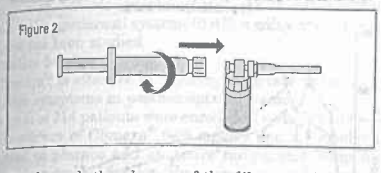
of the Betaseron vial and snaps in place (**Figure 1**). Remove the blister packaging from the vial adapter.

Figure 1



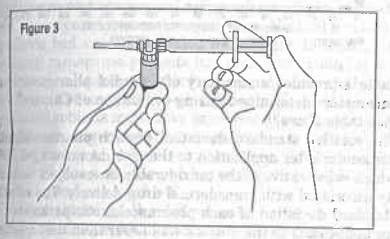
5. Remove the rubber cap from the diluent syringe using a twist and pull motion. Discard the rubber cap.
6. Keeping the syringe assembly attached to the vial, remove the vial from the tray. Be careful not to pull the vial adapter off the top of the vial.
7. Connect the syringe to the vial adapter by turning clockwise and tighten carefully. This will form the *syringe assembly* (**Figure 2**).

Figure 2



8. Slowly push the plunger of the diluent syringe all the way in. This will transfer all of the diluent in the syringe to the Betaseron vial (**Figure 3**). The plunger may return to its original position after you release it.

Figure 3



9. Gently swirl the vial to completely dissolve the white cake of Betaseron. Do not shake. Shaking can cause Betaseron to foam; even gently mixing the solution can cause foaming. If there is foam, allow the vial to sit undisturbed until the foam settles.
10. After the cake is dissolved, look closely at the solution to make sure the solution is clear and colorless and does not contain particles. If the mixture contains particles, or is discolored, do not use. Repeat the steps to prepare your dose using a new tray of Betaseron, prefilled syringe, vial adapter and alcohol prep pads. Contact Berlex at 1-800-788-1467 to obtain replacement product.

Preparing the Injection

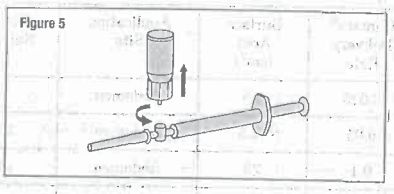
You have completed the steps to reconstitute your Betaseron and are ready for the injection. The injection should be given immediately after mixing and allowing any foam in the solution to settle. If you must delay giving yourself the injection, you may refrigerate the solution and use within three hours of reconstitution. Do not freeze.

1. Push the plunger in and hold it there; then turn the syringe assembly so that the vial is on top. (The syringe is horizontal.) (**Figure 4**).

Figure 4

2. Slowly pull the plunger back to withdraw the entire contents of the Betaseron vial into the syringe.
NOTE: The syringe barrel is marked with numbers from 0.25 to 1.0. If the solution in the vial cannot be drawn up to the 1.0 mark, discard the vial and syringe and start over with a new tray containing a Betaseron vial, prefilled diluent syringe, vial adapter and alcohol prep pads.
3. Turn the syringe assembly so that the needle end is pointing up. Remove any air bubbles by tapping the outer wall of the syringe with your fingers. Slowly push the plunger to the 1 mL mark on the syringe (or to the amount prescribed by your doctor).
NOTE: If too much solution is pushed into the vial, repeat steps 1, 2, and 3.
4. Remove the vial adapter and the vial from the syringe by twisting the vial adapter as shown in Figure 5. This will remove the vial adapter and the vial from the syringe, but will leave the needle on the syringe (**Figure 5**).

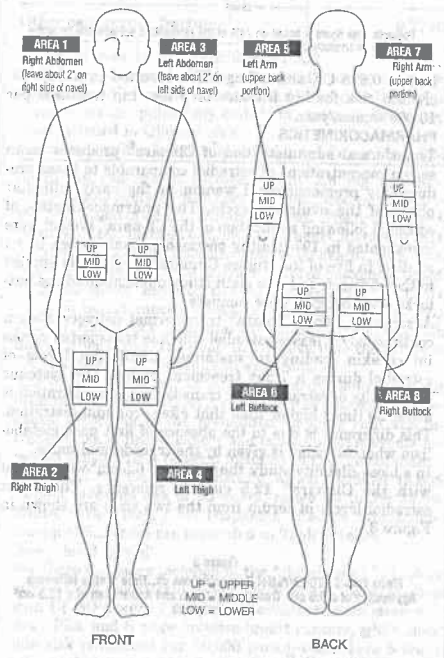
Figure 5



Picking an Injection Site

Betaseron (Interferon beta-1b) is injected under the skin and into the fat layer between the skin and the muscles (subcutaneous tissue). The best areas for injection are where the skin is loose and soft and away from the joints, nerves, and bones. Do not use the area near your navel or waistline. If you are very thin, use only the thigh or outer surface of the arm for injection.

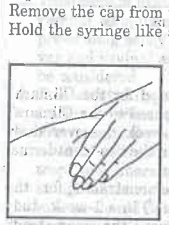
You should pick a different site each time you give yourself an injection. The diagrams show different areas for giving injections. You should not choose the same area for two injections in a row. Keeping a record of your injections will help make sure you rotate your injection sites. You should decide where your injection will be given before you prepare your syringe for injection. If there are any sites that are difficult for you to reach, you can ask someone who has been trained to give injections to help you.



Do not inject in a site where the skin is red, bruised, infected, or scabbed, has broken open, or has lumps, bumps, or pain. Tell your doctor or healthcare provider if you find skin conditions like the ones mentioned here or any other unusual looking areas where you have been given injections.

Using a circular motion, and starting at the injection site and moving outward, clean the injection site with an alcohol wipe. Let the skin area dry before you inject the Betaseron. Remove the cap from the needle.

Hold the syringe like a pencil or dart in one hand.



Gently pinch the skin around the site with the thumb and forefinger of the other hand.

While holding your skin, stick the needle straight into the skin at a 90° angle with a quick, firm motion. Once in your skin, slowly pull back on the plunger. If blood appears in the syringe it means that you have entered a blood vessel. Do not inject Betaseron. Withdraw the needle and repeat the steps to prepare your dose. Choose and clean a new injection site. You should not use the same syringe; discard it in your puncture-proof container.

If no blood appears, slowly push the plunger all the way in until the syringe is empty.

Remove the needle from the skin; then place a dry cotton ball or gauze pad over the injection site.

Gently massage the injection site for a few moments with the dry cotton ball or gauze pad.

Throw away the 1 mL syringe in the disposal container.

Disposing of syringes and needles

Used needles and syringes may be placed in a container made specially for disposing of used syringes and needles (called a "Sharps" container), or a hard plastic container with a screw-on cap or metal container with a plastic lid labeled "*Used Syringes*". Do not use glass or clear plastic containers. You should always check with your healthcare provider for instructions on how to properly dispose of used vials, needles and syringes. You should follow any special state or local laws regarding the proper disposal of needles and syringes.

DO NOT throw the needle or syringe in the household trash or recycle.

Always keep the disposal container out of the reach of children.

How Should I Store Betaseron?

Betaseron should be stored at room temperature (77°F), but may be stored between 59° and 86°F. Avoid freezing.

This Medication Guide has been approved by the U.S. Food and Drug Administration

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Montville, NJ 07045

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(6052800 BERLEX)

Shown in Product Identification Guide, page 308

CLIMARA®

℞

[klī-mărə]

(estradiol transdermal system)
Continuous Delivery for
Once-Weekly Application

℞ **only**

PRESCRIBING INFORMATION
Climara® estradiol transdermal system

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

CARDIOVASCULAR AND OTHER RISKS

Estrogens with and without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with oral conjugated equine estrogens (CE 0.625mg) combined with medroxyprogesterone acetate (MPA 2.5mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**). Other doses of conjugated estrogens with medroxyprogesterone, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Climara®, estradiol transdermal system, is designed to release 17β-estradiol continuously upon application to intact skin. Six (6.5, 9.375, 12.5, 15.0, 18.75 and 25.0 cm^2) systems are available to provide nominal *in vivo* delivery of 0.025, 0.0375, 0.05, 0.060, 0.075 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 9.375, 12.5, 15.0, 18.75 or 25.0 cm^2, and contains 2.0, 2.85, 3.8, 4.55, 5.7 or 7.6 mg of estradiol USP respectively. The composition of the systems per unit area is identical. Estradiol USP (17β-estradiol) is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.39. The structural formula is:

(See chemical structure at top of next column)

The Climara® system comprises two layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film,

Continued on next page

Information on Berlex products (appearing here) is based on the most current information available at the time of publication closing. Further information for these and other Berlex products can be obtained from Medical & Product Services at Berlex, Inc. by calling 1-888-BERLEX-4.

Amevive—Cont.

PRECAUTIONS

Effects on the Immune System

Patients receiving other immunosuppressive agents or phototherapy should not receive concurrent therapy with AMEVIVE® because of the possibility of excessive immunosuppression. The duration of the period following treatment with AMEVIVE® before one should consider starting other immunosuppressive therapy has not been evaluated.

The safety and efficacy of vaccines, specifically live or live-attenuated vaccines, administered to patients being treated with AMEVIVE® have not been studied. In a study of 46 patients with chronic plaque psoriasis, the ability to mount immunity to tetanus toxoid (recall antigen) and an experimental neo-antigen was preserved in those patients undergoing AMEVIVE® therapy.

Allergic Reactions

Hypersensitivity reactions (urticaria, angioedema) were associated with the administration of AMEVIVE®. If an anaphylactic reaction or other serious allergic reaction occurs, administration of AMEVIVE® should be discontinued immediately and appropriate therapy initiated.

Information for Patients

Patients should be informed of the need for regular monitoring of white blood cell (lymphocyte) counts during therapy and that AMEVIVE® must be administered under the supervision of a physician. Patients should also be informed that AMEVIVE® reduces lymphocyte counts, which could increase their chances of developing an infection or a malignancy. Patients should be advised to inform their physician promptly if they develop any signs of an infection or malignancy while undergoing a course of treatment with AMEVIVE®.

Female patients should also be advised to notify their physicians if they become pregnant while taking AMEVIVE® (or within 8 weeks of discontinuing AMEVIVE®) and be advised of the existence of and encouraged to enroll in the Pregnancy Registry. Call 1-866-AMEVIVE (1-866-263-8483) to enroll into the Registry (see **PRECAUTIONS, Pregnancy**).

Laboratory Tests

CD4+ T lymphocyte counts should be monitored weekly during the 12-week dosing period and used to guide dosing. Patients should have normal CD4+ T lymphocyte counts prior to an initial or a subsequent course of treatment with AMEVIVE®. Dosing should be withheld if CD4+ T lymphocyte counts are below 250 cells/μL. AMEVIVE® should be discontinued if CD4+ T lymphocyte counts remain below 250 cells/μL for one month.

Drug Interactions

No formal interaction studies have been performed. The duration of the period following treatment with AMEVIVE® before one should consider starting other immunosuppressive therapy has not been evaluated.

Carcinogenesis, Mutagenesis, and Fertility

In a chronic toxicity study, cynomolgus monkeys were dosed weekly for 52 weeks with intravenous alefacept at 1 mg/kg/dose or 20 mg/kg/dose. One animal in the high dose group developed a B-cell lymphoma that was detected after 28 weeks of dosing. Additional animals in both dose groups developed B-cell hyperplasia of the spleen and lymph nodes. All animals in the study were positive for an endemic primate gammaherpes virus also known as lymphocryptovirus (LCV). Latent LCV infection is generally asymptomatic, but can lead to B-cell lymphomas when animals are immune suppressed.

In a separate study, baboons given 3 doses of alefacept at 1 mg/kg every 8 weeks were found to have centroblast proliferation in B-cell dependent areas in the germinal centers of the spleen following a 116-day washout period.

The role of AMEVIVE® in the development of the lymphoid malignancy and the hyperplasia observed in non-human primates and the relevance to humans is unknown. Immunodeficiency-associated lymphocyte disorders (plasmacytic hyperplasia, polymorphic proliferation, and B-cell lymphomas) occur in patients who have congenital or acquired immunodeficiencies including those resulting from immunosuppressive therapy.

No carcinogenicity or fertility studies were conducted.

Mutagenicity studies were conducted *in vitro* and *in vivo*; no evidence of mutagenicity was observed.

Pregnancy (Category B)

Women of childbearing potential make up a considerable segment of the patient population affected by psoriasis. Since the effect of AMEVIVE® on pregnancy and fetal development, including immune system development, is not known, health care providers are encouraged to enroll patients currently taking AMEVIVE® who become pregnant into the Biogen Pregnancy Registry by calling 1-866-AMEVIVE (1-866-263-8483).

Reproductive toxicology studies have been performed in cynomolgus monkeys at doses up to 5 mg/kg/week (about 62 times the human dose based on body weight) and have revealed no evidence of impaired fertility or harm to the fetus due to AMEVIVE®. No abortifacient or teratogenic effects were observed in cynomolgus monkeys following intravenous bolus injections of AMEVIVE® administered weekly during the period of organogenesis to gestation. AMEVIVE® underwent trans-placental passage and produced *in utero* exposure in the developing monkeys. *In utero*, serum levels of exposure in these monkeys were 23% of maternal serum levels. No evidence of fetal toxicity including adverse effects on immune system development was observed in any of these animals.

Animal reproduction studies, however, are not always predictive of human response and there are no adequate and well-controlled studies in pregnant women. Because the risk to the development of the fetal immune system and postnatal immune function in humans is unknown, AMEVIVE® should be used during pregnancy only if clearly needed. If pregnancy occurs while taking AMEVIVE®, continued use of the drug should be assessed.

Nursing Mothers

It is not known whether AMEVIVE® is excreted in human milk. Because many drugs are excreted in human milk, and because there exists the potential for serious adverse reactions in nursing infants from AMEVIVE®, a decision should be made whether to discontinue nursing while taking the drug or to discontinue the use of the drug, taking into account the importance of the drug to the mother.

Geriatric Use

Of the 1357 patients who received AMEVIVE® in clinical trials, a total of 100 patients were ≥ 65 years of age and 13 patients were ≥ 75 years of age. No differences in safety or efficacy were observed between older and younger patients, but there were not sufficient data to exclude important differences. Because the incidence of infections and certain malignancies is higher in the elderly population, in general, caution should be used in treating the elderly.

Pediatric Use

The safety and efficacy of AMEVIVE® in pediatric patients have not been studied. AMEVIVE® is not indicated for pediatric patients.

ADVERSE REACTIONS

The most serious adverse reactions were:

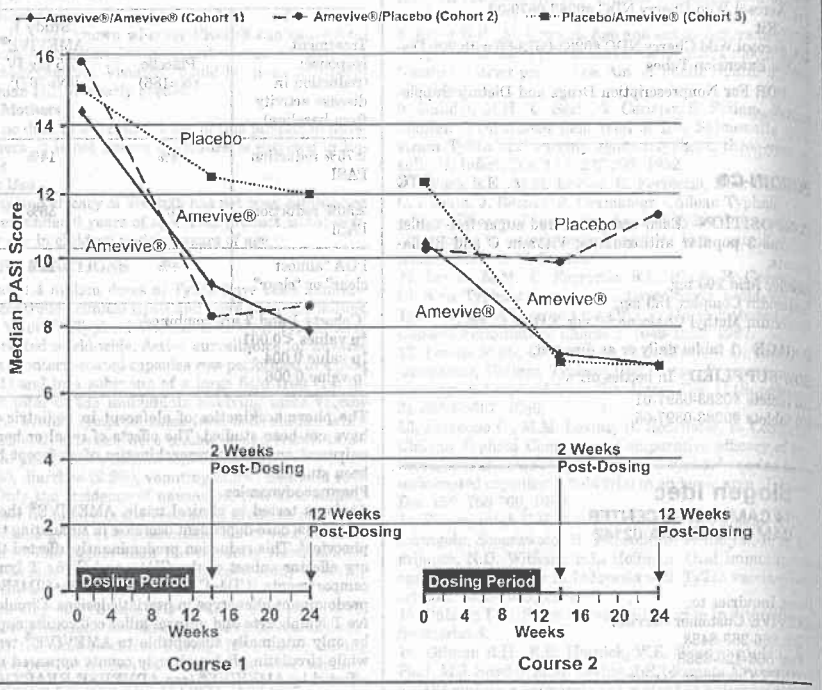
- Lymphopenia (see **WARNINGS**)
- Malignancies (see **WARNINGS**)
- Serious Infections requiring hospitalization (see **WARNINGS**)
- Hypersensitivity Reactions (see **PRECAUTIONS, Allergic Reactions**)

Commonly observed adverse events seen in the first course of placebo-controlled clinical trials with at least a 2% higher incidence in the AMEVIVE®-treated patients compared to placebo-treated patients were: pharyngitis, dizziness, increased cough, nausea, pruritus, myalgia, chills, injection site pain, injection site inflammation, and accidental injury. The only adverse event that occurred at a 5% or higher incidence among AMEVIVE®-treated patients compared to placebo-treated patients was chills (1% placebo *vs.* 6% AMEVIVE®), which occurred predominantly with intravenous administration.

The adverse reactions which most commonly resulted in clinical intervention were cardiovascular events including coronary artery disorder in <1% of patients and myocardial infarct in <1% of patients. These events were not observed in any of the 413 placebo-treated patients. The total number of patients hospitalized for cardiovascular events in the AMEVIVE®-treated group was 1.2% (11/876).

The most common events resulting in discontinuation of treatment with AMEVIVE® were CD4+ T lymphocyte levels below 250 cells/μL (see **WARNINGS**, and **ADVERSE REACTIONS, Effect on Lymphocyte Counts**), headache (0.2%), and nausea (0.2%).

Figure 1. Median PASI Score Over Time



Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

The data described below reflect exposure to AMEVIVE® in a total of 1357 psoriasis patients, 85% of whom received 1 to 2 courses of therapy and the rest received 3 to 6 courses and were followed for up to three years. Of the 1357 total patients, 876 received their first course in placebo-controlled studies. The population studied ranged in age from 16 to 84 years, and included 69% men and 31% women. The patients were mostly Caucasian (89%), reflecting the general psoriatic population. Disease severity at baseline was moderate to severe psoriasis.

Effect on Lymphocyte Counts

In the intramuscular study (Study 2), 4% of patients temporarily discontinued treatment and no patients permanently discontinued treatment due to CD4+ T lymphocyte counts below the specified threshold of 250 cells/μL. In Study 2, 10%, 28%, and 42% of patients had total lymphocyte, CD4+, and CD8+ T lymphocyte counts below normal, respectively. Twelve weeks after a course of therapy (12 weekly doses), 2%, 8%, and 21% of patients had total lymphocyte, CD4+, and CD8+ T cell counts below normal.

In the first course of the intravenous study (Study 1), 10% of patients temporarily discontinued treatment and 2% permanently discontinued treatment due to CD4+ T lymphocyte counts below the specified threshold of 250 cells/μL. During the first course of Study 1, 22% of patients had total lymphocyte counts below normal, 48% had CD4+ T lymphocyte counts below normal and 59% had CD8+ T lymphocyte counts below normal. The maximal effect on lymphocytes was observed within 6 to 8 weeks of initiation of treatment. Twelve weeks after a course of therapy (12 weekly doses), 4% of patients had total lymphocyte counts below normal, 19% had CD4+ T lymphocyte counts below normal, and 36% had CD8+ T lymphocyte counts below normal.

For patients receiving a second course of AMEVIVE® in Study 1, 17% of patients had total lymphocyte counts below normal, 44% had CD4+ T lymphocyte counts below normal, and 56% had CD8+ T lymphocyte counts below normal. Twelve weeks after completing dosing, 3% of patients had total lymphocyte counts below normal, 17% had CD4+ T lymphocyte counts below normal, and 35% had CD8+ T lymphocyte counts below normal (see **WARNINGS**, and **PRECAUTIONS, Laboratory Tests**).

Malignancies

In the 24-week period constituting the first course of placebo-controlled studies, 13 malignancies were diagnosed in 11 AMEVIVE®-treated patients. The incidence of malignancies was 1.3% (11/876) for AMEVIVE®-treated patients compared to 0.5% (2/413) in the placebo group.

Among 1357 patients who received AMEVIVE®, 25 patients were diagnosed with 35 treatment-emergent malignancies. The majority of these malignancies (23 cases) were basal (6) or squamous cell cancers (17) of the skin. Three cases of lymphoma were observed; one was classified as non-Hodgkin's follicle-center cell lymphoma and two were classified as Hodgkin's disease.

Infections

In the 24-week period constituting the first course of placebo-controlled studies, serious infections (infections re-

quiring hospitalization) were seen at a rate of 0.9% (8/876) in AMEVIVE®-treated patients and 0.2% (1/413) in the placebo group. In patients receiving repeated courses of AMEVIVE® therapy, the rates of serious infections were 0.7% (5/756) and 1.5% (3/199) in the second and third course of therapy, respectively. Serious infections among 1357 AMEVIVE®-treated patients included necrotizing cellulitis, peritonsillar abscess, post-operative and burn wound infection, toxic shock, pneumonia, appendicitis, preseptal cellulitis, cholecystitis, gastroenteritis and herpes simplex infection.

Hypersensitivity Reactions

In clinical studies two patients were reported to experience angioedema, one of whom was hospitalized. In the 24-week period constituting the first course of placebo-controlled studies, urticaria was reported in 6 (<1%) AMEVIVE®-treated patients *vs.* 1 patient in the control group. Urticaria resulted in discontinuation of therapy in one of the AMEVIVE®-treated patients.

Hepatic Events

In post-marketing surveillance hepatic events, including a case of hepatitis associated with transient coagulopathy and hyperbilirubinemia, have been reported.

Injection Site Reactions

In the intramuscular study (Study 2), 16% of AMEVIVE®-treated patients and 8% of placebo-treated patients reported injection site reactions. Reactions at the site of injection were generally mild, typically occurred on single occasions, and included either pain (7%), inflammation (4%), bleeding (4%), edema (2%), non-specific reaction (2%), mass (1%), or skin hypersensitivity (<1%). In the clinical trials, a single case of injection site reaction led to the discontinuation of AMEVIVE®.

Immunogenicity

Approximately 3% (35/1306) of patients receiving AMEVIVE® developed low-titer antibodies to alefacept. No apparent correlation of antibody development and clinical response or adverse events was observed. The long-term immunogenicity of AMEVIVE® is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to alefacept in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to alefacept with the incidence of antibodies to other products may be misleading.

Other Observed Adverse Reactions from Clinical Trials

Less common events that were observed at a higher rate in AMEVIVE®-treated patients include rare cases (9) of transaminase elevations to 5 to 10 times the upper limit of normal.

OVERDOSAGE

The highest dose tested in humans (0.75 mg/kg IV) was associated with chills, headache, arthralgia, and sinusitis within one day of dosing. Patients who have been inadvertently administered an excess of the recommended dose should be closely monitored for effects on total lymphocyte count and CD4+ T lymphocyte count.

DOSAGE AND ADMINISTRATION

AMEVIVE® should only be used under the guidance and supervision of a physician.

The recommended dose of AMEVIVE® is 7.5 mg given once weekly as an IV bolus or 15 mg given once weekly as an IM injection. The recommended regimen is a course of 12 weekly injections. Retreatment with an additional 12-week course may be initiated provided that CD4+ T lymphocyte counts are within the normal range, and a minimum of a 12-week interval has passed since the previous course of treatment. Data on retreatment beyond two cycles are limited.

The CD4+ T lymphocyte counts of patients receiving AMEVIVE® should be monitored weekly before initiating dosing and throughout the course of the 12-week dosing regimen. Dosing should be withheld if CD4+ T lymphocyte counts are below 250 cells/μL. The drug should be discontinued if the counts remain below 250 cells/μL for one month (see **PRECAUTIONS, Laboratory Tests**).

Preparation Instructions

AMEVIVE® should be reconstituted by a health care professional using aseptic technique. Each vial is intended for single patient use only.

Do not use an AMEVIVE® dose tray beyond the date stamped on the carton, dose tray lid, AMEVIVE® vial label, or diluent container label.

AMEVIVE® 15 mg lyophilized powder for IM administration should be reconstituted with 0.6 mL of the supplied diluent (Sterile Water for Injection, USP). 0.5 mL of the reconstituted solution contains 15 mg of alefacept.

AMEVIVE® 7.5 mg lyophilized powder for IV administration should be reconstituted with 0.6 mL of the supplied diluent. 0.5 mL of the reconstituted solution contains 7.5 mg of alefacept.

Do not add other medications to solutions containing AMEVIVE®. Do not reconstitute AMEVIVE® with other diluents. Do not filter reconstituted solution during preparation or administration.

All procedures require the use of aseptic technique. Using the supplied syringe and one of the supplied needles, withdraw 0.6 mL of the supplied diluent (Sterile Water for Injection, USP). Keeping the needle pointed at the sidewall of the vial, slowly inject the diluent into the vial of AMEVIVE®. Some foaming will occur, which is normal. To avoid excessive foaming, do not shake or vigorously agitate. The contents should be swirled gently during dissolution. Generally, dissolution of AMEVIVE® takes less than two minutes. The solution should be used as soon as possible after reconstitution.

The reconstituted solution should be clear and colorless to slightly yellow. Visually inspect the solution for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if undissolved material remains.

Following reconstitution, the product should be used immediately or within 4 hours if stored in the vial at 2–8°C (36–46°F). AMEVIVE® NOT USED WITHIN 4 HOURS OF RECONSTITUTION SHOULD BE DISCARDED.

Remove the needle used for reconstitution and attach the other supplied needle. Withdraw 0.5 mL of the AMEVIVE® solution into the syringe. Some foam or bubbles may remain in the vial.

Administration Instructions

For intramuscular use, inject the full 0.5 mL of solution. Rotate injection sites so that a different site is used for each new injection. New injections should be given at least 1 inch from an old site and never into areas where the skin is tender, bruised, red, or hard.

For intravenous use,

- Prepare 2 syringes with 3.0 mL Normal Saline, USP for pre- and post-administration flush.
- Prime the winged infusion set with 3.0 mL saline and insert the set into the vein.
- Attach the AMEVIVE®-filled syringe to the infusion set and administer the solution over no more than 5 seconds.
- Flush the infusion set with 3.0 mL saline, USP.

HOW SUPPLIED

AMEVIVE® for IV administration is supplied in either a carton containing four administration dose packs, or in a carton containing one administration dose pack. Each dose pack contains one 7.5-mg single-use vial of AMEVIVE®, one 10 mL single-use diluent vial (Sterile Water for Injection, USP), one syringe, one 23 gauge, ¾ inch winged infusion set, and two 23 gauge, 1 ¼ inch needles. The NDC number for the four administration dose pack carton is 59627-020-01 The NDC number for the one administration dose pack carton is 59627-020-02.

AMEVIVE® for IM administration is supplied in either a carton containing four administration dose packs, or in a carton containing one administration dose pack. Each dose pack contains one 15-mg single-use vial of AMEVIVE®, one 10 mL single-use diluent vial (Sterile Water for Injection, USP), one syringe, and two 23 gauge, 1 ¼ inch needles. The NDC number for the four administration dose pack carton is 59627-021-03. The NDC number for the one administration dose pack carton is 59627-021-04

AMEVIVE® is reconstituted with 0.6 mL of the 10 mL single-use diluent.

Storage

The dose tray containing AMEVIVE® (lyophilized powder) should be stored at controlled room temperature (15–30°C; 59–86°F). PROTECT FROM LIGHT. Retain in carton until time of use.

Rx only

REFERENCES

1. Bos JD, Hagenaars C, Das PK, et al. Predominance of "memory" T cells (CD4+, CDw29+) over "naive" T cells (CD4+, CD45R+) in both normal and diseased human skin. Arch Dermatol Res 1989; 281:24–30.
2. Ellis C, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med 2001; 345:248–255.
3. Fredriksson T, Pettersson U. Severe psoriasis–oral therapy with a new retinoid. Dermatologica 1978; 157:238–244.

Issued: May/2004

AMEVIVE® (alefacept)

Manufactured by:

BIOGEN, INC.

14 Cambridge Center

Cambridge, MA 02142 USA

1-866-263-8483

U.S. Patents:

4,956,281

5,547,853

5,728,677

5,914,111

5,928,643

6,162,432

Additional U.S. Patents Pending

I63007-2

AVONEX® Rx

[a-vuh-necks]

(Interferon beta-1a)

IM Injection

DESCRIPTION

AVONEX® (Interferon beta-1a) is a 166 amino acid glycoprotein with a predicted molecular weight of approximately 22,500 daltons. It is produced by recombinant DNA technology using genetically engineered 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 of Interferon beta-1a determined specifically by an *in vitro* cytopathic effect bioassay using lung carcinoma cells (A549) and Encephalomyocarditis virus (ECM). AVONEX® 30 mcg contains approximately 6 million IU of antiviral activity using this method. The activity against other standards is not known. Comparison of the activity of AVONEX® with other Interferon betas is not appropriate, because of differences in the reference standards and assays used to measure activity.

30 mcg Lyophilized Powder Vial

A vial of AVONEX® is formulated as a sterile, white to off-white lyophilized powder for intramuscular injection after reconstitution with supplied diluent (Sterile Water for Injection, USP). Each vial of reconstituted AVONEX® contains 30 mcg of Interferon beta-1a; 15 mg Albumin (Human), USP; 5.8 mg Sodium Chloride, USP; 5.7 mg Dibasic Sodium Phosphate, USP; and 1.2 mg Monobasic Sodium Phosphate, USP, in 1.0 mL at a pH of approximately 7.3.

30 mcg Prefilled Syringe

A prefilled syringe of AVONEX® is formulated as a sterile liquid for intramuscular injection. Each 0.5 mL (30 mcg dose) of AVONEX® in a prefilled glass syringe contains 30 mcg of Interferon beta-1a, 0.79 mg Sodium Acetate Trihydrate, USP; 0.25 mg Glacial Acetic Acid, USP; 15.8 mg Arginine Hydrochloride, USP; and 0.025 mg Polysorbate 20 in Water for Injection, USP at a pH of approximately 4.8.

CLINICAL PHARMACOLOGY

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 glycosylated, with each containing a single N-linked complex carbohydrate moiety. Glycosylation of other proteins is known to affect their stability, activity, aggregation, biodistribution, and half-life in blood. However, the effects of glycosylation of interferon beta on these properties have not been fully defined.

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 leads 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 have not been fully defined. Clinical studies conducted in multiple sclerosis patients showed that interleukin 10 (IL-10) levels in cerebrospinal fluid were increased in patients treated with AVONEX® compared to placebo. Serum IL-10 levels were increased 48 hours after intramuscular (IM) injection of AVONEX® and remained elevated for 1 week. However, no relationship has been established between absolute levels of IL-10 and clinical outcome in multiple sclerosis.

Pharmacokinetics

Pharmacokinetics of AVONEX® in multiple sclerosis patients have not been evaluated. The pharmacokinetic and pharmacodynamic profiles of AVONEX® in healthy subjects following doses of 30 mcg through 75 mcg have been investigated. Serum levels of AVONEX® as measured by antiviral activity are slightly above detectable limits following a 30 mcg IM dose, and increase with higher doses.

After an IM dose, serum levels of AVONEX® typically peak between 3 and 15 hours and then decline at a rate consistent with a 10 hour elimination half-life. Serum levels of AVONEX® may be sustained after IM administration due to prolonged absorption from the IM site. Systemic exposure, as determined by AUC and C_{max} values, is greater following IM than subcutaneous (SC) administration.

Subcutaneous administration of AVONEX® should not be substituted for intramuscular administration. Subcutaneous and intramuscular administration have been observed to have non-equivalent pharmacokinetic and pharmacodynamic parameters following administration to healthy volunteers.

Biological response markers (e.g., neopterin and β_2-microglobulin) are induced by AVONEX® following parenteral doses of 15 mcg through 75 mcg in healthy subjects and

Continued on next page

Avonex—Cont.

treated patients. Biological response marker levels increase within 12 hours of dosing and remain elevated for at least 4 days. Peak biological response marker levels are typically observed 48 hours after dosing. The relationship of serum AVONEX® levels or levels of these induced biological response markers to the mechanisms by which AVONEX® exerts its effects in multiple sclerosis is unknown.

Clinical Studies

The clinical effects of AVONEX® in multiple sclerosis were studied in two randomized, multicenter, double-blind, placebo-controlled studies in patients with multiple sclerosis.[1,2] Safety and efficacy of treatment with AVONEX® beyond 3 years is not known.

In Study 1, 301 patients received either 30 mcg of AVONEX® (n=158) or placebo (n=143) by IM injection once weekly. Patients were entered into the trial over a 2½ year period, received injections for up to 2 years, and continued to be followed until study completion. Two hundred eighty-two patients completed 1 year on study, and 172 patients completed 2 years on study. 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.

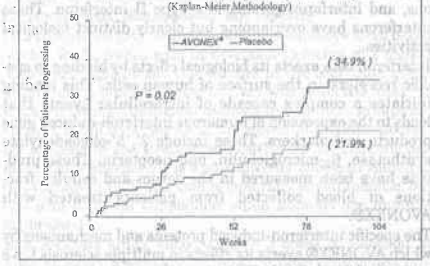
All patients had a definite diagnosis of multiple sclerosis of at least 1 year duration and had at least 2 exacerbations in the 3 years prior to study entry (or 1 per year if the duration of disease was less than 3 years). At entry, study participants were without exacerbation during the prior 2 months and had Kurtzke Expanded Disability Status Scale (EDSS[3]) scores ranging from 1.0 to 3.5. 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 score of at least 1.0 point that was sustained for at least 6 months. An increase in EDSS score reflects accumulation of disability. This endpoint was used to ensure that progression reflected permanent increase in disability rather than a transient effect due to an exacerbation.

Secondary outcomes included exacerbation frequency and results of magnetic resonance imaging (MRI) scans including gadolinium (Gd)-enhanced lesion number and volume and T2-weighted (proton density) lesion volume. Additional secondary endpoints included 2 upper limb (tested in both arms) and 3 lower limb function tests.

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. Thirteen of these 23 patients remained on study and were evaluated for clinical endpoints.

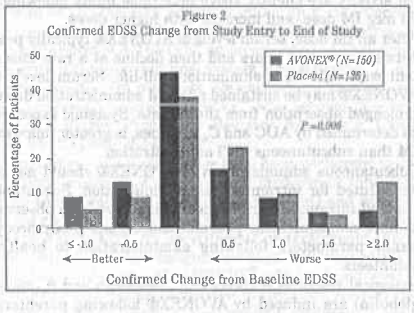
Figure 1
Onset of Sustained Disability Progression by Time on Study
(Kaplan-Meier Methodology)



Note: Disability progression represents at least a 1.0 point increase in EDSS score sustained for at least 6 months.

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 37% relative reduction in the risk of accumulating disability in the AVONEX®-treated group compared to the placebo-treated group.

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



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).

Table 1
Clinical and MRI Endpoints in Study 1

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			
Number of exacerbations in subset completing 2 years (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 in subset completing 2 years (N: 87, 85)	26%	38%	0.10[4]
Annual exacerbation rate (N: 143, 158)[1]	0.82	0.67	0.04[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]

Note: (N: ,) denotes the number of evaluable placebo and AVONEX® 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.*

The rate and frequency of exacerbations were determined as secondary outcomes. For all patients included in the study, irrespective of time on study, the annual exacerbation rate was 0.67 per year in the AVONEX®-treated group and 0.82 per year in the placebo-treated group (p = 0.04).

AVONEX® treatment significantly decreased the frequency of exacerbations in the subset of patients who were enrolled in the study for at least 2 years (87 placebo-treated patients and 85 AVONEX®-treated patients; p = 0.03; see Table 1).

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 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.

The exact relationship between MRI findings and the clinical status of patients is unknown. The prognostic significance of MRI findings in these studies has not been evaluated.

Of the limb function tests, only 1 demonstrated a statistically significant difference between treatment groups (favoring AVONEX®). A summary of the effects of AVONEX® on the clinical and MRI endpoints of this study is presented in Table 1.

[See table 1 above]

In Study 2, 383 patients who had recently experienced an isolated demyelinating event involving the optic nerve, spinal cord, or brainstem/cerebellum, and who had lesions typical of multiple sclerosis on brain MRI, received either 30 mcg AVONEX® (n = 193) or placebo (n = 190) by IM injection once weekly. All patients received intravenous steroid treatment for the initiating clinical exacerbation. Patients were enrolled into the study over a two-year period and followed for up to three years or until they developed a second clinical exacerbation in an anatomically distinct region of the central nervous system. Sixteen percent of subjects on AVONEX® and 14% of subjects on placebo withdrew from the study for a reason other than the development of a second exacerbation[2].

The primary outcome measure was time to development of a second exacerbation in an anatomically distinct region of the central nervous system. Secondary outcomes were brain MRI measures, including the cumulative increase in the number of new or enlarging T2 lesions, T2 lesion volume compared to baseline at 18 months, and the number of Gd-enhancing lesions at 6 months.

Time to development of a second exacerbation was significantly delayed in patients treated with AVONEX® compared to placebo (p = 0.002). The Kaplan-Meier estimates of the percentage of patients developing an exacerbation within 24 months were 38.6% in the placebo group and 21.1% in the AVONEX® group (Figure 3). The relative rate of developing a second exacerbation in the AVONEX® group was 0.56 of the rate in the placebo group (95% confidence interval 0.38 to 0.81). The brain MRI findings are described in Table 2.

[See figure 3 at top of next page]
[See table 2 on next page]

INDICATIONS AND USAGE

AVONEX® (Interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. Safety and efficacy in patients with chronic progressive multiple sclerosis have not been established.

CONTRAINDICATIONS

AVONEX® is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, or any other component of the formulation.

The lyophilized vial formulation of AVONEX® is contraindicated in patients with a history of hypersensitivity to albumin (human).

WARNINGS

Depression and Suicide

AVONEX® should be used with caution in patients with depression or other mood disorders, conditions that are common with multiple sclerosis. Depression and suicide have been reported to occur with increased frequency in patients receiving interferon compounds, including AVONEX®. 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 or other severe psychiatric symptoms, cessation of AVONEX® therapy should be considered. In Study 2, AVONEX®-treated patients were more likely to experience depression than placebo-treated patients. An equal incidence of depression was seen in the placebo-treated and AVONEX®-treated patients in Study 1. Additionally, there have been post-marketing reports of depression, suicidal ideation and/or development of new or worsening of pre-existing other psychiatric disorders, including psychosis. Some of these patients improved upon cessation of AVONEX® dosing.

Anaphylaxis

Anaphylaxis has been reported as a rare complication of AVONEX® use. Other allergic reactions have included dyspnea, orolingual edema, skin rash and urticaria (see ADVERSE REACTIONS).

Decreased Peripheral Blood Counts

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and thrombocytopenia, have been reported from post-marketing experience (see ADVERSE REACTIONS). Some cases of thrombocytopenia have had nadirs below 10,000/μL. Some cases reoccur with rechallenge (see ADVERSE REACTIONS). Patients should be monitored for signs of these disorders (see Precautions: Laboratory Tests).

Albumin (Human)

The lyophilized vial of AVONEX® contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have been identified for albumin. The prefilled syringe of AVONEX® does not contain albumin.

PRECAUTIONS

Seizures

Caution should be exercised when administering AVONEX® to patients with pre-existing seizure disorders. In the two placebo-controlled studies in multiple sclerosis, 4 patients receiving AVONEX® experienced seizures, while no seizures occurred in the placebo group. Three of these 4 patients had no prior history of seizure (see ADVERSE REACTIONS). It is not known whether these events were related to the effects of multiple sclerosis alone, to AVONEX®, or to a combination of both. The effect of AVONEX® administration on the medical management of patients with seizure disorder is unknown.

Cardiomyopathy and Congestive Heart Failure

Patients with cardiac disease, such as angina, congestive heart failure, or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation and continued treatment with AVONEX®. While AVONEX® does not have any known direct-acting cardiac toxicity, during the post-marketing period infrequent cases of congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure have been reported in patients without known predisposition to these events, and without other known etiologies being established. In rare cases, these events have been temporally related to the administration of AVONEX®. In some of these instances recurrence upon rechallenge was observed.

Autoimmune Disorders

Autoimmune disorders of multiple target organs have been reported post-marketing including idiopathic thrombocytopenia, hyper- and hypothyroidism, and rare cases of autoimmune hepatitis have also been reported. Patients should be monitored for signs of these disorders (see Precautions: Laboratory Tests) and appropriate treatment implemented when observed.

Hepatic Injury

Hepatic injury including elevated serum hepatic enzyme levels and hepatitis, some of which have been severe, has been reported post-marketing. In some patients a recurrence of elevated serum levels of hepatic enzymes has occurred upon AVONEX® rechallenge. In some cases, these events have occurred in the presence of other drugs that have been associated with hepatic injury. The potential of additive effects from multiple drugs or other hepatotoxic agents (e.g., alcohol) has not been determined. Patients should be monitored for signs of hepatic injury (see Precautions: Laboratory Tests) and caution exercised when AVONEX® is used concomitantly with other drugs associated with hepatic injury.

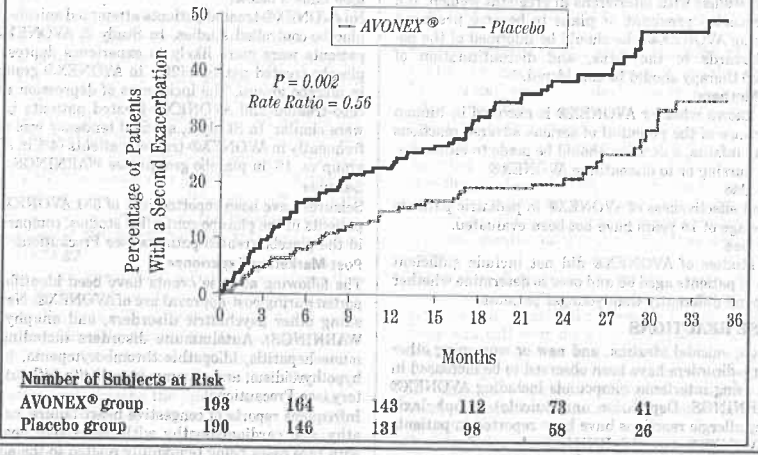
Information to Patients

All patients should be instructed to read the AVONEX® Medication Guide supplied to them. Patients should be cautioned not to change the dosage or the schedule of administration without medical consultation.

Patients should be informed of the most serious (see WARNINGS) and the most common adverse events associated with AVONEX® administration, including symptoms associated with flu syndrome (see ADVERSE REACTIONS). Symptoms of flu syndrome are most prominent at the initiation of therapy and decrease in frequency with continued treatment. Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days.

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

Figure 3
Onset of Second Exacerbation by Time on Study
(Kaplan-Meier Methodology)



Number of Subjects at Risk						
AVONEX® group	193	164	143	112	73	41
Placebo group	190	146	131	98	58	26

Table 2
Brain MRI Data According to Treatment Group

	AVONEX®	Placebo
CHANGE IN T2 VOLUME @18 MONTHS:	N = 119	N = 109
Actual Change (mm^3)[1]*		
Median (25^{th}%, 75^{th}%)	28 (-576, 397)	313 (5, 1140)
Percentage Change[1]*		
Median (25^{th}%, 75^{th}%)	1 (-24, 29)	16 (0, 53)
NUMBER OF NEW OR ENLARGING T2 LESIONS @ 18 MONTHS[1]*:	N = 132	N = 119
	N (%)	N (%)
0	62 (47)	22 (18)
1–3	41 (31)	47 (40)
≥4	29 (22)	50 (42)
Mean (SD)	2.13 (3.19)	4.97 (7.71)
NUMBER OF GD-ENHANCING LESIONS @ 6 MONTHS[2]*:	N = 165	N = 152
	N (%)	N (%)
0	115 (70)	93 (61)
1	27 (16)	16 (11)
>1	23 (14)	43 (28)
Mean (SD)	0.87 (2.28)	1.49 (3.14)

[1]P value <0.001
[2]P value <0.03
*P value from a Mann-Whitney rank-sum test

Patients should be advised about the abortifacient potential of AVONEX® (see Precautions: Pregnancy—Teratogenic Effects).

The prefilled syringe cap contains dry natural rubber.

When a physician determines that AVONEX® can be used outside of the physician's office, persons who will be administering AVONEX® should receive instruction in reconstitution and injection, including the review of the injection procedures. If a patient is to self-administer, the physical ability of that patient to self-inject intramuscularly should be assessed. 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.

Laboratory Tests

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests, are recommended during AVONEX® therapy (see WARNINGS: Decreased Peripheral Blood Counts and PRECAUTIONS: Cardiomyopathy and Congestive Heart Failure, and Autoimmune Disorders). During the placebo-controlled studies in multiple sclerosis, these tests were performed at least every 6 months. There were no significant differences between the placebo and AVONEX® groups in the incidence of liver enzyme elevation, leukopenia, or thrombocytopenia. However, 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. Thyroid function should be monitored periodically. If patients have or develop symptoms of thyroid dysfunction (hypo- or hyperthyroidism), thyroid function tests should be performed according to standard medical practice.

Drug Interactions

No formal drug interaction studies have been conducted with AVONEX®. In the placebo-controlled studies in multiple sclerosis, 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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: No carcinogenicity data for AVONEX® are available in animals or humans.

Mutagenesis: AVONEX® was not mutagenic when tested in the Ames bacterial test and in an *in vitro* cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation. These assays are designed to detect agents that interact directly with and cause damage to cellular DNA. AVONEX® is a glycosylated protein that does not directly bind to DNA.

Impairment of Fertility: No studies were conducted to evaluate the effects of AVONEX® on fertility in normal women or women with multiple sclerosis. It is not known whether AVONEX® can affect human reproductive capacity. Menstrual irregularities were observed in monkeys administered AVONEX® at a dose 100 times the recommended weekly human dose (based upon a body surface area comparison). Anovulation and decreased serum progesterone levels were also noted transiently in some animals. These effects were reversible after discontinuation of drug.

Treatment of monkeys with AVONEX® at 2 times the recommended weekly human dose (based upon a body surface area comparison) had no effects on cycle duration or ovulation.

The accuracy of extrapolating animal doses to human doses is not known. In the placebo-controlled studies in multiple sclerosis, 5% of patients receiving placebo and 6% of patients receiving AVONEX® experienced menstrual disorder. If menstrual irregularities occur in humans, it is not known how long they will persist following treatment.

Pregnancy—Teratogenic Effects

Pregnancy Category C: The reproductive toxicity of AVONEX® has not been studied in animals or humans. In pregnant monkeys given AVONEX® 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

Continued on next page

Avonex—Cont.

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. 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 discontinuation of AVONEX® therapy should be considered.

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 of AVONEX® in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Clinical studies of AVONEX® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

ADVERSE REACTIONS

Depression, suicidal ideation, and new or worsening other psychiatric disorders have been observed to be increased in patients using interferon compounds including AVONEX® (see WARNINGS: Depression and Suicide). Anaphylaxis and other allergic reactions have been reported in patients using AVONEX® (see WARNINGS: Anaphylaxis). Decreased peripheral blood counts have been reported in patients using AVONEX® (see WARNINGS: Decreased Peripheral Blood Counts). Seizures, cardiovascular adverse events, and autoimmune disorders also have been reported in association with the use of AVONEX® (see Precautions).

The adverse reactions most commonly reported in patients associated with the use of AVONEX® were flu-like and other symptoms occurring within hours to days following an injection. Symptoms can include myalgia, fever, fatigue, headaches, chills, nausea, and vomiting. Some patients have experienced paresthesias, hypertonia and myasthenia. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of AVONEX®, or the need for concomitant medication to treat an adverse reaction symptom) were flu-like symptoms and depression.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of AVONEX® cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The data described below reflect exposure to AVONEX® in 351 patients, including 319 patients exposed for 6 months, and 288 patients exposed for greater than one year in placebo-controlled trials. The mean age of patients receiving AVONEX® was 35 years, 74% were women and 89% were Caucasian. Patients received either 30 mcg AVONEX® or placebo.

Table 3 enumerates adverse events and selected laboratory abnormalities that occurred at an incidence of at least 2% higher frequency in AVONEX®-treated subjects than was observed in the placebo group. Reported adverse events have been classified using standard COSTART terms.

[See table 3 below]

No AVONEX®-treated patients attempted suicide in the two placebo-controlled studies. In Study 2, AVONEX®-treated patients were more likely to experience depression than placebo-treated patients (20% in AVONEX® group vs. 13% in placebo group). The incidences of depression in the placebo-treated and AVONEX®-treated patients in Study 1 were similar. In Study 1, suicidal tendency was seen more frequently in AVONEX®-treated patients (4% in AVONEX® group vs. 1% in placebo group) (see WARNINGS).

Seizures

Seizures have been reported in 4 of 351 AVONEX®-treated patients in the placebo-controlled studies, compared to none in the placebo-treated patients (see Precautions: Seizures).

Post-Marketing Experience

The following adverse events have been identified and reported during post-approval use of AVONEX®: New or worsening other psychiatric disorders, and anaphylaxis (see WARNINGS). Autoimmune disorders including autoimmune hepatitis, idiopathic thrombocytopenia, hyper- and hypothyroidism, and seizures in patients without prior history (see Precautions).

Infrequent reports of congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure with rare cases being temporally related to the administration of AVONEX® (see Precautions: Cardiomyopathy and Congestive Heart Failure).

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and thrombocytopenia (see WARNINGS: Decreased Peripheral Blood Counts). Some cases of thrombocytopenia have had nadirs below 10,000/μL. Some of these cases reoccur upon rechallenge.

Hepatic injury including elevated serum hepatic enzyme levels and hepatitis, some of which have been severe, has been reported post-marketing (see Precautions: Hepatic Injury).

Meno- and metrorrhagia, rash (including vesicular rash), rare cases of injection site abscess or cellulitis that may require surgical intervention have also been reported in post-marketing experience.

Because reports of these reactions are voluntary and the population is of an uncertain size, it is not always possible to reliably estimate the frequency of the event or establish a causal relationship to drug exposure.

Adverse Reactions Associated with Subcutaneous Use

AVONEX® has also been evaluated in 290 patients with diseases other than multiple sclerosis, primarily chronic viral hepatitis B and C, in which the doses studied ranged from 15 mcg to 75 mcg, given SC, 3 times a week, for up to 6 months. Inflammation at the site of the subcutaneous injection was observed in 52% of treated patients in these studies. Subcutaneous 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 multiple sclerosis patients participating in Study 1. Injection site edema and injection site hemorrhage were observed in multiple sclerosis patients participating in Study 2.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. In recent studies assessing immunogenicity in multiple sclerosis patients administered AVONEX® for at least 1 year, 5% (21 of 390 patients) showed the presence of neutralizing antibodies at one or more times. The clinical significance of neutralizing antibodies to AVONEX® is unknown.

These data reflect the percentage of patients whose test results were considered positive for antibodies to AVONEX® using a two-tiered assay (ELISA binding assay followed by an antiviral cytopathic effect assay), and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AVONEX® with the incidence of antibodies to other products may be misleading.

Anaphylaxis has been reported as a rare complication of AVONEX® use. Other allergic reactions have included dyspnea, orolingual edema, skin rash and urticaria (see WARNINGS: Anaphylaxis).

DRUG ABUSE AND DEPENDENCE

There is no evidence that abuse or dependence occurs with AVONEX® therapy. However, the risk of dependence has not been systematically evaluated.

OVERDOSAGE

Safety of doses higher than 60 mcg once a week have not been adequately evaluated. The maximum amount of AVONEX® that can be safely administered has not been determined.

DOSAGE AND ADMINISTRATION

The recommended dosage of AVONEX® (Interferon beta-1a) is 30 mcg injected intramuscularly once a week.

AVONEX® is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in intramuscular injection technique. Sites for injection include the thigh or upper arm (see Medication Guide).

Reconstitution of AVONEX® Vials

Use appropriate aseptic technique during the preparation of AVONEX®. To reconstitute lyophilized AVONEX®, use a sterile syringe and MICRO PIN® to inject 1.1 mL of the supplied diluent, Sterile Water for Injection, USP, into the AVONEX® vial. Gently swirl the vial of AVONEX® to dissolve the drug completely. **DO NOT SHAKE.** The reconstituted solution should be clear to slightly yellow without particles. Inspect the reconstituted product visually prior to use. Discard the product if it contains particulate matter or is discolored. Each vial of reconstituted solution contains 30 mcg/1.0 mL Interferon beta-1a.

Withdraw 1.0 mL of reconstituted solution from the vial into a sterile syringe. Replace the cover on the MICRO PIN® and attach the sterile 23 gauge, 1¼ inch needle and inject the solution intramuscularly. The AVONEX® and diluent vials are for single-use only; unused portions should be discarded.

Using Avonex® Prefilled Syringes

The AVONEX® prefilled syringe should be held upright (rubber cap faces up). Remove the protective cover by turning and gently pulling the rubber cap in a clockwise motion. Attach the 23 gauge, 1¼ inch needle and inject the solution intramuscularly. The AVONEX® prefilled syringe is for single-use only.

HOW SUPPLIED

30 mcg Lyophilized Powder Vial

A vial of AVONEX® is supplied as a 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).

AVONEX® lyophilized vials are available in the following package configuration (NDC 59627-001-03): A package containing four Administration Dose Packs (each containing one vial of AVONEX®, one 10 mL diluent vial, two alcohol wipes, one gauze pad, one 3 mL syringe, one MICRO PIN® vial access pin, one 23 gauge, 1¼ inch needle, and one adhesive bandage).

30 mcg Prefilled Syringe

A prefilled syringe of AVONEX® is supplied as a sterile liquid albumin-free formulation containing 30 mcg of Interferon beta-1a, 0.79 mg Sodium Acetate Trihydrate, USP; 0.25 mg Glacial Acetic Acid, USP; 15.8 mg Arginine Hydrochloride, USP; and 0.025 mg Polysorbate 20 in Water for Injection, USP. Each prefilled glass syringe contains 0.5 mL for IM injection.

AVONEX® prefilled syringes are available in the following package configuration (NDC 59627-002-05): A package containing four Administration Dose Packs (each containing

Table 3
Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Studies

Adverse Event	Placebo (N = 333)	AVONEX® (N = 351)
Body as a Whole		
Headache	55%	58%
Flu-like symptoms (otherwise unspecified)	29%	49%
Pain	21%	23%
Asthenia	18%	24%
Fever	9%	20%
Chills	5%	19%
Abdominal pain	6%	8%
Injection site pain	6%	8%
Infection	4%	7%
Injection site inflammation	2%	6%
Chest pain	2%	5%
Injection site reaction	1%	3%
Toothache	1%	3%
Nervous System		
Depression	14%	18%
Dizziness	12%	14%
Respiratory System		
Upper respiratory tract infection	12%	14%
Sinusitis	12%	14%
Bronchitis	5%	8%
Digestive System		
Nausea	19%	23%
Musculoskeletal System		
Myalgia	22%	29%
Arthralgia	6%	9%
Urogenital		
Urinary tract infection	15%	17%
Urine constituents abnormal	0%	3%
Skin and Appendages		
Alopecia	2%	4%
Special Senses		
Eye disorder	2%	4%
Hemic and Lymphatic System		
Injection site ecchymosis	4%	6%
Anemia	1%	4%
Cardiovascular System		
Migraine	3%	5%
Vasodilation	0%	2%

one single-use syringe of AVONEX® and one 23 gauge, 1¼ inch needle), and a recloseable accessory pouch containing 4 alcohol wipes, 4 gauze pads, and 4 adhesive bandages.

Stability and Storage

30 mcg Lyophilized Powder Vial

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

30 mcg Prefilled Syringe

AVONEX® in prefilled syringes must be stored in a 2–8°C (36–46°F) refrigerator. Once removed from the refrigerator, AVONEX® in a prefilled syringe should be allowed to warm to room temperature (about 30 minutes) and used within 12 hours. Do not use external heat sources such as hot water to warm AVONEX® in a prefilled syringe. DO NOT EXPOSE TO HIGH TEMPERATURES. DO NOT FREEZE. Protect from light. Do not use beyond the expiration date stamped on the syringe.

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AVONEX® (Interferon beta-1a)

Manufactured by:

BIOGEN, INC.

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Cambridge, MA 02142 USA

1-800-456-2255

U.S. Patent Pending

I61018-4 (Issue date 03/2004)

Rx only

*Micro Pin® is the trademark of B. Braun Medical Inc.

MEDICATION GUIDE

AVONEX®

Interferon beta-1a

(Including appendix with instructions for using AVONEX® Prefilled Syringe or the AVONEX® vials)

Please read this guide carefully before you start to use AVONEX® (a-vuh-necks) and each time your prescription is refilled since there may be new information. The information in this guide does not take the place of talking with your doctor or healthcare professional.

What is the most important information I should know about AVONEX®?

AVONEX® will not cure multiple sclerosis (MS) but it has been shown to decrease the number of flare-ups and slow the occurrence of some of the physical disability that is common in people with MS. AVONEX® can cause serious side effects, so before you start taking AVONEX®, you should talk with your doctor about the possible benefits of AVONEX® and its possible side effects to decide if AVONEX® is right for you. Potential serious side effects include:

- **Depression**—Some people treated with interferons, including AVONEX®, have become depressed (feeling sad, feeling low or feeling bad about oneself). Some people have thought about killing themselves and a few have committed suicide. Depression is common in people with MS. If you are noticeably sadder or feeling more hopeless, you should tell a family member or friend right away and call your doctor as soon as possible. You should tell the doctor if you have ever had any mental illness, including depression, and if you take any medicines for depression.
- **Risk to pregnancy**—If you become pregnant while taking AVONEX®, you should stop using AVONEX® immediately and call your doctor. AVONEX® may cause you to lose your baby (miscarry) or may cause harm to your unborn child. You and your doctor will need to decide whether the potential benefit of taking AVONEX® is greater than the risks are to your unborn child.
- **Allergic reactions**—Some patients taking AVONEX® have had severe allergic reactions leading to difficulty breathing. Allergic reactions can happen after your first dose or may not happen until after you have taken AVONEX® many times. Less severe allergic reactions such as rash, itching, skin bumps or swelling of the mouth and tongue can also happen. If you think you are having an allergic reaction, stop using AVONEX® immediately and call your doctor.
- **Blood problems**—You may have a drop in the levels of infection-fighting blood cells, red blood cells or cells that help to form blood clots. If the drop in levels are severe, they can lessen your ability to fight infections, make you feel tired or sluggish or cause you to bruise or bleed easily.
- **Seizures**—Some patients have had seizures while taking AVONEX®, including some patients who have never had seizures before. It is not known whether the seizures were related to the effects of their MS, to AVONEX®, or to a combination of both. If you have a seizure while taking AVONEX®, you should stop taking AVONEX® and call your doctor right away.
- **Heart problems**—While AVONEX® is not known to have direct effects on the heart, a few patients who did not have a history of heart problems developed heart muscle problems or congestive heart failure after taking AVONEX®. Some of the symptoms of heart problems are swollen ankles, shortness of breath, decreased ability to exercise, fast heartbeat, tightness in chest, increased need to urinate at night, and not being able to lay flat in bed. If you develop these symptoms or any heart problems while taking AVONEX®, you should call your doctor right away.

For more information on possible side effects with AVONEX®, please read the section on **"What are the possible side effects of AVONEX®?"** in this Medication Guide.

What is AVONEX®?

AVONEX® is a form of a protein called beta interferon that occurs naturally in the body. It is used to treat relapsing forms of multiple sclerosis. It will not cure your MS but may decrease the number of flare-ups of the disease and slow the occurrence of some of the physical disability that is common in people with MS. MS is a life-long disease that affects your nervous system by destroying the protective covering (myelin) that surrounds your nerve fibers. The way AVONEX® works in MS is not known.

Who should not take AVONEX®?

Do not take AVONEX® if you have had an allergic reaction (difficulty breathing, itching, flushing or skin bumps spread widely over the body) to interferon beta.

Do not take the vial formulation of AVONEX® if you have a history of hypersensitivity to albumin (human).

If you have ever had any of the following conditions or serious medical problems, you should tell your doctor before taking AVONEX®:

- Depression (sinking feeling or sadness), anxiety (feeling uneasy or fearful for no reason), or trouble sleeping
- Problems with your thyroid gland
- Blood problems such as bleeding or bruising easily and anemia (low red blood cells) or low white blood cells
- Seizures (for example, epilepsy)
- Heart problems
- Liver disease
- Are planning to become pregnant

You should tell your doctor if you are taking any other prescription or nonprescription medicines. This includes any vitamin or mineral supplements, or herbal products.

You should tell your doctor if you have had a natural rubber sensitivity since the AVONEX® prefilled syringe cap contains dry natural rubber, which may cause allergic reactions.

How should I take AVONEX®?

To get the most benefit from this medicine, it is important that you take AVONEX® exactly as your doctor tells you. AVONEX® is given by injection into the muscle (intramuscular injection) once a week, on the same day (for example, every Monday right before bedtime). If you miss a dose, you should take your next dose as soon as you remember. You should continue your regular schedule the following week. **Do not take AVONEX® on two consecutive days.** Take only the dose your doctor has prescribed for you. Do not change your dose unless you are told to by your doctor. If you take more than your prescribed dose, call your healthcare provider right away. Your doctor may want to monitor you more closely.

You should always follow your doctor's instructions and advice about how to take this medication. If your doctor feels that you, or a family member or friend, may give you the injections, then you and/or the other person should be instructed by your doctor or other healthcare provider in how to prepare and inject your dose of AVONEX®. Do not try to give yourself injections at home until you are sure that you (or the person who will be giving you the injections) fully understands and is comfortable with how to prepare and inject the product. At the end of this guide there are detailed instructions on how to prepare and give yourself an injection of AVONEX® that will help remind you of the instructions from your doctor or healthcare provider.

Always use a new, unopened AVONEX® vial or prefilled syringe for each injection. Never reuse the vials or syringes. It is important to keep your work area, your hands, and your injection site clean to minimize risk of infection. You should wash your hands prior to handling the syringe.

It is important that you change your injection site each week.

Do not inject into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way. Use the alcohol wipe to **thoroughly** clean the skin at the injection site you haven chosen. Using a circular motion, and starting at the injection site and moving outward, clean the injection site with an alcohol wipe. Let the skin area dry before you inject the AVONEX.

AVONEX® comes in two different forms (a powder in a single-use vial and a liquid in a prefilled syringe). **See the attached appendix for detailed instructions for preparing and giving a dose of AVONEX®. These instructions are specific to the form of AVONEX® chosen for you by your healthcare provider.**

What should I avoid while taking AVONEX®?

- **Pregnancy**—You should avoid becoming pregnant while taking AVONEX® until you have talked with your doctor. AVONEX® can cause you to lose your baby (miscarry).
- **Breast-feeding**—You should talk to your doctor if you are breast-feeding an infant. It is not known if the interferon in AVONEX® gets into the breast milk, or if it could harm your nursing baby.

What are the possible side effects of AVONEX®?

- **Flu-like symptoms**—Most people who take AVONEX® have flu-like symptoms (fever, chills, sweating, muscle aches, and tiredness) early during the course of therapy. Usually, these symptoms last for a day after the injection. You may be able to manage these flu-like symptoms by injecting your AVONEX® dose at bedtime and taking over-the-counter pain and fever reducers. For many people, these symptoms lessen or go away over time. Talk to your doctor if these symptoms continue longer than the first few months of therapy, or if they are difficult to manage.
- **Depression**—Some patients taking interferons have become severely depressed and/or anxious. If you feel sad or hopeless you should tell a friend or family member right away and call your doctor immediately. Your doctor or healthcare provider may ask that you stop taking AVONEX®, and/or may recommend that you take a medication to treat your depression. **(See "What is the most important information I should know about AVONEX®?")**
- **Blood problems**—A drop in the levels of white (infection-fighting) blood cells, red blood cells, or a part of your blood that helps to form blood clots (platelets) can happen. If this drop in blood levels is severe, it can lessen your ability to fight infections, make you feel very tired or sluggish, or cause you to bruise or bleed easily. Your doctor may ask you to have periodic blood tests. **(See "What is the most important information I should know about AVONEX®?")**
- **Liver problems**—Your liver function may be affected. Symptoms of changes in your liver include yellowing of the skin and whites of the eyes and easy bruising.
- **Thyroid problems**—Some people taking AVONEX® develop changes in the function of their thyroid. Symptoms of these changes include feeling cold or hot all the time, a change in your weight (gain or loss) without a change in your diet or amount of exercise you get, or feeling emotional.
- **Seizures**—Some patients have had seizures while taking AVONEX®, including patients who have never had seizures before. It is not known whether the seizures were related to the effects of their MS, to AVONEX®, or to a combination of both. If you have a seizure while taking AVONEX®, you should call your doctor right away. **(See "What is the most important information I should know about AVONEX®?")**
- **Heart problems**—While AVONEX® is not known to have any direct effects on the heart, a few patients who did not have a history of heart problems developed heart muscle problems or congestive heart failure after taking AVONEX®. Some of the symptoms of heart problems are swollen ankles, shortness of breath, decreased ability to exercise, fast heartbeat, tightness in chest, increased need to urinate at night, and not being able to lay flat in bed. If you develop these symptoms or any heart problems while taking AVONEX®, you should call your doctor right away. **(See "What is the most important information I should know about AVONEX®?")**

If you get any of the symptoms listed in this section or any listed in the section **"What is the most important information I should know about AVONEX®?"**, you should call your doctor right away. Whether you experience any side effects or not, you and your doctor should periodically discuss your general health. Your doctor may want to monitor you more closely or may ask you to have blood tests more frequently.

General advice about prescription medicines

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This medication has been prescribed for your particular condition. Do not use it for another condition or give this drug to anyone else. If you have questions you should speak with your doctor or healthcare professional. You may also ask your doctor or pharmacist for a copy of the information provided to them with the product.

Keep this and all drugs out of the reach of children.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Biogen, Inc.

14 Cambridge Center

Cambridge, MA 02142 USA

1-800-456-2255

I61018-3(Issue date03/2004)

Medication Guide Appendix: Instructions for Preparing and Giving a Dose with an AVONEX® Prefilled Syringe

Storing AVONEX® Prefilled Syringes

AVONEX® in prefilled syringes should be refrigerated (36–46°F or 2–8°C). Once removed from the refrigerator, AVONEX® in a prefilled syringe should be allowed to warm to room temperature (about 30 minutes) and used within 12

Continued on next page

Avonex—Cont.

hours. Do not use external heat sources such as hot water to warm AVONEX® in a prefilled syringe. Do not expose to high temperatures. Do not freeze. Protect from light.

How do I prepare and inject a dose of AVONEX®?

Find a well lit, clean, flat work surface like a table and collect all the supplies you will need to give yourself or receive an injection. Take one AVONEX® Administration Dose Pack out of the refrigerator about 30 minutes before you plan on injecting your dose to allow it to reach room temperature. A room temperature solution is more comfortable to inject.

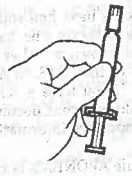
You will need the following supplies:

- single-use prefilled syringe
- sterile needle
- alcohol wipe
- gauze pad
- adhesive bandage
- a puncture resistant container for disposal of used syringes and needles
- 1 syringe diagram card

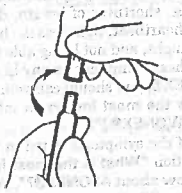
Preparing the AVONEX® prefilled syringe

It is important to keep your work area, your hands, and your injection site clean to minimize risk of infection. You should wash your hands prior to handling the syringe.

1. Check the expiration date. The expiration date is printed on the AVONEX® prefilled syringe, syringe package and the carton. Do not use if the medication is expired.
2. Check the contents of the syringe. The solution in the syringe should be clear and colorless. If the solution is colored or cloudy, do not use the syringe. Get a new syringe.
3. Hold the syringe so the rubber cap is facing down. Take the card with the drawing of the syringe and hold it next to the real syringe so the drawing and the real syringe are side-by-side. Check to make sure the amount of liquid in the syringe is the same or very close to the 0.5 mL arrow shown on the card with the drawing of the prefilled syringe. The top of the liquid may be curved as shown in the drawing. The 0.5 mL arrow should point near the middle of the curved liquid. If the real syringe does not have the correct amount of liquid, DO NOT USE THAT SYRINGE. Call your pharmacist.
4. Hold the AVONEX® prefilled syringe upright (rubber cap facing up).

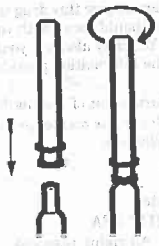


5. Remove the protective rubber cap by turning and gently pulling the cap in a clockwise motion.



6. Open the package with the 23 gauge 1¼ inch needle. Attach the needle by firmly pressing it onto the syringe and turning it a half turn clockwise.

NOTE: If you do not firmly attach the needle to the syringe, it may leak so you may not get your full dose of AVONEX®.



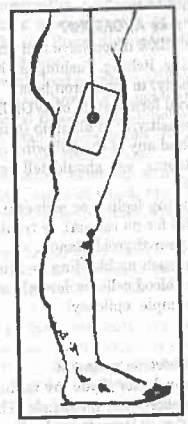
Selecting an injection site

You should use a different site each time you inject. This can be as simple as switching between thighs (if you are always injecting yourself), or if another person is helping you, you can rotate between your upper arms and your thighs. Keeping a record of the date and location of each injection will help you.

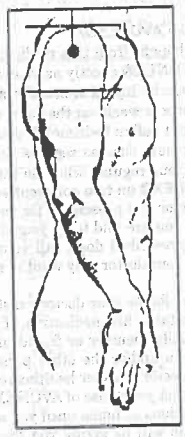
Do not inject into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way.

The best sites for intramuscular injection are the thigh and upper arm:

- thigh

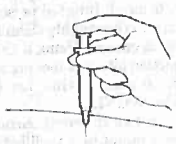


- upper arm



Injecting the AVONEX® dose

1. Use the alcohol wipe to clean the skin at the injection site you choose. Then, pull the protective cover **straight** off the needle; do not twist the cover off.
2. With one hand, stretch the skin out around the injection site. Hold the syringe like a pencil with the other hand, and using a quick motion insert the needle at a 90° angle, through the skin and into the muscle.
3. Once the needle is in, let go of the skin and slowly push the plunger down until the syringe is empty.



4. Take the gauze pad and hold it near the needle at the injection site and pull the needle straight out. Use the gauze pad to apply pressure to the site for a few seconds or rub gently in a circular motion.

5. If there is bleeding at the site, wipe it off and, if necessary, apply an adhesive bandage.
6. After 2 hours, check the injection site for redness, swelling or tenderness. If you have a skin reaction and it does not clear up in a few days, contact your doctor or nurse.
7. Dispose of the used syringe and needle in your puncture resistant container. This is a single-use syringe. DO NOT USE a syringe or needle more than once.

Disposal of syringes and needles

There may be special state and/or local laws for disposing of used needles and syringes. Your doctor, nurse or pharmacist should provide you with instructions on how to dispose of your used needles and syringes.

- **Always keep your disposal container out of the reach of children.**
- DO NOT throw used needles and syringes into the household trash and DO NOT RECYCLE.

Appendix Revision Date: 05/2003

Medication Guide Appendix: Instructions for Preparing and Giving a Dose with an AVONEX® Vial

Storing AVONEX® Vials

Prior to use, AVONEX® should be refrigerated (36–46°F or 2–8°C) but can be kept for up to 30 days at room temperature (77°F or 25°C). You should avoid exposing AVONEX® to high temperatures and freezing. After mixing, AVONEX® solution should be used immediately, within 6 hours when stored refrigerated at 36–46°F or 2–8°C. Do not freeze the AVONEX® solution.

How do I prepare and inject a dose of AVONEX®?

Find a well-lit, clean, flat work surface like a table and collect all the supplies you will need to give yourself or receive an injection. You may want to take one AVONEX® Administration Dose Pack out of the refrigerator about 30 minutes before you plan on injecting your dose to allow it to reach room temperature. A room temperature solution is more comfortable to inject.

You will need the following supplies:

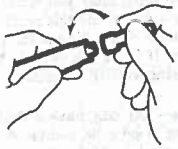
- vial of AVONEX® (white to off-white powder or cake)
- vial of diluent, single-use (Sterile Water for Injection, USP)
- 3 mL syringe
- blue MICRO PIN® (vial access pin)
- sterile needle
- alcohol wipes
- gauze pad
- adhesive bandage
- a puncture resistant container for disposal of used syringes, needles, and MICRO PINS.

Preparing the AVONEX® solution

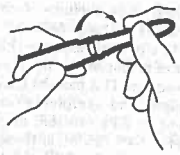
It is important to keep your work area, your hands, and your injection site clean to minimize risk of infection. You should wash your hands prior to preparing the medication.

1. Check the expiration date on the AVONEX® vial and the vial of diluent; do not use if the medication or diluent is expired.
2. Remove the caps from the vial of AVONEX® and the vial of diluent, and clean the rubber stopper on the top of each vial with an alcohol wipe.

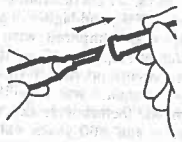
3. Remove the small light blue protective cover from the end of the syringe barrel with a counterclockwise turn.



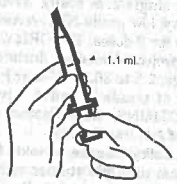
4. Attach the blue MICRO PIN® to the syringe by turning clockwise until secure. *NOTE: Over-tightening can make the MICRO PIN® difficult to remove.*



5. Pull the MICRO PIN® cover straight off; do not twist. Save the cover for later use.



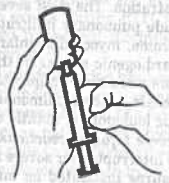
6. Pull back the syringe plunger to the 1.1 mL mark.



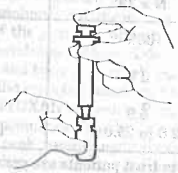
7. Firmly push the MICRO PIN® down through the **center** of the rubber stopper of the diluent vial.

8. Inject the air in the syringe into the diluent vial by pushing down on the plunger until it cannot be pushed any further.
9. Keeping the MICRO PIN® in the vial, turn the diluent vial and syringe upside down.
10. While keeping the MICRO PIN® in the fluid, slowly pull back on the plunger to withdraw 1.1 mL of diluent into the syringe.

11. Gently tap the syringe with your finger to make any air bubbles rise to the top. If bubbles are present, slowly press the plunger in (to push just the bubbles out through the needle). Make sure there is still 1.1 mL of diluent in the syringe.

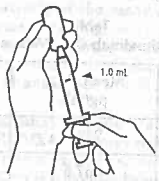


12. Slowly pull the MICRO PIN® out of the diluent vial.
13. Carefully insert the MICRO PIN® through the **center** of the rubber stopper of the vial of AVONEX®. *NOTE: Off-center punctures can push the stopper into the vial. If the stopper falls into the vial, do not use.*
14. **Slowly** inject the diluent into the vial of AVONEX®. DO NOT aim the stream of diluent directly on the AVONEX® powder. Too direct or forceful a stream of diluent onto the powder may cause foaming, and make it difficult to withdraw AVONEX®.

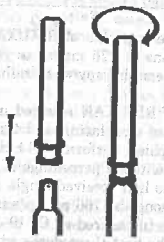


15. Without removing the syringe, **gently** swirl the vial until the AVONEX® is dissolved. ***DO NOT SHAKE.***

16. Check to see that all of the AVONEX® is dissolved. Check the solution in the vial of AVONEX®. It should be clear to slightly yellow in color and should not have any particles. Do not use the vial if the solution is cloudy, has particles in it or is a color other than clear to slightly yellow.
17. Turn the vial and syringe upside down. Slowly pull back on the plunger to withdraw 1.0 mL of AVONEX®. If bubbles appear, push solution slowly back into the vial and withdraw the solution again.



18. With the vial still upside down, tap the syringe **gently** to make any air bubbles rise to the top. Then press the plunger in until the AVONEX® is at the top of the syringe. Check the volume (should be 1.0 mL) and withdraw more medication if necessary. Withdraw the MICRO PIN® and syringe from the vial.
19. Replace the cover on the MICRO PIN® and remove from the syringe with a counterclockwise turn.
20. Attach the sterile needle for injection to the syringe turning clockwise until the needle is secure. A secure attachment will prevent leakage during the injection.



Selecting an injection site

You should use a different site each time you inject. This can be as simple as switching between thighs (if you are always injecting yourself), or if another person is helping you, you can rotate between your upper arms and your thighs. Keeping a record of the date and location of each injection will help you.

Do not inject into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way.

The best sites for intramuscular injection are the thigh and upper arm:

- thigh

[See first figure at top of next column]

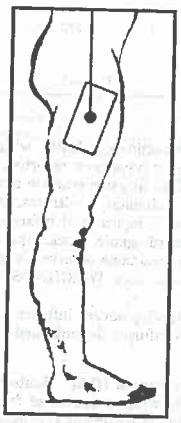
- upper arm

[See second figure at top of next column]

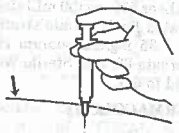
You should rotate injection sites each week. This can be as simple as switching between thighs (if you are always injecting yourself). If another person is helping you, you can rotate among your thighs and upper arms. Make sure that the site you choose is free from any skin irritations.

Injecting the AVONEX® dose

1. Use a new alcohol wipe to clean the skin at one of the recommended intramuscular injection sites. Then, pull the protective cover **straight** off the needle; do not twist the cover off.



2. With one hand, stretch the skin out around the injection site. Hold the syringe like a pencil with the other hand, and using a quick motion insert the needle at a 90° angle, through the skin and into the muscle.
3. Once the needle is in, let go of the skin and slowly push the plunger down until the syringe is empty.



4. Hold a gauze pad near the needle at the injection site and pull the needle straight out. Use the pad to apply pressure to the site for a few seconds or rub gently in a circular motion.

5. If there is bleeding at the site, wipe it off and, if necessary, apply an adhesive bandage.
6. Dispose of the used syringe, needle and 1.0mL MICRO PIN® in your puncture resistant container. DO NOT USE a syringe, MICRO PIN®, or needle more than once. The AVONEX® and diluent vials should be put in the trash.

Disposal of syringes and needles

There may be special state and/or local laws for disposing of used needles and syringes. Your doctor, nurse or pharmacist should provide you with instructions on how to dispose of your used needles and syringes.

- **Always keep your disposal container out of the reach of children.**
- DO NOT throw used needles and syringes into the household trash and DO NOT RECYCLE.

Appendix Revision Date: 03/2004

Continued on next page

NORVASC®—10 mg Tablets (amlodipine besylate equivalent to 10 mg of amlodipine per tablet) are white, round, flat-faced, beveled edged engraved with both "NORVASC" and "10" on one side and plain on the other side and supplied as follows:

NDC 0069-1540-68 Bottle of 90

NDC 0069-1540-41 Unit Dose package of 100

Store bottles at controlled room temperature, 59° to 86°F (15° to 30°C) and dispense in tight, light-resistant container (USP).

Rx only

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017
70-4782-00-1
Revised June 2003

Shown in Product Identification Guide, page 329

REBIF®
[rē-bif]
(interferon beta-1a)

℞

DESCRIPTION

Rebif® (interferon beta-1a) is a purified 166 amino acid glycoprotein with a molecular weight of approximately 22,500 daltons. It is produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of Rebif® is identical to that of natural fibroblast derived human interferon beta. Natural interferon beta and interferon beta-1a (Rebif®) are glycosylated with each containing a single N-linked complex carbohydrate moiety.

Using a reference standard calibrated against the World Health Organization natural interferon beta standard (Second International Standard for Interferon, Human Fibroblast GB 23 902 531), Rebif® has a specific activity of approximately 270 million international units (MIU) of antiviral activity per mg of interferon beta-1a determined specifically by an in vitro cytopathic effect bioassay using WISH cells and Vesicular Stomatitis virus. Rebif® 22 mcg and 44 mcg contains approximately 6 MIU or 12 MIU, respectively, of antiviral activity using this method.

Rebif® (interferon beta-1a) is formulated as a sterile solution in a prefilled syringe intended for subcutaneous (sc) injection. Each 0.5 mL (0.5 cc) of Rebif® contain either 22 mcg or 44 mcg of interferon beta-1a, 2 mg or 4 mg albumin (human) USP, 27.3 mg mannitol USP, 0.4 mg sodium acetate, Water for Injection USP.

CLINICAL PHARMACOLOGY

General

Interferons are a family of naturally occurring proteins that are produced by eukaryotic cells in response to viral infection and other biological inducers. Interferons possess immunomodulatory, antiviral and antiproliferative biological activities. They exert their biological effects by binding to specific receptors on the surface of cells. Three major groups of interferons have been distinguished: alpha, beta, and gamma. Interferons alpha and beta form the Type I interferons and interferon gamma is a Type II interferon. Type I interferons have considerably overlapping but also distinct biological activities. Interferon beta is produced naturally by various cell types including fibroblasts and macrophages. Binding of interferon beta to its receptors initiates a complex cascade of intracellular events that leads to the expression of numerous interferon-induced gene products and markers, including 2′, 5′-oligoadenylate synthetase, beta 2-microglobulin and neopterin, which may mediate some of the biological activities. The specific interferon-induced proteins and mechanisms by which interferon beta-1a exerts its effects in multiple sclerosis have not been fully defined.

Pharmacokinetics

The pharmacokinetics of Rebif® (interferon beta-1a) in people with multiple sclerosis have not been evaluated. In healthy volunteer subjects, a single subcutaneous (sc) injection of 60 mcg of Rebif® (liquid formulation), resulted in a peak serum concentration (C_{max}) of 5.1 ± 1.7 IU/mL (mean ± SD), with a median time of peak serum concentration (T_{max}) of 16 hours. The serum elimination half-life ($t_{1/2}$) was 69 ± 37 hours, and the area under the serum concentration versus time curve (AUC) from zero to 96 hours was 294 ± 31 IU·h/mL. Following every other day sc injections in healthy volunteer subjects, an increase in AUC of approximately 240% was observed, suggesting that accumulation of interferon beta-1a occurs after repeat administration. Total clearance is approximately 33-55 L/hour. There have been no observed gender-related effects on pharmacokinetic parameters. Pharmacokinetics of Rebif® in pediatric and geriatric patients or patients with renal or hepatic insufficiency have not been established.

Pharmacodynamics

Biological response markers (e.g., 2′, 5′-OAS activity, neopterin and beta 2-microglobulin) are induced by interferon beta-1a following parenteral doses administered to healthy volunteer subjects and to patients with multiple sclerosis. Following a single sc administration of 60 mcg of Rebif® intracellular 2′, 5′-OAS activity peaked between 12 to 24 hours and beta-2-microglobulin and neopterin serum concentrations showed a maximum at approximately 24 to 48 hours. All three markers remained elevated for up to four days. Administration of Rebif 22 mcg three times per week (tiw) inhibited mitogen-induced release of pro-inflammatory cytokines (IFN-γ, IL-1, IL-6, TNF-α and TNF-β) by peripheral blood mononuclear cells that, on average, was near double that observed with Rebif® administered once per week (qw) at either 22 or 66 mcg.

The relationships between serum interferon beta-1a levels and measurable pharmacodynamic activities to the mechanism(s) by which Rebif® exerts its effects in multiple sclerosis are unknown. No gender-related effects on pharmacodynamic parameters have been observed.

CLINICAL STUDIES

Two multicenter studies evaluated the safety and efficacy of Rebif® in patients with relapsing-remitting multiple sclerosis.

Study 1 was a randomized, double-blind, placebo controlled study in patients with multiple sclerosis for at least one year, Kurtzke Expanded Disability Status Scale (EDSS) scores ranging from 0 to 5, and at least 2 acute exacerbations in the previous 2 years.[1] Patients with secondary progressive multiple sclerosis were excluded from the study. Patients received sc injections of either placebo (n = 187), Rebif® 22 mcg (n = 189), or Rebif® 44 mcg (n = 184) administered tiw for two years. Doses of study agents were progressively increased to their target doses during the first 4 to 8 weeks for each patient in the study (see **DOSAGE AND ADMINISTRATION**).

The primary efficacy endpoint was the number of clinical exacerbations. Numerous secondary efficacy endpoints were also evaluated and included exacerbation-related parameters, effects of treatment on progression of disability and magnetic resonance imaging (MRI)-related parameters. Progression of disability was defined as an increase in the EDSS score of at least 1 point sustained for at least 3 months. Neurological examinations were completed every 3 months, during suspected exacerbations, and coincident with MRI scans. All patients underwent proton density T2-weighted (PD/T2) MRI scans at baseline and every 6 months. A subset of 198 patients underwent PD/T2 and T1-weighted gadolinium-enhanced (Gd)-MRI scans monthly for the first 9 months. Of the 560 patients enrolled, 533 (95%) provided 2 years of data and 502 (90%) received 2 years of study agent.

Study results are shown in Table 1 and Figure 1. Rebif® at doses of 22 mcg and 44 mcg administered sc tiw significantly reduced the number of exacerbations per patient as compared to placebo. Differences between the 22 mcg and 44 mcg groups were not significant ($p > 0.05$).

The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in lesion area often do not correlate with changes in disability progression. The prognostic significance of the MRI findings in these studies has not been evaluated.

[See table 1 above]

The time to onset of progression in disability sustained for three months was significantly longer in patients treated with Rebif® than in placebo-treated patients. The Kaplan-Meier estimates of the proportions of patients with sustained disability are depicted in Figure 1.

[See figure 1 at top of next column]

The safety and efficacy of treatment with Rebif® beyond 2 years have not been established.

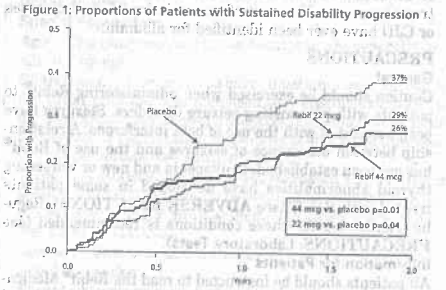
Study 2 was a randomized, open-label, evaluator-blinded, active comparator study.[2] Patients with relapsing-remitting multiple sclerosis with EDSS scores ranging from 0 to 5.5, and at least 2 exacerbations in the previous 2 years were eligible for inclusion. Patients with secondary progressive multiple sclerosis were excluded from the study. Patients were randomized to treatment with Rebif® 44 mcg tiw by sc injection (n=339) or Avonex® 30 mcg qw by intramuscular (im) injection (n=338). Study duration was 48 weeks.

Table 1: Clinical and MRI Endpoints from Study 1

	Placebo	22 mcg tiw	44 mcg tiw
	n = 187	n = 189	n = 184
Exacerbation-related			
Mean number of exacerbations per patient over 2 years[1,2]	2.56	1.82**	1.73***
(Percent reduction)		(29%)	(32%)
Percent (%) of patients exacerbation-free at 2 years[3]	15%	25%*	32%***
Median time to first exacerbation (months)[1,4]	4.5	7.6**	9.6***
MRI	n = 172	n = 171	n = 171
Median percent (%) change of MRI PD-T2 lesion area at 2 years[5]	11.0	-1.2***	-3.8***
Median number of active lesions per patient per scan (PD/T2; 6 monthly)[5]	2.25	0.75***	0.5***

* $p<0.05$ compared to placebo
** $p<0.001$ compared to placebo
*** $p<0.0001$ compared to placebo
(1) Intent-to-treat analysis
(2) Poisson regression model adjusted for center and time on study
(3) Logistic regression adjusted for center. Patients lost to follow-up prior to an exacerbation were excluded from this analysis (n = 185, 183, and 184 for the placebo, 22 mcg tiw, and 44 mcg tiw groups; respectively)
(4) Cox proportional hazard model adjusted for center
(5) ANOVA on ranks adjusted for center. Patients with missing scans were excluded from this analysis

Figure 1: Proportions of Patients with Sustained Disability Progression



The primary efficacy endpoint was the proportion of patients who remained exacerbation-free at 24 weeks. The principal secondary endpoint was the mean number per patient per scan of combined unique active MRI lesions through 24 weeks, defined as any lesion that was T1 active or T2 active. Neurological examinations were performed every three months by a neurologist blinded to treatment assignment. Patient visits were conducted monthly, and mid-month telephone contacts were made to inquire about potential exacerbations. If an exacerbation was suspected, the patient was evaluated with a neurological examination. MRI scans were performed monthly and analyzed in a treatment–blinded manner.

Patients treated with Rebif® 44 mcg sc tiw were more likely to remain relapse-free at 24 and 48 weeks than were patients treated with Avonex® 30 mcg im qw (Table 2). This study does not support any conclusion regarding effects on the accumulation of physical disability.

[See table 2 at top of next page]

The adverse reactions over 48 weeks were generally similar between the two treatment groups. Exceptions included injection site disorders (83% of patients on Rebif® vs. 28% of patients on Avonex®), hepatic function disorders (18% on Rebif® vs. 10% on Avonex®), and leukopenia (6% on Rebif® vs. <1% on Avonex®), which were observed with greater frequency in the Rebif® group compared to the Avonex® group.

INDICATIONS AND USAGE

Rebif® (interferon-beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Efficacy of Rebif® in chronic progressive multiple sclerosis has not been established.

CONTRAINDICATIONS

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

WARNINGS

Depression

Rebif® (interferon beta-1a) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including Rebif®. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to the prescribing physician. If a patient develops depression, cessation of treatment with Rebif® should be considered.

Continued on next page

Rebif—Cont.

Hepatic Injury
A case of fulminant hepatic failure requiring liver transplantation in a patient who initiated Rebif® therapy while taking another potentially hepato-toxic medication has been reported from a non-U.S. postmarking source. Symptomatic hepatic dysfunction, primarily presenting as jaundice, has been reported as a rare complication of Rebif® use. Asymptomatic elevation of hepatic transaminases (particularly SGPT) is common with interferon therapy (see **ADVERSE REACTIONS**). Rebif® should be initiated with caution in patients with active liver disease, alcohol abuse, increased serum SGPT (> 2.5 times ULN), or a history of significant liver disease. Dose reduction should be considered if SGPT rises above times the upper limit of normal. The dose may be gradually re-escalated when enzyme levels have normalized. Treatment with Rebif® should be stopped if jaundice or other clinical symptoms of liver dysfunction appear.

Anaphylaxis
Anaphylaxis has been reported as a rare complication of Rebif® use. Other allergic reactions have included skin rash and urticaria, and have ranged from mild to severe without a clear relationship to dose or duration of exposure. Several allergic reactions, some severe, have occurred after prolonged use.

Albumin (Human)
This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

General
Caution should be exercised when administering Rebif® to patients with pre-existing seizure disorders. Seizures have been associated with the use of beta interferons. A relationship between occurrence of seizures and the use of Rebif® has not been established. Leukopenia and new or worsening thyroid abnormalities have developed in some patients treated with Rebif® (see **ADVERSE REACTIONS**). Regular monitoring for these conditions is recommended (see **PRECAUTIONS: Laboratory Tests**).

Information for Patients
All patients should be instructed to read the Rebif® Medication Guide supplied to them. Patients should be cautioned not to change the dosage or the schedule of administration without medical consultation.
Patients should be informed of the most common and the most severe adverse reactions associated with the use of Rebif® (see **WARNINGS** and **ADVERSE REACTIONS**). Patients should be advised of the symptoms associated with these conditions, and to report them to their physician.
Female patients should be cautioned about the abortifacient potential of Rebif® (see **PRECAUTIONS: Pregnancy**).
Patients should be instructed in the use of aseptic technique when administering Rebif®. Appropriate instruction for self-injection or injection by another person should be provided, including careful review of the Rebif® Medication Guide. If a patient is to self-administer Rebif®, the physical and cognitive ability of that patient to self-administer and properly dispose of syringes should be assessed. The initial injection should be performed under the supervision of an appropriately qualified health care professional. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of severe injection site reactions or necrosis. 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. Patients should be instructed in the technique and importance of proper syringe disposal and be cautioned against reuse of these items.

Laboratory Tests
In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) following introduction of Rebif® therapy and then periodically thereafter in the absence of clinical symptoms. Thyroid function tests are recommended every 6 months in patients with a history of thyroid dysfunction or as clinically indicated. 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 Rebif®. Due to its potential to cause neutropenia and lymphopenia, proper monitoring of patients is required if Rebif® is given in combination with myelosuppressive agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: No carcinogenicity data for Rebif® are available in animals or humans.
Mutagenesis: Rebif® was not mutagenic when tested in the Ames bacterial test and in an *in vitro* cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation.
Impairment of Fertility: No studies have been conducted to evaluate the effects of Rebif® on fertility in humans. In studies in normally cycling female cynomolgus monkeys given daily sc injections of Rebif® for six months at doses of up to 9 times the recommended weekly human dose (based on body surface area), no effects were observed on either menstrual cycling or serum estradiol levels. The validity of extrapolating doses used in animal studies to human doses is not established. In male monkeys, the same doses of Rebif® had no demonstrable adverse effects on sperm count, motility, morphology, or function.

Pregnancy Category C
Rebif® treatment has been associated with significant increases in embryolethal or abortifacient effects in cynomolgus monkeys administered doses approximately 2 times the cumulative weekly human dose (based on either body weight or surface area) either during the period of organogenesis (gestation day 21-89) or later in pregnancy. There were no fetal malformations or other evidence of teratogenesis noted in these studies. These effects are consistent with the abortifacient effects of other type I interferons. There are no adequate and well-controlled studies of Rebif® in pregnant women. However, in Studies 1 and 2, there were 2 spontaneous abortions observed and 5 fetuses carried to term among 7 women in the Rebif® groups. If a woman becomes pregnant or plans to become pregnant while taking Rebif®, she should be informed about the potential hazards to the fetus, and discontinuation of Rebif® should be considered.
A pregnancy registry has been established to monitor pregnancy outcomes of women exposed to Rebif® while pregnant. Health care providers are encouraged to register patients on line at rebifpregnancyregistry.com or by calling MS LifeLines at 1-877-44-REBIF (1-877-447-3243).

Nursing Mothers
It is not known whether Rebif® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Rebif® is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Rebif® in pediatric patients have not been studied.

Geriatric Use: Clinical studies of Rebif® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The most frequently reported serious adverse reactions with Rebif® were psychiatric disorders including depression and suicidal ideation or attempt (see **WARNINGS**). The incidence of depression of any severity in the Rebif®-treated groups and placebo-treated group was approximately 25%. The most commonly reported adverse reactions were injection site disorders, influenza-like symptoms (headache, fatigue, fever, rigors, chest pain, back pain, myalgia), abdom-

Table 2: Clinical and MRI Results from Study 2

	Rebif®	Avonex®	Absolute Difference	Risk of relapse on Rebif® relative to Avonex®
Relapses	N=339	N=338		
Proportion of patients relapse-free at 24 weeks[1]	75%*	63%	12% (95% CI: 5%, 19%)	0.68 (95% CI: 0.54, 0.86)
Proportion of patients relapse-free at 48 weeks	62%**	52%	10% (95% CI: 2%, 17%)	0.81 (95% CI: 0.68, 0.96)
MRI (through 24 weeks)	N=325	N=325		
Median of the mean number of combined unique MRI lesions per patient per scan[2] (25th, 75th percentiles)	0.17* (0.00, 0.67)	0.33 (0.00, 1.25)		

* $p < 0.001$, and ** $p = 0.009$, Rebif® compared to Avonex®
(1) Logistic regression model adjusted for treatment and center, intent to treat analysis
(2) Nonparametric ANCOVA model adjusted for treatment center, with baseline combined unique lesions as the single covariate.

Table 3. Adverse Reactions and Laboratory Abnormalities in Study 1

Body System Preferred Term	Placebo tiw (n=187)	Rebif® 22 mcg tiw (n=189)	Rebif® 44 mcg tiw (n=184)
BODY AS A WHOLE			
Influenza-like symptoms	51%	56%	59%
Headache	63%	65%	70%
Fatigue	36%	33%	41%
Fever	16%	25%	28%
Rigors	5%	6%	13%
Chest Pain	5%	6%	8%
Malaise	1%	4%	5%
INJECTION SITE DISORDERS			
Injection Site Reaction	39%	89%	92%
Injection Site Necrosis	0%	1%	3%
CENTRAL & PERIPH NERVOUS SYSTEM DISORDERS			
Hypertonia	5%	7%	6%
Coordination Abnormal	2%	5%	4%
Convulsions	2%	5%	4%
ENDOCRINE DISORDERS			
Thyroid Disorder	3%	4%	6%
GASTROINTESTINAL SYSTEM DISORDERS			
Abdominal Pain	17%	22%	20%
Dry Mouth	1%	1%	5%
LIVER AND BILIARY SYSTEM DISORDERS			
SGPT Increased	4%	20%	27%
SGOT Increased	4%	10%	17%
Hepatic Function Abnormal	2%	4%	9%
Bilirubinaemia	1%	3%	2%
MUSCULO-SKELETAL SYSTEM DISORDERS			
Myalgia	20%	25%	25%
Back Pain	20%	23%	25%
Skeletal Pain	10%	15%	10%
HEMATOLOGIC DISORDERS			
Leukopenia	14%	28%	36%
Lymphadenopathy	8%	11%	12%
Thrombocytopenia	2%	2%	8%
Anemia	3%	3%	5%
PSYCHIATRIC DISORDERS			
Somnolence	1%	4%	5%
SKIN DISORDERS			
Rash Erythematous	3%	7%	5%
Rash Maculo-Papular	2%	5%	4%
URINARY SYSTEM DISORDERS			
Micturition Frequency	4%	2%	7%
Urinary Incontinence	2%	4%	2%
VISION DISORDERS			
Vision Abnormal	7%	7%	13%
Xerophthalmia	0%	3%	1%

inal pain, depression, elevation of liver enzymes and hematologic abnormalities. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Rebif®, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were injection site disorders, influenza-like symptoms, depression and elevation of liver enzymes (see **WARNINGS**).

In Study 1, 6 patients randomized to Rebif® 44 mcg tiw (3%), and 2 patients who received Rebif® 22 mcg tiw (1%) developed injection site necrosis during two years of therapy. Rebif® was continued in 4 patients and interrupted briefly in one patient. There was one report of injection site necrosis in Study 2 during 48 weeks of Rebif treatment. All events resolved with conservative management; none required skin debridement or grafting.

The rates of adverse reactions and association with Rebif® in patients with relapsing-remitting multiple sclerosis are drawn from the placebo-controlled study, (n = 560) and the active comparator-controlled study (n = 339).

The population encompassed an age range from 18 to 55 years. Nearly three-fourths of the patients were female, and more than 90% were Caucasian, largely reflecting the general demographics of the population of patients with multiple sclerosis.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Rebif® cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

Table 3 enumerates adverse events and laboratory abnormalities that occurred at an incidence that was at least 2% more in either Rebif®-treated group than was observed in the placebo group.

[See table 3 on previous page]

The adverse reactions were generally similar in Studies 1 and 2, taking into account the disparity in study durations.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. In study 1, the presence of neutralizing antibodies (NAb) to Rebif® was determined by collecting and analyzing serum pre-study, and at 6 month time intervals during the 2 years of the clinical trial. Serum NAb were detected in 59/189 (31%) and 45/184 (24%) of Rebif®-treated patients at the 22 mcg and 44 mcg tiw doses, respectively, at one or more times during the study. The clinical significance of the presence of NAb to Rebif® is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to Rebif® using a antiviral cytopathic effect assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of NAb positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Rebif® with the incidence of antibodies to other products may be misleading.

Anaphylaxis and other allergic reactions have been observed with the use of Rebif® (see **WARNINGS: Anaphylaxis**).

DRUG ABUSE AND DEPENDENCE

There is no evidence that abuse or dependence occurs with Rebif® therapy. However, the risk of dependence has not been systematically evaluated.

OVERDOSAGE

Safety of doses higher than 44 mcg sc tiw has not been adequately evaluated. The maximum amount of Rebif® that can be safely administered has not been determined.

DOSAGE AND ADMINISTRATION

Dosages of Rebif® shown to be safe and effective are 22 mcg and 44 mcg injected subcutaneously three times per week. Rebif® should be administered, if possible, at the same time (preferably in the late afternoon or evening) on the same three days (e.g., Monday, Wednesday, and Friday) at least 48 hours apart each week (see **CLINICAL STUDIES**). Generally, patients should be started at 20% of the prescribed dose tiw and increased over a 4-week period to the targeted dose, either 22 mcg or 44 mcg tiw (see **Table 4**). Following the administration of each dose, any residual product remaining in the syringe should be discarded in a safe and proper manner.

Table 4: Schedule for Patient Titration

	Recommended Titration (% of final dose)	Titration dose for Rebif® 22 mcg	Titration dose for Rebif® 44 mcg	Injection Volume
Weeks 1-2	20 %	4.4 mcg	8.8 mcg	0.1 mL
Weeks 3-4	50 %	11 mcg	22 mcg	0.25 mL
Weeks 5+	100 %	22 mcg	44 mcg	0.5 mL

Leukopenia or elevated liver function tests may necessitate dose reductions of 20-50% until toxicity is resolved (see **WARNINGS: Hepatic Injury; PRECAUTIONS: General**).

Rebif® is intended for use under the guidance and supervision of a physician. It is recommended that physicians or qualified medical personnel train patients in the proper technique for self-administering subcutaneous injections using the pre-filled syringe. Patients should be advised to rotate sites for sc injections (see **PRECAUTIONS: Information for Patients**). Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days. Rebif® should be inspected visually for particulate matter and discoloration prior to administration.

Stability and Storage

Rebif® should be stored refrigerated between 2-8°C (36-46°F). DO NOT FREEZE. If a refrigerator is not available, Rebif® may be stored at or below 25°C/77°F for up to 30 days and away from heat and light.

Do not use beyond the expiration date printed on packages. Rebif® contains no preservatives. Each syringe is intended for single use. Unused portions should be discarded.

HOW SUPPLIED

Rebif® is supplied as a sterile, preservative-free solution packaged in graduated, ready to use 0.5 mL pre-filled syringes with 27-gauge, 0.5 inch needle for subcutaneous injection. The following package presentations are available.

Rebif® (interferon beta -1a) 22 mcg Pre-filled syringe

— One Rebif® 22 mcg pre-filled syringe, NDC 44087-0022-1
— Twelve Rebif® 22 mcg pre-filled syringes, NDC 44087-0022-3

Rebif® (interferon beta -1a) 44 mcg Pre-filled syringe

— One Rebif® 44 mcg pre-filled syringe, NDC 44087-0044-1
— Twelve Rebif® 44 mcg pre-filled syringes, NDC 44087-0044-3

Rx only.

REFERENCES

1. PRISMS Study Group. Randomized double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. Lancet 1998; 352: 1498-1504.
2. Data on file.

Manufacturer: Serono, Inc. Rockland, MA 02370
U.S. License # 1574
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Rockland, MA 02370
Pfizer Inc.
New York, NY 10017
Revised: March 2004

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RELPAX® R

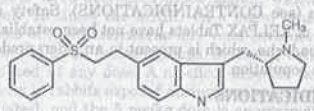
[rĕl-păks]

(eletriptan hydrobromide)

Tablets

DESCRIPTION

RELPAX® (eletriptan) Tablets contain eletriptan hydrobromide, which is a selective 5-hydroxytryptamine 1B/1D (5-HT1B/1D) receptor agonist. Eletriptan is chemically designated as (R)-3-[(1-Methyl-2-pyrrolidinyl) methyl]-5-[2-(phenylsulfonyl)ethyl]-1H-indole, monohydrobromide, and it has the following chemical structure:



The empirical formula is $C_{22}H_{26}N_2O_2S \cdot HBr$, representing a molecular weight of 463.40. Eletriptan hydrobromide is a white to light pale colored powder that is readily soluble in water.

Each RELPAX Tablet for oral administration contains 24.2 or 48.5 mg of eletriptan hydrobromide equivalent to 20 mg or 40 mg of eletriptan, respectively. Each tablet also contains the inactive ingredients microcrystalline cellulose NF, lactose NF, croscarmellose sodium NF, magnesium stearate NF, titanium dioxide USP, hypromellose, triacetin USP and FD&C Yellow No. 6 aluminum lake.

CLINICAL PHARMACOLOGY

Mechanism of Action: Eletriptan binds with high affinity to $5\text{-}HT_{1B}$, $5\text{-}HT_{1D}$ and $5\text{-}HT_{1F}$ receptors, has modest affinity for $5\text{-}HT_{1A}$, $5\text{-}HT_{1E}$, $5\text{-}HT_{2B}$ and $5\text{-}HT_7$ receptors, and little or no affinity for $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, $5\text{-}HT_3$, $5\text{-}HT_4$, $5\text{-}HT_{5A}$ and $5\text{-}HT_6$ receptors. Eletriptan has no significant affinity or pharmacological activity at adrenergic alpha$_1$, alpha$_2$, or beta; dopaminergic D_1 or D_2; muscarinic; or opioid receptors.

Two theories have been proposed to explain the efficacy of 5-HT receptor agonists in migraine. One theory suggests that activation of $5\text{-}HT_1$ receptors located on intracranial blood vessels, including those on the arteriovenous anastomoses, leads to vasoconstriction, which is correlated with the relief of migraine headache. The other hypothesis suggests that activation of $5\text{-}HT_1$ receptors on sensory nerve endings in the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release.

In the anesthetized dog, eletriptan has been shown to reduce carotid arterial blood flow, with only a small increase in arterial blood pressure at high doses. While the effect on blood flow was selective for the carotid arterial bed, decreases in coronary artery diameter were observed. Eletriptan has also been shown to inhibit trigeminal nerve activity in the rat.

Pharmacokinetics:

Absorption: Eletriptan is well absorbed after oral administration with peak plasma levels occurring approximately 1.5 hours after dosing to healthy subjects. In patients with moderate to severe migraine the median T_{max} is 2.0 hours. The mean absolute bioavailability of eletriptan is approximately 50%. The oral pharmacokinetics are slightly more than dose proportional over the clinical dose range. The AUC and C_{max} of eletriptan are increased by approximately 20 to 30% following oral administration with a high fat meal.

Distribution: The volume of distribution of eletriptan following IV administration is 138L. Plasma protein binding is moderate and approximately 85%.

Metabolism: The N-demethylated metabolite of eletriptan is the only known active metabolite. This metabolite causes vasoconstriction similar to eletriptan in animal models. Though the half-life of the metabolite is estimated to be about 13 hours, the plasma concentration of the N-demethylated metabolite is 10-20% of parent drug and is unlikely to contribute significantly to the overall effect of the parent compound.

In vitro studies indicate that eletriptan is primarily metabolized by cytochrome P-450 enzyme CYP3A4 (see WARNINGS, DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY: Drug Interactions).

Elimination: The terminal elimination half-life of eletriptan is approximately 4 hours. Mean renal clearance (CL_R) following oral administration is approximately 3.9 L/h. Non-renal clearance accounts for about 90% of the total clearance.

Special Populations:

Age: The pharmacokinetics of eletriptan are generally unaffected by age.

Eletriptan has been given to only 50 patients over the age of 65. Blood pressure was increased to a greater extent in elderly subjects than in young subjects. The pharmacokinetic disposition of eletriptan in the elderly is similar to that seen in younger adults (see PRECAUTIONS).

There is a statistically significant increased half-life (from about 4.4 hours to 5.7 hours) between elderly (65 to 93 years of age) and younger adult subjects (18 to 45 years of age) (see PRECAUTIONS).

Gender: The pharmacokinetics of eletriptan are unaffected by gender.

Race: A comparison of pharmacokinetic studies run in western countries with those run in Japan have indicated an approximate 35% reduction in the exposure of eletriptan in Japanese male volunteers compared to western males. Population pharmacokinetic analysis of two clinical studies indicates no evidence of pharmacokinetic differences between Caucasians and non Caucasian patients.

Menstrual Cycle: In a study of 16 healthy females, the pharmacokinetics of eletriptan remained consistent throughout the phases of the menstrual cycle.

Renal Impairment: There was no significant change in clearance observed in subjects with mild, moderate or severe renal impairment, though blood pressure elevations were observed in this population (see WARNINGS).

Hepatic Impairment: The effects of severe hepatic impairment on eletriptan metabolism have not been evaluated. Subjects with mild or moderate hepatic impairment demonstrated an increase in both AUC (34%) and half-life. The C_{max} was increased by 18% (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Drug Interactions:

CYP3A4 inhibitors: *In vitro* studies have shown that eletriptan is metabolized by the CYP3A4 enzyme. A clinical study demonstrated about a 3-fold increase in C_{max} and about a 6-fold increase in the AUC of eletriptan when combined with ketoconazole. The half-life increased from 5 hours to 8 hours and the T_{max} increased from 2.8 hours to 5.4 hours. Another clinical study demonstrated about a 2-fold increase in C_{max} and about a 4-fold increase in AUC when erythromycin was co-administered with eletriptan. It has also been shown that co-administration of verapamil and eletriptan yields about a 2-fold increase in C_{max} and about a 3-fold increase in AUC of eletriptan, and that co-administration of fluconazole and eletriptan yields about a 1.4-fold increase in C_{max} and about a 2-fold increase in AUC of eletriptan.

Eletriptan should not be used within at least 72 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir and nelfinavir. Eletriptan should not be used within 72 hours with drugs that have demonstrated potent CYP3A4 inhibition and have this potent effect described in the CONTRAINDICATIONS, WARNINGS or PRECAUTIONS sections of their labeling (see WARNINGS and DOSAGE AND ADMINISTRATION).

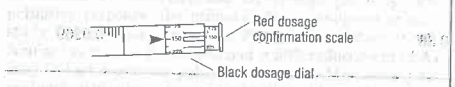
Propranolol: The C_{max} and AUC of eletriptan were increased by 10 and 33% respectively in the presence of propranolol. No interactive increases in blood pressure were observed. No dosage adjustment appears to be needed for patients taking propranolol (see PRECAUTIONS).

The effect of eletriptan on other drugs: The effect of eletriptan on enzymes other than cytochrome P-450 has not been investigated. *In vitro* human liver microsome studies

Continued on next page

- Keep the needle pointing upright and push in the injection button completely. Stop pushing after you hear the first click. A small amount of liquid should come out of the needle indicating that the Pen is ready for use. The amount of liquid seen at the needle tip is part of the extra medicine from the pen. If no liquid appears the first time, repeat these steps until liquid comes out of the needle tip.
- Replace the inner needle cap.

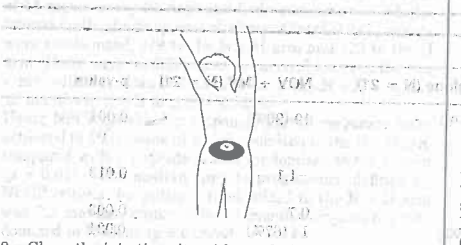
6. Select your prescribed dose by turning the dosage dial (black numbers) to the proper dose mark on the dial in front of the arrow mark. Carefully check the dosage dial before proceeding. Once you have set the dose correctly, load the Pen by pulling out the injection button as far as it will go.
7. Check the red dosage confirmation scale on the injection button to ensure the correct dose has been loaded and that the accurate dose will be injected. The loaded dose is shown by the last mark (flat arrow) on the red dosage confirmation scale that is fully visible.



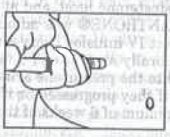
- If you accidentally pull out the injection button with an incorrect dose setting, do not inject. If the set dose is lower than the correct dose to be administered, you can turn the dosage dial to the correct dose and pull out the injection button again. If the set dose is higher than the dose to be administered, discard the dose by pushing all the liquid out into the safety container and repeat the previous steps for setting the dose.

Injecting the dose

Suitable injection sites on the stomach will be advised by your fertility specialist. Occasionally, your fertility specialist may suggest an alternative site.



8. Clean the injection site with an alcohol swab and allow it to air dry.
9. Remove the inner needle cap from the needle on the pen. Do not touch the needle or allow the needle to touch any surface.
10. To inject, insert the needle into the skin at a 90° angle and push the injection button—you will hear the button clicking. After the last click, stop applying pressure on the injection button. Allow the needle to remain in the skin for at least 5 seconds. This will ensure that you inject the full dose.



11. After the injection is complete, remove the needle out of your skin and apply pressure using a gauze pad.
12. Each time you finish an injection, remove and discard the used needle as follows. Hold the Gonal-f® RFF Pen firmly by the drug reservoir. Carefully replace the outer needle cap onto the needle. Gripping the outer needle cap firmly, remove the needle by unscrewing the pen counter-clockwise and dispose of the needle in your safety container.
13. Replace the pen cap and store properly. See "HOW SUPPLIED."

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Gonal-f® RFF Pen (follitropin alfa injection) is a disposable, prefilled multiple-dose delivery system containing a sterile, ready-to-use liquid formulation of follitropin alfa. Each Gonal-f® RFF Pen is filled with 415 IU, 568 IU, or 1026 IU follitropin alfa to deliver a minimum total of 300 IU in 0.5 mL, 450 IU in 0.75 mL, or 900 IU in 1.5 mL, respectively. Each Pen is supplied in a carton containing 29G × 1/2 inch disposable needles to be used for administration.

The following package combinations are available:

NDC 44087-1113-1 One Gonal-f® RFF Pen contains 415 IU to deliver a minimum total of 300 IU/0.5 mL and 5 single-use disposable 29G × ½" needles

NDC 44087-1112-1 One Gonal-f® RFF Pen contains 568 IU to deliver a minimum total of 450 IU/0.75 mL and 7 single-use disposable 29G × ½" needles

NDC 44087-1114-1 One Gonal-f® RFF Pen contains 1026 IU to deliver a minimum total of 900 IU/1.5 mL and 14 single-use disposable 29G × ½" needles

Store the Gonal-f® RFF Pen refrigerated (2°-8°C/36°-46°F) until dispensed. Upon dispensing, the patient may store the pen refrigerated (2°-8°C/36°-46°F) until the expiration date, or at room temperature (20°-25°C/68°-77°F) for up to one month or until the expiration date, whichever occurs first. After the first injection, the pen may be stored refrigerated (2°-8°C/36°-46°F) or at room temperature (20°-25°C/68°-77°F) for up to 28 days. Protect from light. Do not freeze. Discard unused material after 28 days.

Rx only

Manufactured for: SERONO, INC., Rockland, MA 02370 U.S.A.

Revised: May 2004

Shown in Product Identification Guide, page 333

GONAL-F® RFF

(follitropin alfa for injection)
***revised formulation female**
For subcutaneous injection

℞

DESCRIPTION

Gonal-f® RFF (follitropin alfa for injection) is a human follicle stimulating hormone (FSH) preparation of recombinant DNA origin, which consists of two non-covalently linked, non-identical glycoproteins designated as the α- and β-subunits. The α- and β-subunits have 92 and 111 amino acids, respectively, and their primary and tertiary structure are indistinguishable from those of human follicle stimulating hormone. Recombinant FSH production occurs in genetically modified Chinese Hamster Ovary (CHO) cells cultured in bioreactors. Purification by immunochromatography using an antibody specifically binding FSH results in a highly purified preparation with a consistent FSH isoform profile, and a high specific activity. The biological activity of follitropin alfa is determined by measuring the increase in ovary weight in female rats. The *in vivo* biological activity of follitropin alfa has been calibrated against the first International Standard for recombinant human follicle stimulating hormone established in 1995 by the Expert Committee on Biological Standards of the World Health Organization. Gonal-f® RFF contains no luteinizing hormone (LH) activity. Based on available data derived from physico-chemical tests and bioassays, follitropin alfa and follitropin beta, another recombinant follicle stimulating hormone product, are indistinguishable.

Gonal-f® RFF is a sterile, lyophilized powder intended for subcutaneous injection after reconstitution.

Each Gonal-f® RFF single-dose vial is filled with 82 IU (6 µg) follitropin alfa to deliver 75 IU (5.5 µg) and contains 30 mg sucrose, 1.11 mg dibasic sodium phosphate dihydrate, 0.45 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, and 0.05 mg polysorbate 20. Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment. Vials are reconstituted with Sterile Water for Injection, USP.

Under current storage conditions, Gonal-f® RFF may contain up to 10% of oxidized follitropin alfa.

Therapeutic Class: Infertility

HOW SUPPLIED

Gonal-f® RFF (follitropin alfa for injection) is supplied in a sterile, lyophilized form in single-dose vials containing 82 IU with diluent (Sterile Water for Injection, USP) in a pre-filled syringe. Following reconstitution with the diluent as described, upon administration each vial will deliver a dose of 75 IU.

Lyophilized vials may be stored refrigerated or at room temperature (2°-25°C/36°-77°F). Protect from light. Use immediately after reconstitution. Discard unused material. Sterile Water for Injection, USP is provided in a pre-filled syringe. Separate needles are provided for reconstitution (18 G) and administration (27 G).

Note: No antimicrobial or other substance has been added to the Sterile Water for Injection for the single-dose vials. Sterile Water for Injection is not suitable for intravascular injection without its first having been made approximately isotonic by the addition of a suitable solute.

The following package combinations are available:

1 vial Gonal-f® RFF 75 IU and 1 pre-filled syringe Sterile Water for Injection, USP, 1 mL, 1 reconstitution needle (18 gauge), 1 administration needle (27 gauge), NDC 44087-9005-1

10 vials Gonal-f® RFF 75 IU and 10 pre-filled syringes Sterile Water for Injection, USP, 1 mL, 10 reconstitution needles (18 gauge), 10 administration needles (27 gauge), NDC 44087-9005-6

Rx only

Manufactured for: SERONO, INC., Rockland, MA 02370 U.S.A.

Revised: May 2004

NOVANTRONE®

℞

[nō văn trōne]
(mitoxantrone)
for injection concentrate

WARNING

NOVANTRONE® (mitoxantrone for injection concentrate) should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapy agents.

NOVANTRONE® should be given slowly into a freely flowing intravenous infusion. It must never be given subcutaneously, intramuscularly, or intra-arterially. Severe local tissue damage may occur if there is extravasation during administration. (See **ADVERSE REACTIONS, General;** Cutaneous and **DOSAGE AND ADMINISTRATION, Preparation and Administration Precautions**).

NOT FOR INTRATHECAL USE. Severe injury with permanent sequelae can result from intrathecal administration. (See **WARNINGS, General**)

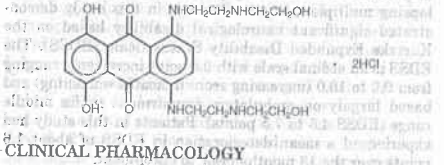
Except for the treatment of acute nonlymphocytic leukemia, NOVANTRONE® therapy generally should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving NOVANTRONE®.

Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with NOVANTRONE® or months to years after termination of therapy. Use of NOVANTRONE® has been associated with cardiotoxicity; this risk increases with cumulative dose. In cancer patients, the risk of symptomatic congestive heart failure (CHF) was estimated to be 2.6% for patients receiving up to a cumulative dose of 140 mg/m^2. For this reason, patients should be monitored for evidence of cardiac toxicity and questioned about symptoms of heart failure prior to initiation of treatment. Patients with multiple sclerosis who reach a cumulative dose of 100 mg/m^2 should be monitored for evidence of cardiac toxicity prior to each subsequent dose. Ordinarily, patients with multiple sclerosis should not receive a cumulative dose greater than 140 mg/m^2. Active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with NOVANTRONE® may occur at lower cumulative doses whether or not cardiac risk factors are present. For additional information, see **WARNINGS, Cardiac Effects,** and **DOSAGE AND ADMINISTRATION.**

Secondary acute myelogenous leukemia (AML) has been reported in cancer patients treated with anthracyclines. NOVANTRONE® is an anthracenedione, a related drug. Secondary AML has also been reported in cancer patients and multiple sclerosis patients who have been treated with NOVANTRONE®. The occurrence of refractory secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. The cumulative risk of developing treatment-related AML, in 1774 patients with breast cancer who received NOVANTRONE® concomitantly with other cytotoxic agents and radiotherapy, was estimated as 1.1% and 1.6% at 5 and 10 years, respectively (see **WARNINGS** section).

DESCRIPTION

NOVANTRONE® (mitoxantrone hydrochloride) is a synthetic antineoplastic anthracenedione for intravenous use. The molecular formula is $C_{22}H_{28}N_4O_6 \cdot 2HCl$ and the molecular weight is 517.41. It is supplied as a concentrate that MUST BE DILUTED PRIOR TO INJECTION. The concentrate is a sterile, nonpyrogenic, dark blue aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (0.80% w/v), sodium acetate (0.005% w/v), and acetic acid (0.046% w/v) as inactive ingredients. The solution has a pH of 3.0 to 4.5 and contains 0.14 mEq of sodium per mL. The product does not contain preservatives. The chemical name is 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl) amino] ethyl]amino]-9,10-anthracenedione dihydrochloride and the structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action: Mitoxantrone, a DNA-reactive agent that intercalates into deoxyribonucleic acid (DNA) through hydrogen bonding, causes crosslinks and strand breaks. Mitoxantrone also interferes with ribonucleic acid (RNA) and is a potent inhibitor of topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA. It has a cytocidal effect on both proliferating and non-proliferating cultured human cells, suggesting lack of cell cycle phase specificity.

Continued on next page

Novantrone—Cont.

NOVANTRONE® has been shown in vitro to inhibit B cell, T cell, and macrophage proliferation and impair antigen presentation, as well as the secretion of interferon gamma, TNFα, and IL-2.

Pharmacokinetics: Pharmacokinetics of mitoxantrone in patients following a single intravenous administration of NOVANTRONE® can be characterized by a three-compartment model. The mean alpha half-life of mitoxantrone is 6 to 12 minutes, the mean beta half-life is 1.1 to 3.1 hours and the mean gamma (terminal or elimination) half-life is 23 to 215 hours (median approximately 75 hours). Pharmacokinetic studies have not been performed in humans receiving multiple daily dosing. Distribution to tissues is extensive; steady-state volume of distribution exceeds 1,000 L/m^2. Tissue concentrations of mitoxantrone appear to exceed those in the blood during the terminal elimination phase. In the healthy monkey, distribution to brain, spinal cord, eye, and spinal fluid is low.

In patients administered 15–90 mg/m^2 of NOVANTRONE® intravenously, there is a linear relationship between dose and the area under the concentration-time curve (AUC).

Mitoxantrone is 78% bound to plasma proteins in the observed concentration range of 26–455 ng/mL. This binding is independent of concentration and is not affected by the presence of phenytoin, doxorubicin, methotrexate, prednisone, prednisolone, heparin, or aspirin.

Metabolism and Elimination: Mitoxantrone is excreted in urine and feces as either unchanged drug or as inactive metabolites. In human studies, 11% and 25% of the dose were recovered in urine and feces, respectively, as either parent drug or metabolite during the 5-day period following drug administration. Of the material recovered in urine, 65% was unchanged drug. The remaining 35% was composed of monocarboxylic and dicarboxylic acid derivatives and their glucuronide conjugates. The pathways leading to the metabolism of NOVANTRONE® have not been elucidated.

Special Populations:

Gender—The effect of gender on mitoxantrone pharmacokinetics is unknown.

Geriatric—In elderly patients with breast cancer, the systemic mitoxantrone clearance was 21.3 L/hr/m^2, compared with 28.3 L/hr/m^2 and 16.2 L/hr/m^2 for non-elderly patients with nasopharyngeal carcinoma and malignant lymphoma, respectively.

Pediatric—Mitoxantrone pharmacokinetics in the pediatric population are unknown.

Race—The effect of race on mitoxantrone pharmacokinetics is unknown.

Renal Impairment—Mitoxantrone pharmacokinetics in patients with renal impairment are unknown.

Hepatic Impairment—Mitoxantrone clearance is reduced by hepatic impairment. Patients with severe hepatic dysfunction (bilirubin >3.4 mg/dL) have an AUC more than three times greater than that of patients with normal hepatic function receiving the same dose. Patients with multiple sclerosis who have hepatic impairment should ordinarily not be treated with NOVANTRONE®. Other patients with hepatic impairment should be treated with caution and dosage adjustment may be required.

Drug Interactions: In vitro drug interaction studies have demonstrated that mitoxantrone did not inhibit CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 across a broad concentration range. The results of in vitro induction studies are inconclusive, but suggest that mitoxantrone may be a weak inducer of CYP450 2E1 activity.

Pharmacokinetic studies of the interaction of NOVANTRONE with concomitantly administered medications in humans have not been performed. The pathways leading to the metabolism of NOVANTRONE have not been elucidated. To date, post-marketing experience has not revealed any significant drug interactions in patients who have received NOVANTRONE for treatment of cancer. Information on drug interactions in patients with multiple sclerosis is limited.

CLINICAL TRIALS

Multiple Sclerosis: The safety and efficacy of NOVANTRONE® in multiple sclerosis were assessed in two randomized, multicenter clinical studies.

One randomized, controlled study (Study 1) was conducted in patients with secondary progressive or progressive relapsing multiple sclerosis. Patients in this study demonstrated significant neurological disability based on the Kurtzke Expanded Disability Status Scale (EDSS). The EDSS is an ordinal scale with 0.5 point increments ranging from 0.0 to 10.0 (increasing score indicates worsening) and based largely on ambulatory impairment in its middle range (EDSS 4.5 to 7.5 points). Patients in this study had experienced a mean deterioration in EDSS of about 1.6 points over the 18 months prior to enrollment.

Patients were randomized to receive placebo, 5 mg/m^2 NOVANTRONE®, or 12 mg/m^2 NOVANTRONE® administered IV every 3 months for 2 years. High-dose methylprednisolone was administered to treat relapses. The intent-to-treat analysis cohort consisted of 188 patients; 149 completed the 2-year study. Patients were evaluated every 3 months, and clinical outcome was determined after 24 months. In addition, a subset of patients was assessed with magnetic resonance imaging (MRI) at baseline, Month 12, and Month 24. Neurologic assessments and MRI reviews were performed by evaluators blinded to study drug and clinical outcome, although the diagnosis of relapse and the decision to treat relapses with steroids were made by unblinded treating physicians. A multivariate analysis of five clinical variables (EDSS, Ambulation Index [AI], number of relapses requiring treatment with steroids, months to first relapse needing treatment with steroids, and Standard Neurological Status [SNS]) was used to determine primary efficacy. The AI is an ordinal scale ranging from 0 to 9 in one point increments to define progressive ambulatory impairment. The SNS provides an overall measure of neurologic impairment and disability, with scores ranging from 0 (normal neurologic examination) to 99 (worst possible score).

Results of Study 1 are summarized in Table 1.

[See table 1 above]

A second randomized, controlled study (Study 2) evaluated NOVANTRONE® in combination with methylprednisolone (MP) and was conducted in patients with secondary progressive or worsening relapsing-remitting multiple sclerosis who had residual neurological deficit between relapses. All patients had experienced at least two relapses with sequelae or neurological deterioration within the previous 12 months. The average deterioration in EDSS was 2.2 points during the previous 12 months. During the screening period, patients were treated with two monthly doses of 1 g of IV MP and underwent monthly MRI scans. Only patients who developed at least one new Gd-enhancing MRI lesion during the 2-month screening period were eligible for randomization. A total of 42 evaluable patients received monthly treatments of 1 g of IV MP alone (n = 21) or ~12 mg/m^2 of IV NOVANTRONE® plus 1 g of IV MP (n = 21) (NOV + MP) for 6 months. Patients were evaluated monthly, and study outcome was determined after 6 months. The primary measure of effectiveness in this study was a comparison of the proportion of patients in each treatment group who developed no new Gd-enhancing MRI lesions at 6 months; these MRIs were assessed by a blinded panel. Additional outcomes were measured, including EDSS and number of relapses, but all clinical measures in this trial were assessed by an unblinded treating physician. Five patients, all in the MP alone arm, failed to complete the study due to lack of efficacy.

The results of this trial are displayed in Table 2.

[See table 2 above]

Advanced Hormone-Refractory Prostate Cancer: A multicenter Phase 2 trial of NOVANTRONE® and low-dose prednisone (N + P) was conducted in 27 symptomatic patients with hormone-refractory prostate cancer. Using NPCP (National Prostate Cancer Project) criteria for disease response, there was one partial responder and 12 patients with stable disease. However, nine patients or 33% achieved a palliative response defined on the basis of reduction in analgesic use or pain intensity.

These findings led to the initiation of a randomized multicenter trial (CCI-NOV22) comparing the effectiveness of (N + P) to low-dose prednisone alone (P). Eligible patients were required to have metastatic or locally advanced disease that had progressed on standard hormonal therapy, a castrate serum testosterone level, and at least mild pain at study entry. NOVANTRONE® was administered at a dose of 12 mg/m^2 by short IV infusion every 3 weeks. Prednisone was administered orally at a dose of 5 mg twice a day. Patients randomized to the prednisone arm were crossed over to the N + P arm if they progressed or if they were not improved after a minimum of 6 weeks of therapy with prednisone alone.

A total of 161 patients were randomized, 80 to the N + P arm and 81 to the P arm. The median NOVANTRONE® dose administered was 12 mg/m^2 per cycle. The median cumulative NOVANTRONE® dose administered was 73 mg/m^2 (range of 12 to 212 mg/m^2).

A primary palliative response (defined as a 2-point decrease in pain intensity in a 6-point pain scale, associated with stable analgesic use, and lasting a minimum of 6 weeks) was achieved in 29% of patients randomized to N + P compared to 12% of patients randomized to P alone (p = 0.011). Two responders left the study after meeting primary response criterion for two consecutive cycles. For the purposes of this analysis, these two patients were assigned a response duration of zero days. A secondary palliative response was defined as a 50% or greater decrease in analgesic use, associated with stable pain intensity, and lasting a minimum of 6 weeks. An overall palliative response (defined as primary plus secondary responses) was achieved in 38% of patients randomized to N + P compared to 21% of patients randomized to P (p = 0.025).

The median duration of primary palliative response for patients randomized to N + P was 7.6 months compared to 2.1 months for patients randomized to P alone (p = 0.0009). The median duration of overall palliative response for patients randomized to N + P was 5.6 months compared to 1.9 months for patients randomized to P alone (p = 0.0004).

Time to progression was defined as a 1-point increase in pain intensity, or a > 25% increase in analgesic use, or evidence of disease progression on radiographic studies, or requirement for radiotherapy. The median time to progression for all patients randomized to N + P was 4.4 months compared to 2.3 months for all patients randomized to P alone (p = 0.0001). Median time to death was 11.3 months for all patients on the N + P arm compared to 10.8 months for all patients on P alone (p = 0.2324).

Table 1: Efficacy Results at Month 24: Study 1

Primary Endpoints	Treatment Groups: Placebo (N = 64)	NOVANTRONE® 5 mg/m^2 (N = 64)	NOVANTRONE® 12 mg/m^2 (N = 60)	p-value: Placebo vs 12 mg/m^2 NOVANTRONE®
Primary efficacy multivariate analysis*		–	–	< 0.0001
Primary clinical variables analyzed:				
EDSS change** (mean)	0.23	−0.23	−0.13	0.0194
Ambulation index change** (mean)	0.77	0.41	0.30	0.0306
Mean number of relapses per patient requiring corticosteroid treatment (adjusted for discontinuation)	1.20	0.73	0.40	0.0002
Months to first relapse requiring corticosteroid treatment (median [1st quartile])	14.2 [6.7]	NR [6.9]	NR [20.4]	0.0004
Standard Neurological Status change** (mean)	0.77	−0.38	−1.07	0.0269
MRI†				
No. of patients with new Gd-enhancing lesions	5/32 (16%)	4/37 (11%)	0/31	0.022
Change in number of T2-weighted lesions; mean (n)**	1.94 (32)	0.68 (34)	0.29 (28)	0.027

NR = not reached within 24 months; MRI = magnetic resonance imaging.
* Wei-Lachin test.
** Month 24 value minus baseline.
† A subset of 110 patients was selected for MRI analysis.
MRI results were not available for all patients at all time points.

Table 2: Efficacy Results. Study 2

Primary Endpoint	MP alone (N = 21)	NOV + MP (N = 21)	p-value
Patients (%) without new Gd-enhancing lesions on MRIs (primary endpoint)*	5 (31%)	19 (90%)	0.001
Secondary Endpoints			
EDSS change (Month 6 minus baseline)* (mean)	−0.1	−1.1	0.013
Annualized relapse rate (mean per patient)	3.0	0.7	0.003
Patients (%) without relapses	7 (33%)	14 (67%)	0.031

MP = methylprednisolone; NOV + MP = NOVANTRONE® plus methylprednisolone.
* Results at Month 6, not including data for 5 withdrawals in the MP alone group.

Forty-eight patients on the P arm crossed over to receive N + P. Of these, thirty patients had progressed on P, while 18 had stable disease on P. The median cycle of crossover was 5 cycles (range of 2 to 16 cycles). Time trends for pain intensity prior to crossover were significantly worse for patients who crossed over than for those who remained on P alone (p = 0.012). Nine patients (19%) demonstrated a palliative response on N + P after crossover. The median time to death for patients who crossed over to N + P was 12.7 months.

The clinical significance of a fall in prostate-specific antigen (PSA) concentrations after chemotherapy is unclear. On the CCI-NOV22 trial, a PSA fall of 50% or greater for two consecutive follow-up assessments after baseline was reported in 33% of all patients randomized to the N + P arm and 9% of all patients randomized to the P arm. These findings should be interpreted with caution since PSA responses were not defined prospectively. A number of patients were inevaluable for response, and there was an imbalance between treatment arms in the numbers of evaluable patients. In addition, PSA reduction did not correlate precisely with palliative response, the primary efficacy endpoint of this study. For example, among the 26 evaluable patients randomized to the N + P arm who had ≥ 50% reduction in PSA, only 13 had a primary palliative response. Also, among 42 evaluable patients on this arm who did not have this reduction in PSA, 8 nonetheless had a primary palliative response.

Investigators at Cancer and Leukemia Group B (CALGB) conducted a Phase 3 comparative trial of NOVANTRONE® plus hydrocortisone (N + H) versus hydrocortisone alone (H) in patients with hormone-refractory prostate cancer (CALGB 9182). Eligible patients were required to have metastatic disease that had progressed despite at least one hormonal therapy. Progression at study entry was defined on the basis of progressive symptoms, increases in measurable or osseous disease, or rising PSA levels. NOVANTRONE® was administered intravenously at a dose of 14 mg/m^2 every 21 days and hydrocortisone was administered orally at a daily dose of 40 mg. A total of 242 subjects were randomized, 119 to the N + H arm and 123 to the H arm. There were no differences in survival between the two arms, with a median of 11.1 months in the N + H arm and 12 months in the H arm (p = 0.3298).

Using NPCP criteria for response, partial responses were achieved in 10 patients (8.4%) randomized to the N + H arm compared with 2 patients (1.6%) randomized to the H arm (p = 0.018). The median time to progression, defined by NPCP criteria, for patients randomized to the N + H arm was 7.3 months compared to 4.1 months for patients randomized to H alone (p = 0.0654).

Approximately 60% of patients on each arm required analgesics at baseline. Analgesic use was measured in this study using a 5-point scale. The best percent change from baseline in mean analgesic use was -17% for 61 patients with available data on the N + H arm, compared with +17% for 61 patients on H alone (p = 0.014). A time trend analysis for analgesic use in individual patients also showed a trend favoring the N + H arm over H alone but was not statistically significant.

Pain intensity was measured using the Symptom Distress Scale (SDS) Pain Item 2 (a 5-point scale). The best percent change from baseline in mean pain intensity was -14% for 37 patients with available data on the N + H arm, compared with +8% for 38 patients on H alone (p = 0.057). A time trend analysis for pain intensity in individual patients showed no difference between treatment arms.

Acute Nonlymphocytic Leukemia: In two large randomized multicenter trials, remission induction therapy for acute nonlymphocytic leukemia (ANLL) with NOVANTRONE® 12 mg/m^2 daily for 3 days as a 10-minute intravenous infusion and cytarabine 100 mg/m^2 for 7 days given as a continuous 24-hour infusion was compared with daunorubicin 45 mg/m^2 daily by intravenous infusion for 3 days plus the same dose and schedule of cytarabine used with NOVANTRONE®. Patients who had an incomplete antileukemic response received a second induction course in which NOVANTRONE® or daunorubicin was administered for 2 days and cytarabine for 5 days using the same daily dosage schedule. Response rates and median survival information for both the U.S. and international multicenter trials are given in Table 3:

[See table 3 above]

In these studies, two consolidation courses were administered to complete responders on each arm. Consolidation therapy consisted of the same drug and daily dosage used for remission induction, but only 5 days of cytarabine and 2 days of NOVANTRONE® or daunorubicin were given. The first consolidation course was administered 6 weeks after the start of the final induction course if the patient achieved a complete remission. The second consolidation course was generally administered 4 weeks later. Full hematologic recovery was necessary for patients to receive consolidation therapy. For the U.S. trial, median granulocyte nadirs for patients receiving NOVANTRONE® + cytarabine for consolidation courses 1 and 2 were 10/mm^3 for both courses, and for those patients receiving daunorubicin + cytarabine nadirs were 170/mm^3 and 260/mm^3, respectively. Median platelet nadirs for patients who received NOVANTRONE® + cytarabine for consolidation courses 1 and 2 were 17,000/mm^3 and 14,000/mm^3, respectively, and were 33,000/mm^3 and 22,000/mm^3 in course 1 and 2 for those patients who received daunorubicin + cytarabine. The benefit of consolidation therapy in ANLL patients who achieve a complete remission remains controversial. However, in the only well-controlled prospective, randomized multicenter trials with NOVANTRONE® in ANLL, consolidation therapy was given to all patients who achieved a complete remission. During consolidation in the U.S. study, two myelosuppression-related deaths occurred on the NOVANTRONE® arm and one on the daunorubicin arm. However, in the international study there were eight deaths on the NOVANTRONE® arm during consolidation which were related to the myelosuppression and none on the daunorubicin arm where less myelosuppression occurred.

Table 3: Response Rates, Time to Response, and Survival in U.S. and International Trials

Trial	% Complete Response (CR)		Median Time to CR (days)		Survival (days)	
	NOV	DAUN	NOV	DAUN	NOV	DAUN
U.S.	63 (62/98)	53 (54/102)	35	42	312	237
International	50 (56/112)	51 (62/123)	36	42	192	230

NOV = NOVANTRONE® + cytarabine
DAUN = daunorubicin + cytarabine

INDICATIONS AND USAGE

NOVANTRONE® is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses). NOVANTRONE® is not indicated in the treatment of patients with primary progressive multiple sclerosis.

The clinical patterns of multiple sclerosis in the studies were characterized as follows: secondary progressive and progressive relapsing disease were characterized by gradual increasing disability with or without superimposed clinical relapses, and worsening relapsing-remitting disease was characterized by clinical relapses resulting in a step-wise worsening of disability.

NOVANTRONE® in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer.

NOVANTRONE® in combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults. This category includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias.

CONTRAINDICATIONS

NOVANTRONE® is contraindicated in patients who have demonstrated prior hypersensitivity to it.

WARNINGS

WHEN NOVANTRONE® IS USED IN HIGH DOSES (> 14 mg/m^2/d x 3 days) SUCH AS INDICATED FOR THE TREATMENT OF LEUKEMIA, SEVERE MYELOSUPPRESSION WILL OCCUR. THEREFORE, IT IS RECOMMENDED THAT NOVANTRONE® BE ADMINISTERED ONLY BY PHYSICIANS EXPERIENCED IN THE CHEMOTHERAPY OF THIS DISEASE. LABORATORY AND SUPPORTIVE SERVICES MUST BE AVAILABLE FOR HEMATOLOGIC AND CHEMISTRY MONITORING AND ADJUNCTIVE THERAPIES, INCLUDING ANTIBIOTICS. BLOOD AND BLOOD PRODUCTS MUST BE AVAILABLE TO SUPPORT PATIENTS DURING THE EXPECTED PERIOD OF MEDULLARY HYPOPLASIA AND SEVERE MYELOSUPPRESSION. PARTICULAR CARE SHOULD BE GIVEN TO ASSURING FULL HEMATOLOGIC RECOVERY BEFORE UNDERTAKING CONSOLIDATION THERAPY (IF THIS TREATMENT IS USED) AND PATIENTS SHOULD BE MONITORED CLOSELY DURING THIS PHASE. NOVANTRONE® ADMINISTERED AT ANY DOSE CAN CAUSE MYELOSUPPRESSION.

General: Patients with preexisting myelosuppression as the result of prior drug therapy should not receive NOVANTRONE® unless it is felt that the possible benefit from such treatment warrants the risk of further medullary suppression.

The safety of NOVANTRONE® (mitoxantrone for injection concentrate) in patients with hepatic insufficiency is not established (see **CLINICAL PHARMACOLOGY**).

Safety for use by routes other than intravenous administration has not been established.

NOVANTRONE® is not indicated for subcutaneous, intramuscular, or intra-arterial injection. There have been reports of local/regional neuropathy, some irreversible, following intra-arterial injection.

NOVANTRONE® must not be given by intrathecal injection. There have been reports of neuropathy and neurotoxicity, both central and peripheral, following intrathecal injection. These reports have included seizures leading to coma and severe neurologic sequelae, and paralysis with bowel and bladder dysfunction.

Topoisomerase II inhibitors, including NOVANTRONE®, have been associated with the development of acute leukemia and myelodysplasia.

Cardiac Effects: Because of the possible danger of cardiac effects in patients previously treated with daunorubicin or doxorubicin, the benefit-to-risk ratio of NOVANTRONE® therapy in such patients should be determined before starting therapy.

Functional cardiac changes including decreases in left ventricular ejection fraction (LVEF) and irreversible congestive heart failure can occur with NOVANTRONE®. Cardiac toxicity may be more common in patients with prior treatment with anthracyclines, prior mediastinal radiotherapy, or with preexisting cardiovascular disease. Such patients should have regular cardiac monitoring of LVEF from the initiation of therapy. Cancer patients who received cumulative doses of 140 mg/m^2 either alone or in combination with other chemotherapeutic agents had a cumulative 2.6% probability of clinical congestive heart failure. In comparative oncology trials, the overall cumulative probability rate of moderate or severe decreases in LVEF at this dose was 13%.

Multiple Sclerosis: Functional cardiac changes may occur in patients with multiple sclerosis treated with NOVANTRONE®. In one controlled trial (Study 1, see **CLINICAL TRIALS, Multiple Sclerosis**), two patients (2%) of 127 receiving NOVANTRONE®, one receiving a 5 mg/m^2 dose and the other receiving the 12 mg/m^2 dose, had LVEF values that decreased to below 50%. An additional patient receiving 12 mg/m^2, who did not have LVEF measured, had a decrease in another echocardiographic measurement of ventricular function (fractional shortening) that led to discontinuation from the trial (see **ADVERSE REACTIONS, Multiple Sclerosis**). There were no reports of congestive heart failure in either controlled trial.

Evaluation of LVEF (by echocardiogram or MUGA) is recommended prior to administration of the initial dose of NOVANTRONE®. Ordinarily, multiple sclerosis patients with a baseline LVEF of < 50% should not be treated with NOVANTRONE®. Subsequent LVEF evaluations are recommended if signs or symptoms of congestive heart failure develop, and prior to all doses administered to patients who have received a cumulative dose of ≥ 100 mg/m^2. NOVANTRONE® should not ordinarily be administered to multiple sclerosis patients who have received a cumulative lifetime dose of ≥ 140 mg/m^2, or those with either LVEF of < 50% or a clinically significant reduction in LVEF.

Leukemia: Acute congestive heart failure may occasionally occur in patients treated with NOVANTRONE® for ANLL. In first-line comparative trials of NOVANTRONE® + cytarabine vs daunorubicin + cytarabine in adult patients with previously untreated ANLL, therapy was associated with congestive heart failure in 6.5% of patients on each arm. A causal relationship between drug therapy and cardiac effects is difficult to establish in this setting since myocardial function is frequently depressed by the anemia, fever and infection, and hemorrhage that often accompany the underlying disease.

Hormone-Refractory Prostate Cancer: Functional cardiac changes such as decreases in LVEF and congestive heart failure may occur in patients with hormone-refractory prostate cancer treated with NOVANTRONE®. In a randomized comparative trial of NOVANTRONE® plus low-dose prednisone vs low-dose prednisone, 7 of 128 patients (5.5 %) treated with NOVANTRONE® had a cardiac event defined as any decrease in LVEF below the normal range, congestive heart failure (n = 3), or myocardial ischemia. Two patients had a prior history of cardiac disease. The total NOVANTRONE® dose administered to patients with cardiac effects ranged from > 48 to 212 mg/m^2.

Among 112 patients evaluable for safety on the NOVANTRONE® + hydrocortisone arm of the CALGB trial, 18 patients (19%) had a reduction in cardiac function, 5 patients (5%) had cardiac ischemia, and 2 patients (2%) experienced pulmonary edema. The range of total NOVANTRONE® doses administered to these patients is not available.

Pregnancy: NOVANTRONE® may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. Mitoxantrone is considered a potential human teratogen because of its mechanism of action and the developmental effects demonstrated by related agents. Treatment of pregnant rats during the organogenesis period of gestation was associated with fetal growth retardation at doses ≥ 0.1 mg/kg/day (0.01 times the recommended human dose on a mg/m^2 basis). When pregnant rabbits were treated during organogenesis, an increased incidence of premature delivery was observed at doses ≥ 0.1 mg/kg/day (0.01 times the recommended human dose on a mg/m^2 basis). No teratogenic effects were observed in these studies, but the maximum doses tested were well below the recommended human dose (0.02 and 0.05 times in rats and rabbits, respectively, on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Women with multiple sclerosis who are biologically capable of becoming pregnant should have a pregnancy test prior to each dose, and the results should be known prior to administration of the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to the fetus.

Secondary Leukemia: Secondary leukemia has been reported in cancer patients and multiple sclerosis patients

Continued on next page

Novantrone—Cont.

treated with NOVANTRONE®. The largest published report involved 1774 patients with breast cancer treated with NOVANTRONE® in combination with methotrexate with or without mitomycin. In this study, the cumulative probability of developing secondary leukemia was estimated to be 1.1% and 1.6% at 5 and 10 years, respectively. The second largest report involved 449 patients with breast cancer treated with NOVANTRONE®, usually in combination with radiotherapy and/or other cytotoxic agents. In this study, the cumulative probability of developing secondary leukemia was estimated to be 2.2% at 4 years.

There are insufficient long-term follow-up data to estimate the risk of leukemia or myelodysplasia in patients with multiple sclerosis treated with NOVANTRONE®.

PRECAUTIONS

General: Therapy with NOVANTRONE® should be accompanied by close and frequent monitoring of hematologic and chemical laboratory parameters, as well as frequent patient observation.

Systemic infections should be treated concomitantly with or just prior to commencing therapy with NOVANTRONE®.

Information for Patients: NOVANTRONE® may impart a blue-green color to the urine for 24 hours after administration, and patients should be advised to expect this during therapy. Bluish discoloration of the sclera may also occur. Patients should be advised of the signs and symptoms of myelosuppression.

Patients with multiple sclerosis should be provided with the Patient Package Insert at the time that the decision is made to treat with NOVANTRONE® and prior to and in close temporal proximity to each treatment. In addition, the physician should discuss the issues addressed in the Patient Package Insert with the patient.

Laboratory Tests: A complete blood count, including platelets, should be obtained prior to each course of NOVANTRONE® and in the event that signs and symptoms of infection develop. Liver function tests should also be performed prior to each course of therapy. NOVANTRONE® therapy in multiple sclerosis patients with abnormal liver function tests is not recommended because NOVANTRONE® clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments.

In leukemia treatment, hyperuricemia may occur as a result of rapid lysis of tumor cells by NOVANTRONE®. Serum uric acid levels should be monitored and hypouricemic therapy instituted prior to the initiation of antileukemic therapy.

Women with multiple sclerosis who are biologically capable of becoming pregnant, even if they are using birth control, should have a pregnancy test, and the results should be known, before receiving each dose of NOVANTRONE® (see **WARNINGS, Pregnancy**).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis--Intravenous treatment of rats and mice, once every 21 days for 24 months, with NOVANTRONE® resulted in an increased incidence of fibroma and external auditory canal tumors in rats at a dose of 0.03 mg/kg (0.02 fold the recommended human dose, on a mg/m^2 basis), and hepatocellular adenoma in male mice at a dose of 0.1 mg/kg (0.03 fold the recommended human dose, on a mg/m^2 basis). Intravenous treatment of rats, once every 21 days for 12 months with NOVANTRONE® resulted in an increased incidence of external auditory canal tumors in rats at a dose of 0.3 mg/kg (0.15 fold the recommended human dose, on a mg/m^2 basis).

Mutagenesis—NOVANTRONE® was clastogenic in the in vivo rat bone marrow assay. NOVANTRONE® was also clastogenic in two in vitro assays; it induced DNA damage in primary rat hepatocytes and sister chromatid exchanges in Chinese hamster ovary cells. NOVANTRONE® was mutagenic in bacterial and mammalian test systems (Ames/Salmonella and E. coli and L5178Y TK+/-mouse lymphoma).

Drug Interactions: Mitoxantrone and its metabolites are excreted in bile and urine, but it is not known whether the metabolic or excretory pathways are saturable, may be inhibited or induced, or if mitoxantrone and its metabolites undergo enterohepatic circulation. To date, post-marketing experience has not revealed any significant drug interactions in patients who have received NOVANTRONE® for treatment of cancer. Information on drug interactions in patients with multiple sclerosis is limited.

Following concurrent administration of NOVANTRONE® with corticosteroids, no evidence of drug interactions has been observed.

Special Populations:

Hepatic Impairment—Patients with multiple sclerosis who have hepatic impairment should ordinarily not be treated with NOVANTRONE®. NOVANTRONE® should be administered with caution to other patients with hepatic impairment. In patients with severe hepatic impairment, the AUC is more than three times greater than the value observed in patients with normal hepatic function.

Pregnancy: Pregnancy Category D (see **WARNINGS**).

Nursing Mothers: NOVANTRONE® is excreted in human milk and significant concentrations (13 ng/mL) have been reported for 28 days after the last administration. Because of the potential for serious adverse reactions in infants from NOVANTRONE®, breast feeding should be discontinued before starting treatment.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Multiple Sclerosis: Clinical studies of Novantrone did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Hormone-Refractory Prostate Cancer: One hundred forty-six patients aged 65 and over and 52 younger patients (<65 years) have been treated with Novantrone in controlled clinical studies. These studies did not include sufficient numbers of younger patients to determine whether they respond differently from older patients. However, greater sensitivity of some older individuals cannot be ruled out.

Acute Nonlymphocytic Leukemia: Although definitive studies with Novantrone have not been performed in geriatric patients with ANLL, toxicity may be more frequent in the elderly. Elderly patients are more likely to have age-related comorbidities due to disease or disease therapy.

ADVERSE REACTIONS

Multiple Sclerosis: NOVANTRONE® has been administered to 149 patients with multiple sclerosis in two randomized clinical trials, including 21 patients who received NOVANTRONE® in combination with corticosteroids.

In Study 1, the proportion of patients who discontinued treatment due to an adverse event was 9.7% (n = 6) in the 12 mg/m^2 NOVANTRONE® arm (leukopenia, depression, decreased LV function, bone pain and emesis, renal failure, and one discontinuation to prevent future complications from repeated urinary tract infections) compared to 3.1% (n = 2) in the placebo arm (hepatitis and myocardial infarction). The following clinical adverse experiences were significantly more frequent in the NOVANTRONE® groups: nausea, alopecia, urinary tract infection, and menstrual disorders, including amenorrhea.

Table 4a summarizes clinical adverse events of all intensities occurring in ≥ 5% of patients in either dose group of NOVANTRONE® and that were numerically greater on drug than on placebo in Study 1. The majority of these events were of mild to moderate intensity, and nausea was the only adverse event that occurred with severe intensity in more than one patient (three patients [5%] in the 12 mg/m^2 group). Of note, alopecia consisted of mild hair thinning.

Two of the 127 patients treated with NOVANTRONE® in Study 1 had decreased LVEF to below 50% at some point during the 2 years of treatment. An additional patient receiving 12 mg/m^2 did not have LVEF measured, but had an other echocardiographic measure of ventricular function (fractional shortening) that led to discontinuation from the study.

[See table 4a above]

The proportion of patients experiencing any infection during Study 1 was 67% for the placebo group, 85% for the 5 mg/m^2 group, and 81% for the 12 mg/m^2 group. However, few of these infections required hospitalization: one placebo patient (tonsillitis); three 5 mg/m^2 patients (enteritis, urinary tract infection, viral infection), and four 12 mg/m^2 patients (tonsillitis, urinary tract infection [two], endometritis).

Table 4b summarizes laboratory abnormalities that occurred in ≥ 5% of patients in either NOVANTRONE® dose group, and that were numerically more frequent than in the placebo group.

[See table 4b above]

There was no difference among treatment groups in the incidence or severity of hemorrhagic events.

In Study 2, NOVANTRONE® was administered once a month. Clinical adverse events most frequently reported in the NOVANTRONE® group included amenorrhea (53% of female patients), alopecia (33% of patients), nausea (29% of patients), and asthenia (24% of patients). Tables 5a and 5b respectively summarize adverse events and laboratory abnormalities occurring in > 5% of patients in the NOVANTRONE® group and numerically more frequent than in the control group.

Table 4a: Adverse Events of Any Intensity Occurring in ≥ 5% of Patients on Any Dose of NOVANTRONE® and That Were Numerically Greater Than in the Placebo Group Study 1

Preferred Term	Percent of Patients		
	Placebo (N = 64)	5 mg/m^2 NOVANTRONE® (N = 65)	12 mg/m^2 NOVANTRONE® (N = 62)
Nausea	20	55	76
Alopecia	31	38	61
Menstrual disorder	26	51	61
Amenorrhea*	3	28	43
Upper respiratory tract infection	52	51	53
Urinary tract infection	13	29	32
Stomatitis	8	15	19
Arrhythmia	8	6	18
Diarrhea	11	25	16
Urine abnormal	6	5	11
ECG abnormal	3	5	11
Constipation	6	14	10
Back pain	5	6	8
Sinusitis	2	3	6
Headache	5	6	6

* Percentage of female patients.

Table 4b: Laboratory Abnormalities Occurring in ≥ 5% of Patients* on Either Dose of NOVANTRONE® and That Were More Frequent Than in the Placebo Group Study 1

Event	Percent of Patients		
	Placebo (N = 64)	5 mg/m^2 NOVANTRONE® (N = 65)	12 mg/m^2 NOVANTRONE® (N = 62)
Leukopenia[a]	0	9	19
Gamma-GT increased	3	3	15
SGOT increased	8	9	8
Granulocytopenia[b]	2	6	6
Anemia	2	9	6
SGPT increased	3	6	5

* Assessed using World Health Organization (WHO) toxicity criteria.
a. < 4000 cells/mm^3
b. < 2000 cells/mm^3

Table 5a: Adverse Events of Any Intensity Occurring in > 5% of Patient* in the NOVANTRONE® Group and Numerically More Frequent Than in the Control Group Study 2

Event	Percent of Patients	
	MP (n = 21)	N + MP (n = 21)
Amenorrhea[a]	0	53
Alopecia	0	33
Nausea	0	29
Asthenia	0	24
Pharyngitis/throat infection	5	19
Gastraigia/stomach burn/epigastric pain	5	14
Aphthosis	0	10
Cutaneous mycosis	0	10
Rhinitis	0	10
Menorrhagia[a]	0	7

N = NOVANTRONE®, MP = methylprednisolone
* Assessed using National Cancer Institute (NCI) common toxicity criteria
a. Percentage of female patients.

Table 5b: Laboratory Abnormalities Occurring in > 5% of Patients* in the NOVANTRONE® Group and Numerically More Frequent Than in the Control Group Study 2

Event	Percent of Patients	
	MP (n = 21)	N + MP (n = 21)
WBC low[a]	14	100
ANC low[b]	10	100
Lymphocyte low	43	95
Hemoglobin low	48	43
Platelets low[c]	0	33

SGOT high	5	15
SGPT high	10	15
Glucose high	5	10
Potassium low	0	10

N = NOVANTRONE®, MP = methylprednisolone
[a] Assessed using National Cancer Institute (NCI) common toxicity criteria.
a. < 4000 cells/mm^3
b. < 1500 cells/mm^3
c. < 100,000 cells/mm^3

Leukopenia and neutropenia were reported in the N +MP group (see Table 5b). Neutropenia occurred within 3 weeks after NOVANTRONE® administration and was always reversible. Only mild to moderate intensity infections were reported in 9 of 21 patients in the N +MP group and in 3 of 21 patients in the MP group; none of these required hospitalization. There was no difference among treatment groups in the incidence or severity of hemorrhagic events. There were no withdrawals from Study 2 for safety reasons.

Leukemia: NOVANTRONE® has been studied in approximately 600 patients with ANLL. Table 6 represents the adverse reaction experience in the large U.S. comparative study of mitoxantrone + cytarabine vs daunorubicin + cytarabine. Experience in the large international study was similar. A much wider experience in a variety of other tumor types revealed no additional important reactions other than cardiomyopathy (see **WARNINGS**). It should be appreciated that the listed adverse reaction categories include overlapping clinical symptoms related to the same condition, e.g., dyspnea, cough and pneumonia. In addition, the listed adverse reactions cannot all necessarily be attributed to chemotherapy as it is often impossible to distinguish effects of the drug and effects of the underlying disease. It is clear, however, that the combination of NOVANTRONE® + cytarabine was responsible for nausea and vomiting, alopecia, mucositis/stomatitis, and myelosuppression.

Table 6 summarizes adverse reactions occurring in patients treated with NOVANTRONE® + cytarabine in comparison with those who received daunorubicin + cytarabine for therapy of ANLL in a large multicenter randomized prospective U.S. trial.

Adverse reactions are presented as major categories and selected examples of clinically significant subcategories

[See table 6 at right]

Hormone-Refractory Prostate Cancer: Detailed safety information is available for a total of 353 patients with hormone-refractory prostate cancer treated with NOVANTRONE®, including 274 patients who received NOVANTRONE® in combination with corticosteroids.

Table 7 summarizes adverse reactions of all grades occurring in ≥ 5% of patients in Trial CCI-NOV22.

Table 7: Adverse Events of Any Intensity Occurring in ≥ 5% of Patients Trial CCI-NOV22

Event	N + P (n = 80) %	P (n = 81) %
Nausea	61	35
Fatigue	39	14
Alopecia	29	0
Anorexia	25	6
Constipation	16	14
Dyspnea	11	5
Nail bed changes	11	0
Edema	10	4
Systemic infection	10	7
Mucositis	10	0
UTI	9	4
Emesis	9	5
Pain	8	9
Fever	6	3
Hemorrhage/bruise	6	1
Anemia	5	3
Cough	5	0
Decreased LVEF	5	0
Anxiety/depression	5	3
Dyspepsia	5	6
Skin infection	5	3
Blurred vision	3	5

N = NOVANTRONE®, P = prednisone

No nonhematologic adverse events of Grade 3/4 were seen in > 5% of patients.

Table 8 summarizes adverse events of all grades occurring in ≥ 5% of patients in Trial CALGB 9182.

[See table 8 at right]

General:

Allergic Reaction—Hypotension, urticaria, dyspnea, and rashes have been reported occasionally. Anaphylaxis/anaphylactoid reactions have been reported rarely.

Cutaneous—Extravasation at the infusion site has been reported, which may result in erythema, swelling, pain, burning, and/or blue discoloration of the skin. Extravasation can result in tissue necrosis with resultant need for debridement and skin grafting. Phlebitis has also been reported at the site of the infusion.

Hematologic—Topoisomerase II inhibitors, including NOVANTRONE®, in combination with other antineoplastic agents, have been associated with the development of acute leukemia (see **WARNINGS**).

Table 6: Adverse Events Occurring in ANLL Patients Receiving NAVANTRONE® or Daunorubicin

Event	Induction [% pts entering induction] NOV N = 102	Induction [% pts entering induction] DAUN N = 102	Consolidation [% pts entering induction] NOV N = 55	Consolidation [% pts entering induction] DAUN N = 49
Cardiovascular	26	28	11	24
CHF	5	6	0	0
Arrhythmias	3	3	4	4
Bleeding	37	41	20	6
GI	16	12	2	2
Petechiae/ecchymoses	7	9	11	2
Gastrointestinal	88	85	58	51
Nausea/vomiting	72	67	31	31
Diarrhea	47	47	18	8
Abdominal pain	15	9	9	4
Mucositis/stomatitis	29	33	18	8
Hepatic	10	11	14	2
Jaundice	3	8	7	0
Infections	66	73	60	43
UTI	7	2	7	2
Pneumonia	9	7	9	0
Sepsis	34	36	31	18
Fungal infections	15	13	9	6
Renal failure	8	6	0	2
Fever	78	71	24	18
Alopecia	37	40	22	16
Pulmonary	43	43	24	14
Cough	13	9	9	2
Dyspnea	18	20	6	0
CNS	30	30	34	35
Seizures	4	4	2	8
Headache	10	9	13	8
Eye	7	6	2	4
Conjunctivitis	5	1	0	0

NOV = NOVANTRONE®, DAUN = daunorubicin

Table 8. Adverse Events of Any Intensity Occurring in ≥ 5% of Patients, Trial CALGB 9182

Event	N + H (n = 112) %	H (n = 113) n	H (n = 113) %
Decreased WBC	96	87	4
Granulocytes/bands	88	79	3
Decreased hemoglobin	83	75	42
Lymphocytes	78	72	27
Pain	45	41	44
Platelets	43	39	8
Alkaline Phosphatase	41	37	42
Malaise/fatigue	37	34	16
Hyperglycemia	33	31	32
Edema	31	30	15
Nausea	28	26	9
Anorexia	24	22	16
BUN	24	22	22
Transaminase	22	20	16
Alopecia	20	20	1
Cardiac function	19	18	0
Infection	18	17	4
Weight loss	18	17	13
Dyspnea	16	15	9
Diarrhea	16	14	4
Fever in absence of infection	15	14	7
Weight gain	15	14	16
Creatinine	14	13	11
Other gastrointestinal	13	14	11
Vomiting	12	11	6
Other neurologic	11	11	5
Hypocalcemia	10	10	5
Hematuria	9	11	5
Hyponatremia	9	9	3
Sweats	9	9	2
Other liver	8	8	8
Stomatitis	8	8	1
Cardiac dysrhythmia	7	7	3
Hypokalemia	7	7	4
Neuro/constipation	7	7	2
Neuro/motor	7	7	3
Neuro/mood	6	6	2
Skin	6	6	4
Cardiac ischemia	6	5	1
Chills	5	5	0
Hemorrhage	5	5	3
Myalgias/arthralgias	5	5	3
Other kidney/bladder	5	5	3
Other endocrine	5	6	3
Other pulmonary	5	5	3
Hypertension	4	4	5
Impotence/libido	4	7	3
Proteinuria	4	6	3
Sterility	3	5	3

N= NOVANTRONE®, H = hydrocortisone

Leukemia—Myelosuppression is rapid in onset and is consistent with the requirement to produce significant marrow hypoplasia in order to achieve a response in acute leukemia. The incidences of infection and bleeding seen in the U.S. trial are consistent with those reported for other standard induction regimens.

Hormone-Refractory Prostate Cancer—In a randomized study where dose escalation was required for neutrophil counts greater than 1000/mm^3, Grade 4 neutropenia (ANC <500 /mm^3) was observed in 54% of patients treated with

Continued on next page

Novantrone—Cont.

NOVANTRONE® + low-dose prednisone. In a separate randomized trial where patients were treated with 14 mg/m^2, Grade 4 neutropenia in 23% of patients treated with NOVANTRONE® + hydrocortisone was observed. Neutropenic fever/infection occurred in 11% and 10% of patients receiving NOVANTRONE® + corticosteroids, respectively, on the two trials. Platelets < 50,000/mm^3 were noted in 4% and 3% of patients receiving NOVANTRONE® + corticosteroids on these trials, and there was one patient death on NOVANTRONE® + hydrocortisone due to intracranial hemorrhage after a fall.

Gastrointestinal—Nausea and vomiting occurred acutely in most patients and may have contributed to reports of dehydration, but were generally mild to moderate and could be controlled through the use of antiemetics. Stomatitis/mucositis occurred within 1 week of therapy.

Cardiovascular—Congestive heart failure, tachycardia, EKG changes including arrhythmias, chest pain, and asymptomatic decreases in left ventricular ejection fraction have occurred. (See **WARNINGS**)

Pulmonary—Interstitial pneumonitis has been reported in cancer patients receiving combination chemotherapy that included NOVANTRONE®.

OVERDOSAGE

There is no known specific antidote for NOVANTRONE®. Accidental overdoses have been reported. Four patients receiving 140–180 mg/m^2 as a single bolus injection died as a result of severe leukopenia with infection. Hematologic support and antimicrobial therapy may be required during prolonged periods of severe myelosuppression.

Although patients with severe renal failure have not been studied, NOVANTRONE® is extensively tissue bound and it is unlikely that the therapeutic effect or toxicity would be mitigated by peritoneal or hemodialysis.

DOSAGE AND ADMINISTRATION

(SEE ALSO **WARNINGS**)

Multiple Sclerosis: The recommended dosage of NOVANTRONE® is 12 mg/m^2 given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months.

Evaluation of LVEF (by echocardiogram or MUGA) is recommended prior to administration of the initial dose of NOVANTRONE®. Subsequent LVEF evaluations are recommended if signs or symptoms of congestive heart failure develop, and prior to all doses administered to patients who have received a cumulative dose of ≥ 100 mg/m^2. NOVANTRONE® should not ordinarily be administered to multiple sclerosis patients who have received a cumulative lifetime dose of ≥ 140 mg/m^2, or those with either LVEF of < 50% or a clinically-significant reduction in LVEF.

Complete blood counts, including platelets, should be monitored prior to each course of NOVANTRONE® and in the event that signs or symptoms of infection develop. NOVANTRONE® generally should not be administered to multiple sclerosis patients with neutrophil counts less than 1500 cells/mm^3. Liver function tests should also be monitored prior to each course. NOVANTRONE® therapy in multiple sclerosis patients with abnormal liver function tests is not recommended because NOVANTRONE® clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments.

Women with multiple sclerosis who are biologically capable of becoming pregnant, even if they are using birth control, should have a pregnancy test, and the results should be known, before receiving each dose of NOVANTRONE® (see **WARNINGS, Pregnancy**).

Hormone-Refractory Prostate Cancer: Based on data from two Phase 3 comparative trials of NOVANTRONE® plus corticosteroids versus corticosteroids alone, the recommended dosage of NOVANTRONE® is 12 to 14 mg/m^2 given as a short intravenous infusion every 21 days.

Combination Initial Therapy for ANLL in Adults: For induction, the recommended dosage is 12 mg/m^2 of NOVANTRONE® daily on Days 1–3 given as an intravenous infusion, and 100 mg/m^2 of cytarabine for 7 days given as a continuous 24 hour infusion on Days 1–7.

Most complete remissions will occur following the initial course of induction therapy. In the event of an incomplete antileukemic response, a second induction course may be given. NOVANTRONE® should be given for 2 days and cytarabine for 5 days using the same daily dosage levels.

If severe or life-threatening nonhematologic toxicity is observed during the first induction course, the second induction course should be withheld until toxicity resolves.

Consolidation therapy which was used in two large randomized multicenter trials consisted of NOVANTRONE®, 12 mg/m^2 given by intravenous infusion daily on Days 1 and 2 and cytarabine, 100 mg/m^2 for 5 days given as a continuous 24-hour infusion on Days 1–5. The first course was given approximately 6 weeks after the final induction course, the second was generally administered 4 weeks after the first. Severe myelosuppression occurred. (See **CLINICAL PHARMACOLOGY**)

Hepatic Impairment: For patients with hepatic impairment, there is at present no laboratory measurement that allows for dose adjustment recommendations. (See **CLINICAL PHARMACOLOGY, Special Populations**, Hepatic Impairment)

Preparation and Administration Precautions

NOVANTRONE® CONCENTRATE MUST BE DILUTED PRIOR TO USE.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The dose of NOVANTRONE® should be diluted to at least 50 mL with either 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP). NOVANTRONE® may be further diluted into Dextrose 5% in Water, Normal Saline or Dextrose 5% with Normal Saline and used immediately. DO NOT FREEZE.

NOVANTRONE® should not be mixed in the same infusion as heparin since a precipitate may form. Because specific compatibility data are not available, it is recommended that NOVANTRONE® not be mixed in the same infusion with other drugs. The diluted solution should be introduced slowly into the tubing as a freely running intravenous infusion of 0.9% Sodium Chloride Injection (USP) or 5% Dextrose Injection (USP) over a period of not less than 3 minutes. Unused infusion solutions should be discarded immediately in an appropriate fashion. In the case of multidose use, after penetration of the stopper, the remaining portion of the undiluted NOVANTRONE® concentrate should be stored not longer than 7 days between 15°–25°C (59°–77°F) or 14 days under refrigeration. DO NOT FREEZE. CONTAINS NO PRESERVATIVE.

Care in the administration of NOVANTRONE® will reduce the chance of extravasation. NOVANTRONE® should be administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP (0.9%) or 5% Dextrose Injection, USP. The tubing should be attached to a Butterfly needle or other suitable device and inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. Care should be taken to avoid extravasation at the infusion site and to avoid contact of NOVANTRONE® with the skin, mucous membranes, or eyes. NOVANTRONE® SHOULD NOT BE ADMINISTERED SUBCUTANEOUSLY. If any signs or symptoms of extravasation have occurred, including burning, pain, pruritis, erythema, swelling, blue discoloration, or ulceration, the injection or infusion should be immediately terminated and restarted in another vein. During intravenous administration of NOVANTRONE® extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If it is known or suspected that subcutaneous extravasation has occurred, it is recommended that intermittent ice packs be placed over the area of extravasation and that the affected extremity be elevated. Because of the progressive nature of extravasation reactions, the area of injection should be frequently examined and surgery consultation obtained early if there is any sign of a local reaction.

Skin accidentally exposed to NOVANTRONE® should be rinsed copiously with warm water and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA 1985;253:1590.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia 1983;1:426.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center, CA Cancer J Clin 1983;33:258.
6. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm 1990;47:1033.
7. Controlling occupational exposure to hazardous drugs. Am J Health-SystemPharm 1996;53:1669.

HOW SUPPLIED

NOVANTRONE® (mitoxantrone for injection concentrate) is a sterile aqueous solution containing mitoxantrone hydrochloride at a concentration equivalent to 2 mg mitoxantrone free base per mL supplied in vials for multidose use as follows:

NDC 44087-1520-1—10 mL/multidose vial (20 mg)
NDC 44087-1525-1—12.5 mL/multidose vial (25 mg)
NDC 44087-1530-1—15 mL/multidose vial (30 mg)

NOVANTRONE® (mitoxantrone for injection concentrate) should be stored between 15°–25°C (59°–77°F). DO NOT FREEZE.

Issue Date 4/2003

Manufactured for: Serono Inc. Rockland, MA 02370, USA

CI 7833-2

Marketed by:
Serono, Inc.
For Multiple Sclerosis*

Marketed by:
(osi)™ oncology
For Oncology*

*See Indications

(osi) oncology is a trademark of OSI Pharmaceuticals Inc., Melville, NY 11747, USA

OVIDREL® PreFilled Syringe

[ō-vī-drĕl]

(choriogonadotropin alfa injection)

FOR SUBCUTANEOUS USE

DESCRIPTION

Ovidrel® PreFilled Syringe (choriogonadotropin alfa injection) is a sterile liquid preparation of choriogonadotropin alfa (recombinant human Chorionic Gonadotropin, r-hCG). Choriogonadotropin alfa is a water soluble glycoprotein consisting of two non-covalently linked subunits - designated α and β - consisting of 92 and 145 amino acid residues, respectively, with carbohydrate moieties linked to ASN-52 and ASN-78 (on alpha subunit) and ASN-13, ASN-30, SER-121, SER-127, SER-132 and SER-138 (on beta subunit). The primary structure of the α - chain of r-hCG is identical to that of the α - chain of hCG, FSH and LH. The glycoform pattern of the α - subunit of r-hCG is closely comparable to urinary derived hCG (u-hCG), the differences mainly being due to the branching and sialylation extent of the oligosaccharides. The β - chain has both O- and N-glycosylation sites and its structure and glycosylation pattern are also very similar to that of u-hCG.

The production process involves expansion of genetically modified Chinese Hamster Ovary (CHO) cells from an extensively characterized cell bank into large scale cell culture processing. Choriogonadotropin alfa is secreted by the CHO cells directly into the cell culture medium that is then purified using a series of chromatographic steps. This process yields a product with a high level of purity and consistent product characteristics including glycoforms and biological activity. The biological activity of choriogonadotropin alfa is determined using the seminal vesicle weight gain test in male rats described in the "Chorionic Gonadotrophins" monograph of the European Pharmacopoeia. The *in vivo* biological activity of choriogonadotropin alfa has been calibrated against the third international reference preparation IS75/587 for chorionic gonadotropin.

Ovidrel® PreFilled Syringe is a sterile, liquid intended for subcutaneous (SC) injection. Each Ovidrel® PreFilled Syringe is filled with 0.515 mL containing 257.5 µg of choriogonadotropin alfa, 28.1mg mannitol, 505 µg 85% O-phosphoric acid, 103 µg L-methionine, 51.5 µg Poloxamer 188, Sodium Hydroxide (for pH adjustment), and Water for Injection to deliver 250 µg of choriogonadotropin alfa in 0.5 mL. The pH of the solution is 6.5 to 7.5.

Therapeutic Class: Infertility

CLINICAL PHARMACOLOGY

The physicochemical, immunological, and biological activities of recombinant hCG are comparable to those of placental and human pregnancy urine-derived hCG. Choriogonadotropin alfa stimulates late follicular maturation and resumption of oocyte meiosis, and initiates rupture of the pre-ovulatory ovarian follicle. Choriogonadotropin alfa, the active component of Ovidrel® PreFilled Syringe, is an analogue of Luteinizing Hormone (LH) and binds to the LH/hCG receptor of the granulosa and theca cells of the ovary to effect these changes in the absence of an endogenous LH surge. In pregnancy, hCG, secreted by the placenta, maintains the viability of the corpus luteum to provide the continued secretion of estrogen and progesterone necessary to support the first trimester of pregnancy. Ovidrel® PreFilled Syringe is administered when monitoring of the patient indicates that sufficient follicular development has occurred in response to FSH treatment for ovulation induction.

Pharmacokinetics

When given by intravenous administration, the pharmacokinetic profile of Ovidrel® followed a biexponential model and was linear over a range of 25 µg to 1000 µg. Pharmacokinetic parameter estimates following SC administration of Ovidrel® 250 µg to females are presented in Table 1.

Table 1: Pharmacokinetic Parameters (mean ± SD) of r-hCG after Single-Dose Administration of Ovidrel® in Healthy Female Volunteers

	Ovidrel® 250 µg SC
C_{max} (IU/L)	121 ± 44
t_{max} (h)*	24 (12–24)
AUC (h•IU/L)	7701 ± 2101
t½ (h)	29 ± 6
F	0.4 ± 0.1

C_{max}: peak concentration (above baseline), t_{max}: time of C_{max}, AUC: total area under the curve, t½: elimination half-life, F: bioavailability

* median (range)

Alclometasone Dipropionate USP, 0.05%, Rx	O
Amcinonide 0.1% Rx	C, L
Amiodarone HCl Tablets, 200 mg Rx Light Orange, Round, Flat	TARO Scored/ 56/Blank
Ammonium Lactate 12%	C, L
Betamethasone Dipropionate USP, 0.05% Rx	C
Betamethasone Dipropionate (Augmented), 0.05%, Rx	C, G
Betamethasone Valerate USP, 0.1% Rx	C
Carbamazepine Tablets USP (Chewable), 100 mg Rx White, w/Pink Speckles, Cherry Odor Round	TARO/16/Blank
Carbamazepine Tablets USP, 200 mg Rx White, Round, Flat	TARO/11/Blank
Carbamazepine 100 mg/5mL Rx Orange Color & Flavor Oral Suspension	Susp
Clobetasol Propionate, USP 0.05% Rx	C,O,G,S
Clobetasol Propionate (Emollient) USP, 0.05% Rx	C,E
Clomipramine Hydrochloride Capsules, 25 mg Rx Dark Blue Cap, Light Blue Body	CLOM 25
Clomipramine Hydrochloride Capsules, 50 mg Rx Yellow Opaque	CLOM 50
Clomipramine Hydrochloride Capsules, 75 mg Rx White Opaque	CLOM 75
Clorazepate Dipotassium Tablets USP, 3.75 mg C-IV Rx Pale Violet, Slightly Mottled, Round, Flat	T Scored 45/Blank
Clorazepate Dipotassium Tablets USP, 7.5 mg C-IV Rx Orange, Slightly Mottled, Round, Flat	T Scored 46/Blank
Clorazepate Dipotassium Tablets USP, 15 mg C-IV Rx Pale Pink, Slightly Mottled, Round, Flat	T Scored 47/Blank
Clotrimazole 1% Rx	C,S
Clotrimazole and Betamethasone Dipropionate USP, Rx	C, L
Desonide 0.05% Rx	C,O
Desoximetasone USP, 0.05% Rx	C,G
Desoximetasone USP, 0.25% Rx	C,O
Diflorasone Diacetate 0.05% Rx	C,O
Econazole Nitrate Cream 1% Rx	C
Enalapril Maleate and Hydrochlorothiazide Tablets, USP 5/12.5 mg Rx Ivory, Caplet-Shaped Compressed Tablets	T4/Blank
Enalapril Maleate and Hydrochlorothiazide Tablets, USP 10/25 mg Rx Peach, Caplet-Shaped Compressed Tablets	T3/Blank
Enalapril Maleate Tablets, USP 2.5 mg Rx Yellow, Round, Biconvex	T Scored 2/Blank
Enalapril Maleate Tablets, USP 5 mg Rx Yellow, Round, Biconvex	T Scored 5/Blank
Enalapril Maleate Tablets, USP 10 mg Rx Pink, Round, Convex	T Scored 10/Blank
Enalapril Maleate Tablets, USP 20 mg Rx Orange, Round, Convex	T Scored 20/Blank
Etodolac Capsules USP, 200 mg Rx Dark Pink, Black Body	ETO 200
Etodolac Capsules USP, 300 mg Rx Pink, Black Body	ETO 300
Etodolac Tablets USP, 400 mg Rx Peach, Oval, Film Coated	T88/Blank
Etodolac Tablets USP, 500 mg Rx Blue, Oval, Film Coated	TARO/89
Etodolac Extended-Release Tablets, 400 mg Rx Pink, Round, Film Coated	T400/Blank
Etodolac Extended-Release Tablets, 500 mg Rx Green, Oblong, Convex	T500/Blank
Etodolac Extended-Release Tablets, 600 mg Rx Grey, Oval, Convex	T600/Blank
Fluconazole Tablets 50 mg Pink, Rectangular with rounded edge	FL50/TARO
Fluconazole Tablets 100 mg Pink, Rectangular with rounded edge	FL100/TARO
Fluconazole Tablets 150 mg Pink, Rectangular with rounded edge	FL150/TARO
Fluconazole Tablets 200 mg Pink, Rectangular with rounded edge	FL200/TARO
Fluocinonide USP, 0.05% Rx	C,O,G,S,
Fluocinonide USP, 0.05% (Emulsified Base) Rx	C,EB
Fluorouracil Topical 2% and 5% Rx	S
Fluticasone 0.05% Rx	C
Fluticasone 0.005% Rx	O
Gentamicin Sulfate USP, 0.1% Rx	C, O
Hydrocortisone USP, 1% Rx	C
Hydrocortisone USP, 2.5% Rx	C, L, O
Hydrocortisone Valerate USP, 0.2% Rx	C,O
Ketoconazole 2%	C
Ketoconazole Tablets USP, 200 mg Rx White to Off-White, Round, Flat	T Scored 57/Blank
Lidocaine USP, 5% Rx	O
Phenytoin USP, 125 mg/5mL Orange with orange-vanilla flavor	Susp
Nystatin USP, 100,000 units per gram Rx	C
Nystatin and Triamcinolone Acetonide USP, Rx	C,O
Terconazole Vaginal Cream 0.8% Rx	VC
Triamcinolone Acetonide USP, 0.1% Rx	DP
Warfarin Sodium Tablets, USP 1 mg Rx Pink, Capsule Shape, Flat	1/WARFARIN/TARO
Warfarin Sodium Tablets, USP 2 mg Rx Lavender, Capsule Shape, Flat	2/WARFARIN/TARO
Warfarin Sodium Tablets, USP 2.5 mg Rx Green, Capsule Shape, Flat	2½/WARFARIN/TARO
Warfarin Sodium Tablets, USP 3 mg Rx Tan, Capsule Shape, Flat	3/WARFARIN/TARO
Warfarin Sodium Tablets, USP 4 mg Rx Blue, Capsule Shape, Flat	4/WARFARIN/TARO
Warfarin Sodium Tablets, USP 5 mg Rx Peach, Capsule Shape, Flat	5/WARFARIN/TARO
Warfarin Sodium Tablets, USP 6 mg Rx Teal, Capsule Shape, Flat	6/WARFARIN/TARO
Warfarin Sodium Tablets, USP 7.5 mg Rx Yellow, Capsule Shape, Flat	7½/WARFARIN/TARO
Warfarin Sodium Tablets, USP 10 mg Rx White, Capsule Shape, Flat	10/WARFARIN/TARO

*Front/Back of Tablet & Body and Cap of Capsule
†C-Cream, O-Ointment, L-Lotion, G-Gel, OS-Otic Solution, S-Solution, Susp-Suspension, DP-Dental Paste, E-Emollient, EB-Emulsified Base, VC-Vaginal Cream

Teva Neuroscience, Inc.

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For Medical Information Contact:
1-800-887-8100

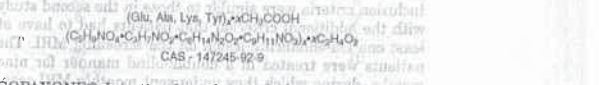
COPAXONE®

(glatiramer acetate injection)

DESCRIPTION

COPAXONE® is the brand name for glatiramer acetate (formerly known as copolymer-1). Glatiramer acetate, the active ingredient of COPAXONE®, consists of the acetate salts 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 average molecular weight of glatiramer acetate is 5,000–9,000 daltons. Glatiramer acetate is identified by specific antibodies.

Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:



COPAXONE® Injection is a clear, colorless to slightly yellow, sterile, non-pyrogenic solution for subcutaneous injection. Each 1.0 mL of solution contains 20 mg of glatiramer acetate and 40 mg of mannitol, USP. The pH range of the solution is approximately 5.5 to 7.0. The biological activity of COPAXONE® is determined by its ability to block the induction of EAE in mice.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism(s) by which glatiramer acetate exerts its effects in patients with Multiple Sclerosis (MS) is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in several animal species through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and *in vitro* systems suggest that upon its administration, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery.

Because glatiramer acetate can modify immune functions, concerns exist about its potential to alter naturally occurring immune responses. Results of a limited battery of tests designed to evaluate this risk produced no finding of concern; nevertheless, there is no logical way to absolutely exclude this possibility (see **PRECAUTIONS**).

Pharmacokinetics

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

Clinical Trials

Evidence supporting the effectiveness of glatiramer acetate in decreasing the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RR MS) derives from two placebo-controlled trials, both of which used a glatiramer acetate dose of 20 mg/day. (No other dose or dosing regimen has been studied in placebo-controlled trials of RR MS.)

One trial was performed at a single center. It enrolled 50 patients who were randomized to receive daily doses of either glatiramer acetate, 20 mg subcutaneously, or placebo (glatiramer acetate, n=25; placebo, n=25). Patients were diagnosed with RR MS by standard criteria, and had had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Disability Scale Score (DSS), a standard scale ranging from 0–Normal to 10–Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair.

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

Continued on next page

Copaxone—Cont.

The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the 2 years of the trial, but two other important outcomes were also specified as endpoints: 1) the frequency of attacks during the trial, and 2) the change in the number of attacks compared with the number which occurred during the previous 2 years.

Table 1 presents the values of the three outcomes described above, as well as several protocol specified secondary measures. These values are based on the intent-to-treat population (i.e., all patients who received at least 1 dose of treatment and who had at least 1 on-treatment assessment).

[See table 1 at right]

The second trial was a multicenter trial of similar design which was performed in 11 US centers. A total of 251 patients (glatiramer acetate, 125; placebo, 126) were enrolled. The primary outcome measure was the Mean 2-Year Relapse Rate. The table below presents the values of this outcome for the intent-to-treat population, as well as several secondary measures:

[See table 2 at right]

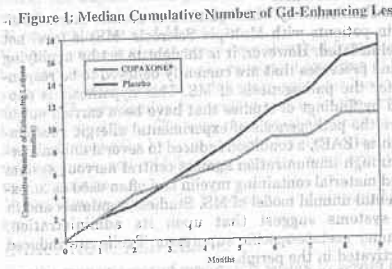
In both studies glatiramer acetate exhibited a clear beneficial effect on relapse rate, and it is based on this evidence that glatiramer acetate is considered effective.

A third study was a multi-national study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RR MS (119 on glatiramer acetate and 120 on placebo) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over the nine months. Table 3 summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

[See table 3 at right]

The following figure displays the results of the primary outcome on a monthly basis.

Figure 1: Median Cumulative Number of Gd-Enhancing Lesions



p= 0.0030 for the difference between the placebo-treated (n=120) and glatiramer acetate-treated (n=119) groups

Table 1: Study 1 Efficacy Results

Outcome	Glatiramer Acetate (N=25)	Placebo (N=25)	P-Value
% Relapse-Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate Compared to Pre-Study	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

*Progression was defined as an increase of at least 1 point on the DSS, persisting for at least 3 consecutive months.

Table 2: Study 2 Efficacy Results

Outcome	Glatiramer Acetate (N=125)	Placebo (N=126)	P-Value
Mean No. of Relapses	1.19/2 years	1.68/2 years	0.055
% Relapse-Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Progression-Free Patients	98/125 (78%)	95/126 (75%)	0.48
Mean Change in DSS	-0.05	+0.21	0.023

Table 3: Study 3 MRI Results

Outcome	Glatiramer Acetate (N=119)	Placebo (N=120)	P-Value
Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	11	17	0.0030

INDICATIONS AND USAGE

COPAXONE® Injection is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis.

CONTRAINDICATIONS

COPAXONE® Injection is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

WARNINGS

The only recommended route of administration of COPAXONE® Injection is the subcutaneous route. COPAXONE® Injection should not be administered by the intravenous route.

PRECAUTIONS

General

Patients should be instructed in self-injection techniques to assure the safe administration of COPAXONE® Injection (see **PRECAUTIONS: Information for Patients** and the **COPAXONE® INJECTION PATIENT INFORMATION** Leaflet). Current data indicate that no special caution is required for patients operating an automobile or using complex machinery.

Considerations Regarding the Use of a Product Capable of Modifying Immune Responses

Because glatiramer acetate can modify immune response, it could possibly interfere with useful immune functions. For example, treatment with glatiramer acetate might, in theory, interfere with the recognition of foreign antigens in a way that would undermine the body's tumor surveillance and its defenses against infection. There is no evidence that glatiramer acetate does this, but there has as yet been no systematic evaluation of this risk. Because glatiramer acetate is an antigenic material, it is possible that its use may lead to the induction of host responses that are untoward, but systematic surveillance for these effects has not been undertaken.

Although glatiramer acetate is intended to minimize the autoimmune response to myelin, there is the possibility that continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.

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

Information for Patients

To assure safe and effective use of COPAXONE® Injection, the following information and instructions should be given to patients:

1. Inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while taking this medication.
2. Inform your physician if you are nursing.
3. Do not change the dose or dosing schedule without consulting your physician.
4. Do not stop taking the drug without consulting your physician.

Patients should be instructed in the use of aseptic techniques when administering COPAXONE® Injection. Appropriate instructions for the self-injection of COPAXONE® Injection should be given, including a careful review of the **COPAXONE® INJECTION PATIENT INFORMATION** Leaflet. The first injection should be performed under the supervision of an appropriately qualified health care professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the reuse of needles or syringes and instructed in safe disposal procedures. They should use a puncture-resistant container for disposal of used needles and syringes. Patients should be instructed on the safe disposal of full containers according to local laws.

Awareness of Adverse Reactions: Physicians are advised to counsel patients about adverse reactions associated with the use of COPAXONE® Injection (see **ADVERSE REACTIONS** section). In addition, patients should be advised to read the **COPAXONE® INJECTION PATIENT INFORMATION** Leaflet and resolve any questions regarding it prior to beginning COPAXONE® Injection therapy.

Laboratory Tests

Data collected during premarketing development do not suggest the need for routine laboratory monitoring.

Drug Interactions

Interactions between COPAXONE® Injection and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® Injection with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. COPAXONE® Injection has not been formally evaluated in combination with Interferon beta.

Drug/Laboratory Test Interactions

None are known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a two-year carcinogenicity study, mice were administered up to 60 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m^2 basis). No increase in systemic neoplasms was observed. In males of the high dose group (60 mg/kg/day), but not in females, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a two-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m^2 basis). No increase in systemic neoplasms was observed.

Mutagenesis

Glatiramer acetate was not mutagenic in four strains of *Salmonella typhimurium* and two strains of *Escherichia coli* (Ames test) or in the *in vitro* mouse lymphoma assay in L5178Y cells. Glatiramer acetate was clastogenic in two separate *in vitro* chromosomal aberration assays in cultured human lymphocytes; it was not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

In a multigeneration reproduction and fertility study in rats, glatiramer acetate at subcutaneous doses of up to 36 mg/kg (18 times the human therapeutic dose on a mg/m^2 basis) had no adverse effects on reproductive parameters.

Pregnancy

Pregnancy Category B. No adverse effects on embryofetal development occurred in reproduction studies in rats and rabbits receiving subcutaneous doses of up to 37.5 mg/kg of glatiramer acetate during the period of organogenesis (18 and 36 times the therapeutic human dose on a mg/m^2 basis, respectively). In a prenatal and postnatal study in which rats received subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, glatiramer acetate should be used during pregnancy only if clearly needed.

Labor and Delivery

In a prenatal and postnatal study, in which rats received subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery were observed. The relevance of these findings to humans is unknown.

Nursing Mothers

It is not known whether glatiramer acetate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COPAXONE® is administered to a nursing woman.

Pediatric Use
The safety and efficacy of COPAXONE® Injection have not been established in individuals under 18 years of age.

Use in the Elderly
COPAXONE® Injection has not been studied specifically in elderly patients.

Use in Patients with Impaired Renal Function
The pharmacokinetics of glatiramer acetate in patients with impaired renal function have not been determined.

ADVERSE REACTIONS

During premarketing clinical trials approximately 900 individuals received at least one dose of glatiramer acetate.
In controlled clinical trials the most commonly observed adverse experiences associated with the use of glatiramer acetate and not seen at an equivalent frequency among placebo-treated patients were: injection site reactions, vasodilatation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety, and hypertonia.
Approximately 8% of the 893 subjects receiving glatiramer acetate discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: injection site reaction (6.5%), vasodilatation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness, and tremor.

Immediate Post-Injection Reaction
Approximately 10% of MS patients exposed to glatiramer acetate in premarketing studies experienced a constellation of symptoms immediately after injection that included flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. In clinical trials, the symptoms were generally transient and self-limited and did not require specific treatment. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care.
Whether an immunologic or non-immunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

Chest Pain
Approximately 21% of glatiramer acetate patients in the pre-marketing controlled studies (compared to 11% 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 this chest pain to an injection of glatiramer acetate was not always known. The pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. There has been only one episode of chest pain during which a full EKG was performed; that EKG showed no evidence of ischemia. 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.

Incidence in Controlled Clinical Studies: The following table lists treatment-emergent signs and symptoms that occurred in at least 2% of MS patients treated with glatiramer acetate in the pre-marketing placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with glatiramer acetate than in patients treated with placebo. These trials include the first two controlled trials in RR MS patients and a controlled trial in patients with Chronic-Progressive MS. Adverse reactions were usually mild in intensity.
The prescriber should be aware that these figures cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis on which to estimate the relative contribution of drug and nondrug factors to the adverse reaction incidences in the population studied. (See table above)
Other events which occurred in at least 2% of glatiramer acetate 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, neck rigidity, 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.

Controlled Trials in Patients with Multiple Sclerosis: Incidence of Glatiramer Acetate Adverse Reactions ≥2% and More Frequent than Placebo

Preferred Term	Glatiramer Acetate (N = 201) N	%	Placebo (N = 206) N	%
Body as a Whole				
Asthenia	83	41	78	38
Back Pain	33	16	30	15
Bacterial Infection	11	5	9	4
Chest Pain	43	21	22	11
Chills	8	4	2	1
Cyst	5	2	1	0
Face Edema	12	6	2	1
Fever	17	8	15	7
Flu Syndrome	38	19	35	17
Infection	101	50	99	48
Injection Site Erythema	132	66	40	19
Injection Site Hemorrhage	11	5	6	3
Injection Site Induration	26	13	1	0
Injection Site Inflammation	98	49	22	11
Injection Site Mass	54	27	21	10
Injection Site Pain	147	73	78	38
Injection Site Pruritus	80	40	12	6
Injection Site Urticaria	10	5	0	0
Injection Site Welt	22	11	5	2
Neck Pain	16	8	9	4
Pain	56	28	52	25
Cardiovascular System				
Migraine	10	5	5	2
Palpitations	35	17	16	8
Syncope	10	5	5	2
Tachycardia	11	5	8	4
Vasodilatation	55	27	21	10
Digestive System				
Anorexia	17	8	15	7
Diarrhea	25	12	23	11
Gastroenteritis	6	3	2	1
Gastrointestinal Disorder	10	5	8	4
Nausea	44	22	34	17
Vomiting	13	6	8	4
Hemic and Lymphatic System				
Ecchymosis	16	8	13	6
Lymphadenopathy	25	12	12	6
Metabolic and Nutritional				
Edema	5	3	1	0
Peripheral Edema	14	7	8	4
Weight Gain	7	3	0	0
Musculoskeletal System				
Arthralgia	49	24	39	19
Nervous System				
Agitation	8	4	4	2
Anxiety	46	23	40	19
Confusion	5	2	1	0
Foot Drop	6	3	4	2
Hypertonia	44	22	37	18
Nervousness	4	2	2	1
Nystagmus	5	2	2	1
Speech Disorder	5	2	3	1
Tremor	14	7	7	3
Vertigo	12	6	11	5
Respiratory System				
Bronchitis	18	9	12	6
Dyspnea	38	19	15	7
Laryngismus	10	5	7	3
Rhinitis	29	14	27	13
Skin and Appendages				
Erythema	8	4	4	2
Herpes Simplex	8	4	6	3
Pruritus	36	18	26	13
Rash	37	18	30	15
Skin Nodule	4	2	1	0
Sweating	31	15	21	10
Urticaria	9	4	5	2
Special Senses				
Ear Pain	15	7	12	6
Eye Disorder	8	4	1	0
Urogenital System				
Dysmenorrhea	12	6	10	5
Urinary Urgency	20	10	17	8
Vaginal Moniliasis	16	8	9	4

Urogenital System: Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.
Data on adverse reactions occurring in the controlled clinical trials were analyzed to evaluate differences based on sex. No clinically significant differences were identified. Ninety-two percent of patients in these clinical trials were Caucasian. This percentage reflects the racial composition of the MS population. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically relevant age subgroups.
Laboratory analyses were performed on all patients participating in the clinical program for glatiramer acetate. Clinically significant laboratory values for hematology, chemistry, and urinalysis were similar for both glatiramer acetate and placebo groups in blinded clinical trials. No patient receiving glatiramer acetate withdrew from any trial because of abnormal laboratory findings.

Other Adverse Events Observed During Clinical Trials
Glatiramer acetate was administered to 979 individuals during premarketing clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by the 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 standardized categories using COSTART dictionary terminology. All reported events occurring at least twice and potentially important events occurring once are listed below, except those already listed in the previous table, those too general to be informative, trivial events, and other reactions which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group. Additional adverse reactions reported during the post-marketing period are included.
Events are further classified within body system categories and listed in order of decreasing frequency using the follow-

Continued on next page

Copaxone—Cont.

ing 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; *Rare* adverse events are those occurring in less than 1/1000 patients.

Body as a Whole:
- ◆ *Frequent:* Injection site edema, injection site atrophy, abscess, injection site hypersensitivity.
- ◆ *Infrequent:* Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, and photosensitivity reaction.

Cardiovascular:
- ◆ *Frequent:* Hypertension.
- ◆ *Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

Digestive:
- ◆ *Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue 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:* Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

Respiratory:
- ◆ *Frequent:* Hyperventilation, hay-fever.
- ◆ *Infrequent:* Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages:
- ◆ *Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy, and warts.
- ◆ *Infrequent:* Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

Special Senses:
- ◆ *Frequent:* Visual field defect.
- ◆ *Infrequent:* Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

Urogenital:
- ◆ *Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious papanicolaou smear, urinary frequency and vaginal hemorrhage.
- ◆ *Infrequent:* Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, carcinoma *in situ* cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Postmarketing Clinical Experience

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

Body as a Whole: sepsis; LE syndrome; hydrocephalus; enlarged abdomen; injection site hypersensitivity; allergic reaction; anaphylactoid reaction

Cardiovascular System: thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy; cardiomegaly; arrhythmia; angina pectoris

Digestive System: tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Hemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukemia

Metabolic and Nutritional Disorders: hypercholesterolemia

Musculoskeletal System: rheumatoid arthritis; generalized spasm

Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasia; convulsion; neuralgia

Respiratory System: pulmonary embolus; pleural effusion; carcinoma of lung; hay fever

Special Senses: glaucoma; blindness; visual field defect

Urogenital System: urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency

DRUG ABUSE AND DEPENDENCE

No evidence or experience suggests that abuse or dependence occurs with COPAXONE® Injection therapy; however, the risk of dependence has not been systematically evaluated.

DOSAGE AND ADMINISTRATION

The recommended dose of COPAXONE® Injection for the treatment of RR MS is 20 mg/day injected subcutaneously.

Instructions for Use

Remove one blister with the syringe inside from the COPAXONE® Injection Pre-filled syringes package from the refrigerator. Let the pre-filled syringe package stand at room temperature for 20 minutes to allow the solution to warm up to room temperature. Store all unused syringes in the refrigerator. Inspect the product visually and discard or return the product to the pharmacist before use if it contains any particulate matter.

Sites for self-injection include arms, abdomen, hips, and thighs. The pre-filled syringe is suitable for single use only; unused portions should be discarded. (See the **COPAXONE® Injection PATIENT INFORMATION** Leaflet for **INSTRUCTIONS FOR INJECTING COPAXONE®.**)

HOW SUPPLIED

COPAXONE® Injection is supplied as a single-use pre-filled syringe containing 1.0 mL of a clear, colorless to slightly yellow, sterile, non-pyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol, USP in cartons of 30 single-use pre-filled syringes, 33 alcohol preps (wipes) and instructions for use.

The recommended storage condition for the COPAXONE® Injection is refrigeration (2°C to 8°C / 36°F to 46°F). However, excursions from recommended storage conditions to room temperature conditions (15° to 30°C / 59° to 86°F) for up to one week have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided.

COPAXONE® Injection contains no preservative. Do not use if the solution contains any particulate matter.

COPAXONE® Injection is available in packs of 30 single-use Pre-Filled Syringes (NDC 0088-1153-30).

Rx Only.

PATIENT INFORMATION

COPAXONE® (glatiramer acetate injection)

Read this information carefully before you use COPAXONE®. Read the information you get when you refill your COPAXONE® prescriptions because there may be new information. This information does not take the place of your doctor's advice. Ask your doctor or pharmacist if you do not understand some of this information or if you want to know more about this medicine.

What is COPAXONE®?

COPAXONE® (co-PAX-own) is a medicine you inject to treat Relapsing-Remitting Multiple Sclerosis. Although COPAXONE® is not a cure, patients treated with COPAXONE® have fewer relapses.

Who should not use COPAXONE®?

- COPAXONE® is not recommended for use in pregnancy. So, tell your doctor if you are pregnant or if you plan to become pregnant while taking this medicine.
- Tell your doctor if you are nursing. It is not known if COPAXONE® is passed through the breast milk to the baby.
- Do not use COPAXONE® if you are allergic to glatiramer acetate or mannitol.

What are the possible side effects of COPAXONE®?

- **Call your doctor right away if you develop any of the following symptoms: hives, skin rash with irritation, dizziness, sweating, chest pain, trouble breathing, or severe pain at the injection site.** Do not give yourself any more injections until your doctor tells you to begin again.
- The most common side effects of COPAXONE® are redness, pain, swelling, itching, or a lump at the injection site. These reactions are usually mild and seldom require medical care.
- Some patients report a short-term reaction right after injecting COPAXONE®. This reaction can involve flushing (feeling of warmth and/or redness), chest tightness or pain with heart palpitations, anxiety, and trouble breathing. These symptoms generally appear within minutes after an injection, last a few minutes, then go away by themselves without further problems.
- **If symptoms become severe, call the emergency phone number in your area.**
- Do not give yourself any more injections until your doctor tells you to begin again.

These are not all the possible side effects of COPAXONE®. For a complete list, ask your doctor or pharmacist. Tell your doctor about any side effects you have while taking COPAXONE®.

How should I use COPAXONE®?

- The recommended dose of COPAXONE® for the treatment of Relapsing-Remitting Multiple Sclerosis is 20 mg once a day injected subcutaneously (in the fatty layer under the skin).
- Look at the medicine in the pre-filled syringe. If the medicine is cloudy or has particles in it, do not use it. Instead, call Shared Solutions at 1-800-887-8100 for assistance.
- Have a friend or relative with you if you need help, especially when you first start giving yourself injections.
- Each pre-filled syringe should be used for only one injection. Do not reuse the pre-filled syringe. After use, throw it away properly.
- Do not change the dose or dosing schedule or stop taking the medicine without talking with your doctor.

How do I inject COPAXONE®?

There are 3 basic steps for injecting COPAXONE® pre-filled syringes:

1. Gather the materials.
2. Choose the injection site.
3. Give yourself the injection.

Step 1: Gather the materials

1. First, place each of the items you will need on a clean, flat surface in a well-lit area:
   - 1 blister pack with COPAXONE® Pre-Filled Syringe
     Remove only 1 blister pack from the COPAXONE® Pre-Filled Syringe carton. Keep all unused syringes in the Pre-Filled Syringe carton and store them in the refrigerator.
   - Alcohol prep (wipe)
   - Dry cotton ball (not supplied)
2. Let the blister pack with the syringe inside warm up to room temperature for 20 minutes.
3. To prevent infection, wash and dry your hands. Do not touch your hair or skin after washing.
4. There may be small air bubbles in the syringe. To avoid loss of medicine when using COPAXONE® pre-filled syringes, do not expel (or do not attempt to expel) the air bubble from the syringe before injecting the medicine.

Step 2: Choose the injection site

- There are 7 possible injection areas on your body: arms, thighs, hips and lower stomach area (abdomen) (See Figure 1).

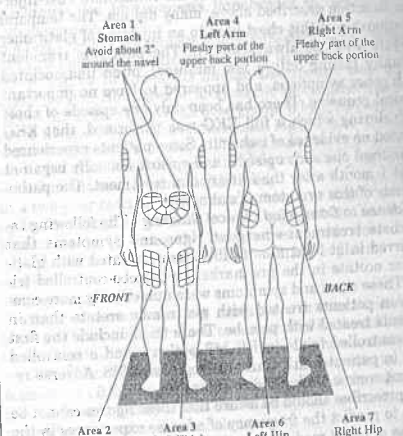


Figure 1

- Each day, pick a different injection area from one of the 7 areas. **Do not inject in the same area more than once a week.**
- Within each injection area there are multiple injection sites. Have a plan for rotating your injection sites. Keep a record of your injection sites, so you know where you have injected.
- There are some sites in your body that may be hard to reach for self-injection (like the back of your arm), and you may need help.

Step 3: Give yourself the injection

1. Remove the syringe from its protective blister pack by peeling back the paper label. Before use, look at the liquid in the syringe. If it is cloudy or contains any particles, do not use it and call Shared Solutions at 1-800-887-8100 for assistance. If the liquid is clear, place the syringe on the clean, flat surface.
2. Choose an injection site on your body. Clean the injection site with a new alcohol prep and let the site air dry to reduce stinging.
3. Pick up the syringe as you would a pencil. Remove the needle shield from the needle.

[See figure 2 at top of next column]

4. With your other hand, pinch about a 2-inch fold of skin between your thumb and index finger (See Figure 2).

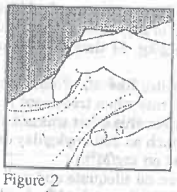


Figure 2

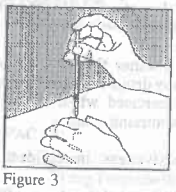


Figure 3

5. Insert the needle at a 90-degree angle (straight in), resting the heel of your hand against your body. When the needle is all the way in release the fold of skin (See Figure 3).
6. To inject the medicine, hold the syringe steady and push down the plunger.
7. When you have injected all of the medicine, pull the needle straight out.
8. Press a dry cotton ball on the injection site for a few seconds. **Do not rub the injection site.**
9. Throw away the syringe in a safe hard-walled plastic container.

What is the proper use and disposal of Pre-Filled Syringes?
Each Pre-Filled Syringe should be used for only 1 injection. Throw away all used Pre-Filled Syringes in a hard-walled plastic container, such as an empty liquid laundry detergent bottle. Keep the container closed tightly and out of the reach of children. When the container is full, check with your doctor, pharmacist, or nurse about proper disposal, as laws vary from state to state.

How should I store COPAXONE® Pre-Filled Syringes?
Keep the COPAXONE® Pre-Filled Syringe carton in the refrigerator, out of the reach of children.
The COPAXONE® package should be refrigerated as soon as you get it, at 36-46°F (2-8°C). If you cannot store COPAXONE® in a refrigerator, you can store it at room temperature, 59-86°F (15-30°C), for up to 7 days. Do not store COPAXONE® at room temperature for longer than 7 days. **Do not freeze COPAXONE®.** If a COPAXONE® pre-filled syringe freezes, throw it away in a proper container. COPAXONE® is light sensitive. Protect it from light when not injecting. Do not use the pre-filled syringe if the solution contains particles or is cloudy.

General advice about prescription medicines
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use COPAXONE® for a condition for which it was not prescribed. Do not give COPAXONE® to other people, even if they have the same condition you have. It may harm them. This leaflet summarizes the most important information about COPAXONE®. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about COPAXONE® that is written for health professionals. Also, you can call Shared Solutions for any questions about COPAXONE® and its use. The phone number for Shared Solutions is 1-800-887-8100.

Manufactured in Israel by **TEVA Pharmaceutical Industries Ltd.**, Kfar Saba 44102, Israel
Manufactured By: **Baxter Pharmaceutical Solutions LLC**, Bloomington, IN 47403
Manufactured For: **TEVA Neuroscience, Inc.**, Kansas City, MO 64131
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Shown in Product Identification Guide, page 334

Ther-Rx Corporation

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CHROMAGEN®

[krō-mă-jĕn]
Soft Gelatin Capsules
Rx Only

DESCRIPTION
Each capsule contains:
Iron ..... 70 mg Ferrochel® (elemental iron)*
Vitamin C ..... 150 mg Ester-C®†
Vitamin B_{12} ..... 10 mcg (cyanocobalamin)
Dessicated stomach substance ..... 100 mg
Each capsule also contains soybean oil, gelatin, glycerine USP, yellow beeswax, lecithin – unbleached, titanium dioxide, methylparaben, ethyl vanillin, FD&C Red #40, FD&C Yellow #6, propylparaben, FD&C Blue #1.

INDICATIONS
For the treatment of all anemias responsive to oral iron therapy, such as hypochromic anemia associated with pregnancy, chronic or acute blood loss, dietary restriction, metabolic disease and post-surgical convalescence.

CONTRAINDICATIONS
Hemochromatosis and hemosiderosis are contraindications to iron therapy.

WARNING
Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

Allergy Alert: These gelcaps contain a soy product.

PRECAUTION
Pediatric Use: Safety and effectiveness in pediatric patients has not been established.

ADVERSE REACTIONS
Average capsule doses in sensitive individuals or excessive dosage may cause nausea, skin rash, vomiting, diarrhea, precordial pain, or flushing of the face or extremities.

DOSAGE AND ADMINISTRATION
Usual adult dose is 1 soft gelatin capsule daily.

HOW SUPPLIED
Chromagen® capsules for oral administration are supplied as red soft gelatin capsules, imprinted "THX 0129" in grey ink in child-resistant, unit-dose packages of 100 capsules (10 × 10 Unit Dose Packs) (NDC 64011-129-11).
Store at controlled room temperature 15°-30°C (59°-86°F). Avoid excessive heat 40°C (104°F). Avoid freezing.

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* Ferrochel® (ferrous bis-glycinate chelate) is a registered trademark of Albion International, Inc., Clearfield, Utah, and is protected under US Patent Nos. 4,599,152 and 4,830,716.

† Ester-C® is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate. Ester-C® is a licensed trademark of Zila Nutraceuticals, Inc.

Manufactured by:
Accucaps Industries, Ltd.-Canada for
Ther-Rx Corporation
Saint Louis, MO 63044
P4223 Rev. 06/03

Shown in Product Identification Guide, page 334

CHROMAGEN® FA

Soft Gelatin Capsules
Rx Only

DESCRIPTION
Each capsule contains:
Iron ..... 70 mg Ferrochel® (elemental iron)*
Vitamin C ..... 150 mg Ester-C®†
Folic Acid USP ..... 1 mg
Vitamin B_{12} ..... 10 mcg (cyanocobalamin)

Each capsule also contains soybean oil, gelatin, glycerine USP, yellow beeswax, lecithin – unbleached, titanium dioxide, methylparaben, black ferric oxide, D&C Yellow #10, ethyl vanillin, propylparaben, FD&C Red #40, FD&C Blue #1.

INDICATIONS
For the treatment of all anemias responsive to oral iron therapy, such as hypochromic anemia associated with pregnancy, chronic or acute blood loss, dietary restriction, metabolic disease and post-surgical convalescence.

CONTRAINDICATIONS
Hemochromatosis and hemosiderosis are contraindications to iron therapy. Folic acid is contraindicated in patients with pernicious anemia (see PRECAUTIONS).

WARNING
Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

Allergy Alert: These gelcaps contain a soy product.

PRECAUTIONS
Folic acid alone is improper therapy in the treatment of pernicious anemia and other megaloblastic anemias where Vitamin B_{12} is deficient.
Folic acid in doses above 1.0 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurological manifestations remain progressive.
Pediatric Use: Safety and effectiveness in pediatric patients has not been established.

ADVERSE REACTIONS
Average capsule doses in sensitive individuals or excessive dosage may cause nausea, skin rash, vomiting, diarrhea, precordial pain, or flushing of the face and extremities.

DOSAGE AND ADMINISTRATION
Usual adult dose is 1 soft gelatin capsule daily.

HOW SUPPLIED
Chromagen® FA capsules for oral administration are supplied as green and brown soft gelatin capsules, imprinted "THX 0130" in grey ink in child-resistant, unit-dose packages of 100 capsules (10 × 10 Unit Dose Packs) (NDC 64011-130-11).
Store at controlled room temperature 15°- 30°C (59°- 86°F). Avoid excessive heat 40°C (104°F). Avoid freezing.

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* Ferrochel® (ferrous bis-glycinate chelate) is a registered trademark of Albion International, Inc., Clearfield, Utah, and is protected under US Patent Nos. 4,599,152 and 4,830,716.

† Ester-C® is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate. Ester-C® is a licensed trademark of Zila Nutraceuticals, Inc.

Manufactured by:
Accucaps Industries, Ltd.-Canada for
Ther-Rx Corporation
Saint Louis, MO 63044
P4224 Rev. 06/03

Shown in Product Identification Guide, page 334

CHROMAGEN® FORTE

Soft Gelatin Capsules
Rx Only

DESCRIPTION
Each capsule contains:
Iron ..... 70 mg Ferrochel® (elemental iron)*
..... 81 mg ferrous fumarate (elemental iron)
Vitamin C ..... 60 mg Ester-C®†
Folic Acid USP .. 1 mg
Vitamin B_{12} ..... 10 mcg (cyanocobalamin)

Each capsule also contains soybean oil, gelatin, glycerine USP, yellow beeswax, lecithin – unbleached, titanium dioxide, methylparaben, ethyl vanillin, FD&C Red #40, FD&C Yellow #6, propylparaben, FD&C Blue #1.

INDICATIONS
For the treatment of all anemias responsive to oral iron therapy, such as hypochromic anemia associated with pregnancy, chronic or acute blood loss, dietary restriction, metabolic disease and post-surgical convalescence.

CONTRAINDICATIONS
Hemochromatosis and hemosiderosis are contraindications to iron therapy. Folic acid is contraindicated in patients with pernicious anemia (see PRECAUTIONS).

WARNING
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Continued on next page