This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Interferon beta-1b, Betaseron

DESCRIPTION

Betaseron® (Interferon beta-lb) 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-lb. Each vial contains 0.3 mg of Interferon beta-lb. 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 interferon-induced proteins that are responsible for the pleiotropic bioactivities of Interferon beta-1b. A number of these proteins (including neopterin, ß$_2$-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

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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 28.9 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, $ß_2$- microglobulin, MxA protein, and the immunosuppressive cytokine, IL-10) increased significantly above baseline six-12 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)

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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.

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† 1 2 3 4 ≥5	20 32 20 15 15 21	22 31 28 15 7 16	29 39 17 14 9 8	0.151	0.077	**0.001**
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	**0.126**
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.

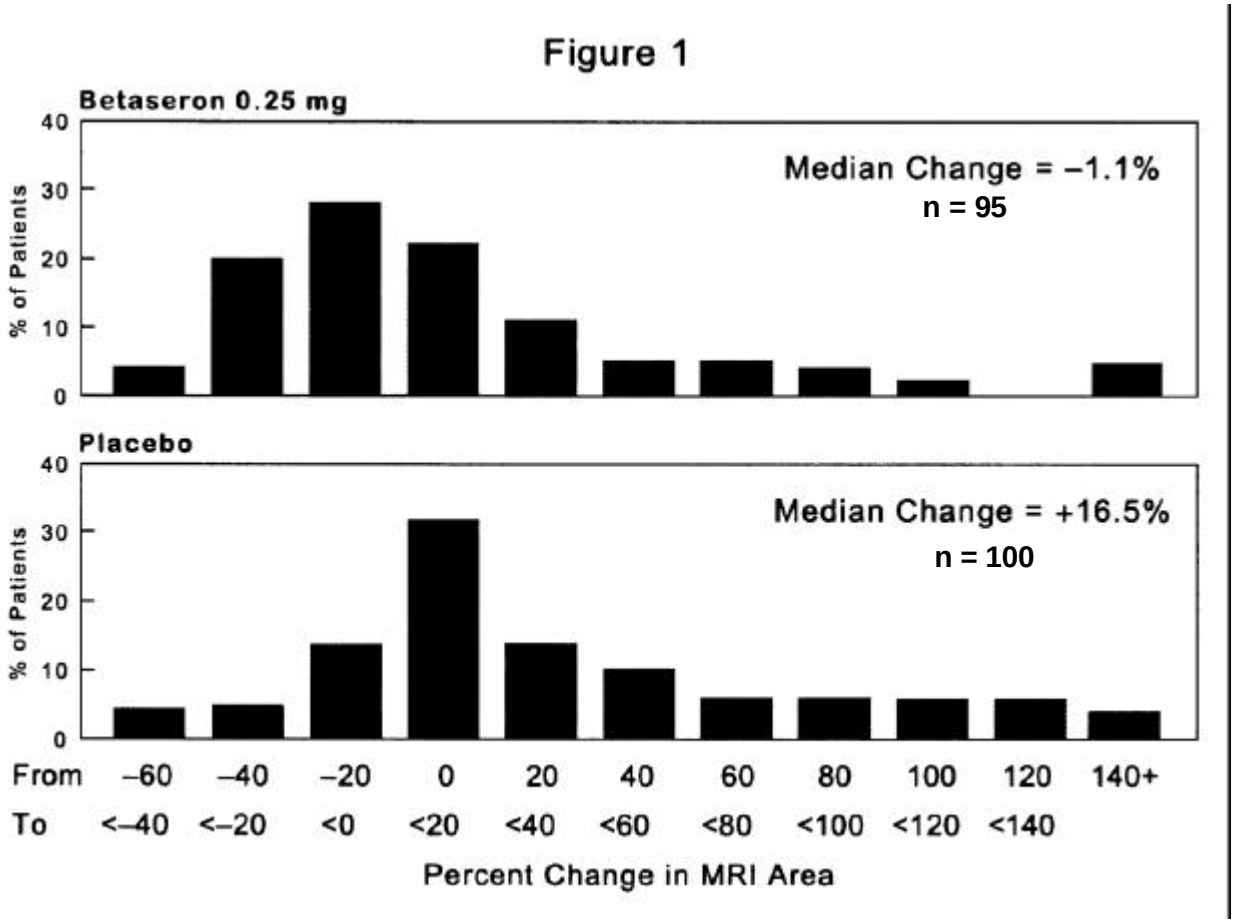
This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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



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

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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.

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.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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 overlaying 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.

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.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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 **Rotating Injection Sites** section of **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

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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 result 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.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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 3 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 3
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%

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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%

Adverse Reaction	**Placebo (n=789)**	**Betaseron (n=1115)**
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:

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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, 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 4).

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Table 4. 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, use a sterile syringe and needle to inject 1.2 mL of the diluent supplied, Sodium Chloride, 0.54% Solution, into the Betaseron vial. Gently swirl the vial of Betaseron to dissolve the drug completely; do not shake. 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. Inspect the reconstituted product visually and discard the product before use if it contains particulate matter or is discolored. After reconstitution with the accompanying diluent, 1 mL of Betaseron solution contains 0.25 mg Interferon beta-1b.

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 separate vial containing 2 mL of diluent (Sodium Chloride, 0.54% solution) is included for each vial of drug. Betaseron and the diluent are for single use only; unused portions should be discarded. (see **Medication Guide** for self-injection procedures.) Store at room temperature.

NDC 50419-523-01 0.3 mg/vial

NDC 50419-523-15 15 vials, 0.3 mg/vial

Rx Only.

REFERENCES

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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

Manufactured by: CHIRON Corporation Emeryville, CA 94608

U.S. License No. 1106

Distributed by: BERLEX Laboratories Montville, NJ 07045

U.S. Patent No. 4,588,585; 4,959,314; 4,737,462; 4,450,103

© 1993 Berlex Laboratories All rights reserved.
Printed in U.S.A. on recycled paper
Part Number XXXX Revision date XXXX