CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103471

LABELING

Betaseron®
Interferon beta-1b

L-1147

DESCRIPTION

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

The specific activity of Betaseron is approximately 32 million international units (IU)/mg Interferon beta-1b. Each vial contains 0.3 mg (9.6 million IU) 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. Dextrose and Albumin Human, USP (15 mg each/vial) are added as stabilizers. Prior to 1993, a different analytical standard was used to determine potency. It assigned 54 million IU to 0.3 mg Interferon beta-1b.

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

CLINICAL PHARMACOLOGY

General: Interferons are a family of naturally occurring proteins, which have molecular weights ranging from 15,000 to 21,000 daltons. Three major classes of Interferons have been identified: alfa, beta, and gamma. Interferon beta-1b, Interferon alfa, and Interferon gamma have overlapping yet distinct biologic activities.[1-6] The activities of Interferon beta-1b are species-restricted and, therefore, the most pertinent pharmacologic information on Betaseron (Interferon beta-1b) is derived from studies of human cells in culture and in humans.

Biologic Activities: Interferon beta-1b has been shown to possess both antiviral and immunoregulatory activities. The mechanisms by which Betaseron exerts its actions in multiple sclerosis (MS) are not clearly understood. However, it is known that the biologic response-modifying properties of Interferon beta-1b are mediated through its interactions with specific cell receptors found on the surface of human cells. The binding of Interferon beta-1b to these receptors induces the expression of a number of interferon-induced gene products (e.g., 2',5'-oligoadenylate synthetase, protein kinase, and indoleamine 2,3-dioxygenase) that are believed to be the mediators of the biological actions of Interferon beta-1b.[1,3,6-10] A number of these Interferon-induced products have been readily measured in the serum and cellular fractions of blood collected from patients treated with Interferon beta-1b.[11,12]

Pharmacokinetics: Because serum concentrations of Interferon beta-1b are low or not detectable following subcutaneous administration of 0.25 mg (8 million IU) 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 (16 million IU) 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 1 to 8 hours, with a mean peak serum interferon concentration of 40 IU/mL. Bioavailability, based on a total dose of 0.5 mg (16 million IU) Betaseron given as two subcutaneous injections at different sites, was approximately 50%.

After intravenous administration of Betaseron (0.006 mg [0.2 million IU] to 2.0 mg [64 million IU]), 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 (64 million IU), 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 2 weeks resulted in no accumulation of Interferon beta-1b in the serum of patients. Pharmacokinetic parameters after single and multiple intravenous doses of Betaseron were comparable.

Clinical Trials: The effectiveness of Betaseron in relapsing-remitting MS was evaluated in a double-blind, multiclinic (11 sites: 4 Canadian and 7 United States), randomized, parallel, placebo-controlled clinical investigation of 2 years duration. The study enrolled MS patients, aged 18 to 50, who were ambulatory (Kurtzke expanded disability status scale [EDSS] of ≤5.5), exhibited a relapsing-remitting clinical course, met Poser's criteria[13] for clinically definite and/or laboratory supported definite MS and had experienced at least two exacerbations over 2 years preceding the trial without exacerbation in the preceding month. Patients who had received prior immunosuppressant therapy were excluded.

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

Patients selected for study were randomized to treatment with either placebo (N=123), 0.05 mg (1.6 million IU) of Betaseron (N=125), or 0.25 mg (8 million IU) of Betaseron (N=124) self-administered subcutaneously every other day. Outcome based on the 372 randomized patients was evaluated after 2 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 assessment measures were 1) frequency of exacerbations per patient and 2) proportion of exacerbation free patients. A number of secondary outcome measures were also employed as described in Table 1.

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

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

Of the 372 patients randomized, 72 (19%) failed to complete 2 full years on their assigned treatments. The reasons given for withdrawal varied with treatment assignment. Excessive use of steroids accounted for 11 of the 26 placebo withdrawals, but only 2 of the 21 withdrawals from the 0.05 mg (1.6 million IU) assigned group and 1 of the 25 withdrawals from the 0.25 mg (8 million IU) assigned group. Withdrawals for adverse events attributed to study article, however, were more common among Betaseron-treated patients: 1, 5, and 10 withdrew from the placebo, 0.05 mg (1.6 million IU), and 0.25 mg (8 million IU) groups, respectively.

Over the 2-year period, there were 25 MS-related hospitalizations in the 0.25 mg (8 million IU) 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 (8 million IU) Betaseron (Interferon beta-1b) group and 15 in the placebo group. The average number of days of MS-related steroid use was 41 days in the 0.25 mg (8 million IU) Betaseron group and 55 days in the placebo group (p=0.004).

TABLE 1
2 Year Study Results
Primary and Secondary Clinical Endpoints

Efficacy Parameters		Treatment Groups			Statistical Comparisons p-value		
Primary Endpoints		Placebo (N=123)	0.05 mg (1.6 mIU) (N=125)	0.25 mg (8 mIU) (N=124)	Placebo vs 0.05 mg (1.6 mIU)	0.05 mg (1.6 mIU) vs 0.25 mg (8 mIU)	Placebo vs 0.25 mg (8 mIU)
Annual exacerbation rate		1.31	1.14	0.90	0.005	0.113	0.0001
Proportion of exacerbation-free patients†		16%	18%	25%	0.609	0.288	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	0.126
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 (9 from placebo, 6 from 0.05 mg, and 8 from 0.25 mg) dropped out of the study before completing 6 months of therapy. These patients are excluded from this analysis
†† Sequelae and Functional Neurologic Status, both required by protocol, were not analyzed individually but are included as a function of the EDSS.
‡ EDSS scores range from 0-10, with higher scores reflecting greater disability.
‡‡ Scripps neurologic rating scores range from 0-100, with smaller scores reflecting greater disability

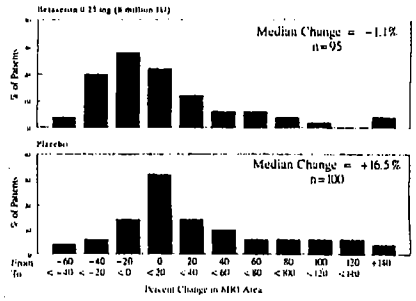
MRI data were also analyzed for patients in this study. A frequency distribution of the observed percent changes in MRI area at the end of 2 years was obtained by grouping the percentages in successive intervals of equal width. Figure 1 displays a histogram of the proportions of patients who fell into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

In an evaluation of frequent MRI scans (every 6 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 (8 million IU) treatment group (p=0.006).

MRI scanning is viewed as a useful means to visualize changes in white matter that are believed to be a reflection of the pathologic changes that, appropriately located within the central nervous system (CNS), account for some of the signs and symptoms that typify relapsing-remitting MS. The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in lesion area often do not correlate with clinical exacerbations probably because many of the lesions affect so-called "silent" regions of the CNS. Moreover, it is not clear what fraction of the lesions seen on MRI become foci of irreversible demyelinization (i.e., classic white matter plaques). The prognostic significance of the MRI findings in this study has not been evaluated.

At the end of 2 years on assigned treatment, patients in the study had the option of continuing on treatment under blinded conditions. Approximately 80% of patients under each treatment accepted. Although there was a trend toward patient benefit in the Betaseron groups during the third year, particularly in the 0.25 mg (8 million IU) group, there was no statistically significant difference

Figure 1
Distribution of Change in MRI Area



between the Betaseron-treated vs. placebo-treated patients in exacerbation rate, or in any of the secondary endpoints described in Table 1. As noted above, in the 2-year analysis, there was a 31% reduction in exacerbation rate in the 0.25 mg (8 million IU) group, compared with placebo. The p-value for this difference was 0.0001. In the analysis of the third year alone, the difference between treatment groups was 28%. The p-value was 0.065. The lower number of patients may account for the loss of statistical significance, and lack of direct comparability among the patient groups in this extension study make the interpretation of these results difficult. The third year MRI data did not show a trend toward additional benefit in the Betaseron arm compared with the placebo arm.

Throughout the clinical trial, serum samples from patients were monitored for the development of antibodies to Interferon beta-1b. In patients receiving 0.25 mg (8 million IU) of Betaseron (N=124) every other day in the clinical trial, 45% were found to have serum neutralizing activity at one or more of the time points tested. The relationship between antibody formation and clinical efficacy is not known.

INDICATIONS AND USAGE

Betaseron (Interferon beta-1b) is indicated for use in ambulatory patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations. (See **CLINICAL PHARMACOLOGY, Clinical Trials** section.) Relapsing-remitting MS is characterized by recurrent attacks of neurologic dysfunction followed by complete or incomplete recovery. The safety and efficacy of Betaseron in chronic-progressive MS has not been evaluated.

CONTRAINDICATIONS

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

WARNINGS

One suicide and 4 attempted suicides were observed among 372 study patients during a 3-year period. All five patients received Betaseron (three in the 0.05 mg [1.6 million IU] group and two in the 0.25 mg [8 million IU] group). There were no attempted suicides in patients on study who did not receive Betaseron. Depression and suicide have been reported to occur in patients receiving interferon alfa, a related compound. Patients to be treated with Betaseron should be informed that depression and suicidal ideation may be a side effect of the treatment and should report these symptoms immediately to the prescribing physician. Patients exhibiting depression should be monitored closely and cessation of therapy should be considered.

PRECAUTIONS

General: Patients should be instructed in injection techniques to assure the safe self-administration of Betaseron. (See **PRECAUTIONS: Information to patients,** and **Betaseron® (Interferon beta-1b) Patient Information sheet.**)

Information to patients:

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 given including careful review of the **Betaseron® (Interferon beta-1b) Patient Information** sheet. If possible, 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

Eighty-five percent of patients in the controlled MS trial reported injection site reactions at one or more times during therapy. In general, these were transient and did not require discontinuation of therapy, but the nature and severity of all reported reactions should be carefully assessed. Patient understanding and use of aseptic self-injection technique and procedures should be periodically reevaluated.

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

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

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

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

Patients should be advised about the abortifacient potential of Betaseron (see **PRECAUTIONS, Pregnancy — Teratogenic effects**).

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

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

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

Betaseron administration to three cancer patients over a dose range of 0.025 mg (0.8 million IU) to 2.2 mg (71 million IU) led to a dose-dependent inhibition of antipyrine elimination.[14] The effect of alternate-day administration of 0.25 mg (8 million IU) of Betaseron on drug metabolism in MS patients is unknown.

Carcinogenesis: The carcinogenic potential of Betaseron was evaluated by studying its effect on the morphological transformation of the mammalian cell line BALBc-3T3. No significant increases in transformation frequency were noted. No carcinogenicity data are available in animals or humans.

Betaseron was not mutagenic when assayed for genotoxicity in the Ames bacterial test in the presence or absence of metabolic activation.

Impairment of fertility: Studies in rhesus monkeys at doses up to 0.33 mg (10.7 million IU)/kg/day which were designed to measure effects on menstrual cycle and hormone profiles have not been completed. It is not known whether Betaseron can affect human reproductive capacity.

Pregnancy — Teratogenic effects: Pregnancy Category C: Betaseron was not teratogenic at doses up to 0.42 mg (13.3 million IU)/kg/day in rhesus monkeys, but demonstrated a dose-related abortifacient activity when administered at doses ranging from 0.028 mg (0.89 million IU)/kg/day (2.8 times the recommended human dose based on body surface area comparison) to 0.42 mg (13.3 million IU)/kg/day (40 times the recommended human dose based on body surface area comparison). The extrapolability of animal doses to human doses is not known. Lower doses were not studied in monkeys. Spontaneous abortions while on treatment were reported in patients (N=4) who participated in the Betaseron MS 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 (Interferon beta-1b), 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 as to whether either to discontinue nursing or discontinue the drug, taking into account the importance of drug to the mother.

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

ADVERSE REACTIONS

Experience with Betaseron in patients with MS is limited to a total of 147 patients at the recommended dose of 0.25 mg (8 million IU) every other day or more. Consequently, adverse events that are associated with the use of Betaseron in MS patients at a low incidence may not have been observed in premarketing studies. 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 (85%) and injection site necrosis (5%) occurred after administration of Betaseron. Inflammation, pain, hypersensitivity, necrosis, and non-specific reactions were significantly associated ($p < 0.05$) with the 0.25 mg (8 million IU) Betaseron-treated group. Only inflammation, pain, and necrosis were reported as severe events. The incidence rate for injection site reactions was calculated over the course of 3 years. This incidence rate decreased over time, with 79% of patients experiencing the event during the first 3 months of treatment compared to 47% during the last 6 months. The median time to the first occurrence of an injection site reaction was 7 days. Patients with injection site reactions reported these events 183.7 days per year. Three patients withdrew from the 0.25 mg (8 million IU) Betaseron-treated group for injection site pain.

Flu-like symptom complex was reported in 76% of the patients treated with 0.25 mg (8 million IU) Betaseron (Interferon beta-1b). A patient was defined as having a flu-like symptom complex if flu-like symptoms or at least two of the following symptoms were concurrently reported: fever, chills, myalgia, malaise, or sweating. Only myalgia, fever, and chills were reported as severe in more than 5% of the patients. The incidence rate for flu-like symptom complex was also calculated over the course of 3 years. The incidence rate of these events decreased over time, with 51% of patients experiencing the event during the first 3 months of treatment compared to 4% during the last 6 months. The median time to the first occurrence of flu-like symptom complex was 3 days and the median duration per patient was 10.4 days per year.

Laboratory abnormalities included absolute neutrophil count less than 1500/mm³ (18%) (no patients had absolute neutrophil counts less than 500/mm³), WBC less than 3000/mm³ (16%), SGPT greater than 5 times baseline value (19%), and total bilirubin greater than 2.5 times baseline value (6%). Three patients were withdrawn from treatment with 0.25 mg (8 million IU) Betaseron for abnormal liver enzymes including one following dose reduction (see **PRECAUTIONS, Laboratory Tests**).

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

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

Additional common adverse clinical and laboratory events associated with the use of Betaseron are listed in the following paragraphs. These events occurred at an incidence of 5% or more in the 124 MS patients treated with 0.25 mg (8 million IU) of Betaseron every other day for periods of up to 3 years in the controlled trial, and at an incidence that was at least twice that observed in the 123 placebo patients. Common adverse clinical and laboratory events associated with the use of Betaseron were: injection site reaction (85%), injection site necrosis (5%), flu-like symptoms (53%), palpitation (8%), hypertension (7%), tachycardia (6%), peripheral vascular disorders (5%), gastrointestinal disorders (6%), absolute neutrophil count < 1500/mm³ (18%), WBC < 3000/mm³ (16%), SGPT > 5 times baseline value (19%), total bilirubin > 2.5 times baseline value (6%), somnolence (6%), dyspnea (8%), laryngitis (6%), menstrual disorder (17%), cystitis (8%), breast pain (7%), pelvic pain (6%), and menorrhagia (6%).

A total of 277 MS patients have been treated with Betaseron in doses ranging from 0.025 mg (0.8 million IU) to 0.5 mg (16 million IU). During the first 3 years of treatment, withdrawals due to clinical adverse events or laboratory abnormalities not mentioned above included: fatigue (2%, 6 patients), cardiac arrhythmia (< 1%, 1 patient), allergic urticarial skin reaction to injections (< 1%, 1 patient), headache (< 1%, 1 patient), unspecified adverse events (< 1%, 1 patient), and "felt sick" (< 1%, 1 patient).

The table that follows enumerates adverse events and laboratory abnormalities that occurred at an incidence of 2% or more among the 124 MS patients treated with 0.25 mg (8 million IU) Betaseron (Interferon beta-1b) every other day for periods of up to 3 years in the controlled trial and at an incidence that was at least 2% more than that observed in the 123 placebo patients. Reported adverse events have been reclassified using the standard COSTART glossary to reduce the total number of terms employed in the table. In the following table, terms so general as to be uninformative, and those events where a drug cause was remote have been excluded.

TABLE 2
Adverse Reactions and Laboratory Abnormalities

Adverse Reaction	Placebo N=123	0.25 mg (8 mIU) N=124
Body as a Whole		
Injection site reaction*	37%	85%
Headache	77%	84%
Fever*	41%	59%
Flu-like symptom complex*	56%	76%
Pain	48%	52%
Asthenia*	35%	49%
Chills*	19%	46%
Abdominal pain	24%	32%
Malaise*	3%	15%
Generalized edema	6%	8%
Pelvic pain	3%	6%
Injection site necrosis*	0%	5%
Cyst	2%	4%
Necrosis	0%	2%
Suicide attempt	0%	2%
Cardiovascular System		
Migraine	7%	12%
Palpitation*	2%	8%
Hypertension	2%	7%
Tachycardia	3%	6%
Peripheral vascular disorder	2%	5%
Hemorrhage	1%	3%
Digestive System		
Diarrhea	29%	35%
Constipation	18%	24%
Vomiting	19%	21%
Gastrointestinal disorder	3%	6%
Endocrine System		
Goiter	0%	2%
Hemic and Lymphatic System		
Lymphocytes less than 1500/mm³	67%	82%
ANC < 1500/mm³*	5%	18%
WBC < 3000/mm³*	5%	16%
Lymphadenopathy	11%	14%
Metabolic and Nutritional Disorders		
SGPT > 5 times baseline*	6%	19%
Glucose < 55 mg/dL	13%	15%
Total bilirubin > 2.5 times baseline	2%	6%
Urine protein > 1+	3%	5%
SGOT > 5 times baseline*	0%	4%
Weight gain	0%	4%
Weight loss	2%	4%
Musculoskeletal System		
Myalgia*	28%	44%
Myasthenia	10%	13%
Nervous System		
Dizziness	28%	35%
Hypertonia	24%	26%
Anxiety	13%	15%
Nervousness	5%	8%
Somnolence	3%	6%
Confusion	2%	4%
Speech disorder	1%	3%
Convulsion	0%	2%
Hyperkinesia	0%	2%
Amnesia	0%	2%
Respiratory System		
Sinusitis	26%	36%
Dyspnea*	2%	8%
Laryngitis	2%	6%

TABLE 2 (continued)
Adverse Reactions and Laboratory Abnormalities

Adverse Reaction	Placebo N=123	0.25 mg (8 mIU) N=124
Skin and Appendages		
Sweating*	11%	23%
Alopecia	2%	4%
Special Senses		
Conjunctivitis	10%	12%
Abnormal vision	4%	7%
Urogenital System		
Dysmenorrhea	11%	18%
Menstrual disorder*	8%	17%
Metrorrhagia	8%	15%
Cystitis	4%	8%
Breast pain	3%	7%
Menorrhagia	3%	6%
Urinary urgency	2%	4%
Fibrocystic breast	1%	3%
Breast neoplasm	0%	2%

*Significantly associated with Betaseron treatment.

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

Other events observed during premarketing evaluation of various doses of Betaseron (Interferon beta-1b) in 1440 patients are listed in the paragraph that follows. Because most of the events were observed in open and uncontrolled studies, the role of Betaseron in their causation cannot be reliably determined.

Body as a Whole: abscess, adenoma, anaphylactoid reaction, ascites, cellulitis, hernia, hydrocephalus, hypothermia, infection, peritonitis, photosensitivity, sarcoma, sepsis, and shock; **Cardiovascular System:** angina pectoris, arrhythmia, atrial fibrillation, cardiomegaly, cardiac arrest, cerebral hemorrhage, cerebral ischemia, endocarditis, heart failure, hypotension, myocardial infarct, pericardial effusion, postural hypotension, pulmonary embolus, spider angioma, subarachnoid hemorrhage, syncope, thrombophlebitis, thrombosis, varicose vein, vasospasm, venous pressure increased, ventricular extrasystoles, and ventricular fibrillation; **Digestive System:** aphthous stomatitis, cardiospasm, cheilitis, cholecystitis, cholelithiasis, duodenal ulcer, dry mouth, enteritis, esophagitis, fecal impaction, fecal incontinence, flatulence, gastritis, gastrointestinal hemorrhage, gingivitis, glossitis, hematemesis, hepatic neoplasia, hepatitis, hepatomegaly, ileus, increased salivation, intestinal obstruction, melena, nausea, oral leukoplakia, oral moniliasis, pancreatitis, periodontal abscess, proctitis, rectal hemorrhage, salivary gland enlargement, stomach ulcer, and tenesmus; **Endocrine System:** Cushing's Syndrome, diabetes insipidus, diabetes mellitus, hypothyroidism, and inappropriate ADH; **Hemic and Lymphatic System:** chronic lymphocytic leukemia, hemoglobin less than 9.4 g/100 mL, petechia, platelets less than 75,000/mm³, and splenomegaly; **Metabolic and Nutritional Disorders:** alcohol intolerance, alkaline phosphatase greater than 5 times baseline value, BUN greater than 40 mg/dL, calcium greater than 11.5 mg/dL, cyanosis, edema, glucose greater than 160 mg/dL, glycosuria, hypoglycemic reaction, hypoxia, ketosis, and thirst; **Musculoskeletal System:** arthritis, arthrosis, bursitis, leg cramps, muscle atrophy, myopathy, myositis, ptosis, and tenosynovitis; **Nervous System:** abnormal gait, acute brain syndrome, agitation, apathy, aphasia, ataxia, brain edema, chronic brain syndrome, coma, delirium, delusions, dementia, depersonalization, diplopia, dystonia, encephalopathy, euphoria, facial paralysis, foot drop, hallucinations, hemiplegia, hypalgesia, hyperesthesia, incoordination, intracranial hypertension, libido decreased, manic reaction, meningitis, neuralgia, neuropathy, neurosis, nystagmus, oculogyric crisis, ophthalmoplegia, papilledema, paralysis, paranoid reaction, psychosis, reflexes decreased, stupor, subdural hematoma, torticollis, tremor, and urinary retention; **Respiratory System:** apnea, asthma, atelectasis, carcinoma of lung, hemoptysis, hiccup, hyperventilation, hypoventilation, interstitial pneumonia, lung edema, pleural effusion, pneumonia, and pneumothorax; **Skin and Appendages:** contact dermatitis, erythema nodosum, exfoliative dermatitis, furunculosis, hirsutism, leukoderma, lichenoid dermatitis, maculopapular rash, psoriasis, seborrhea, skin benign neoplasm, skin carcinoma, skin hypertrophy, skin necrosis, skin ulcer, urticaria, and vesiculobullous rash; **Special Senses:** blepharitis, blindness, deafness, dry eyes, ear pain, iritis, keratoconjunctivitis, mydriasis, otitis externa, otitis media, parosmia, photophobia, retinitis, taste loss, taste perversion, and visual field defect; **Urogenital System:** anuria, balanitis, breast engorgement, cervicitis, epididymitis, gynecomastia, hematuria, impotence, kidney calculus, kidney failure, kidney tubular disorder, leukorrhea, nephritis, nocturia, oliguria, polyuria, salpingitis, urethritis, urinary incontinence, uterine fibroids enlarged, uterine neoplasm, and vaginal hemorrhage.

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.

DOSAGE AND ADMINISTRATION

The recommended dose of Betaseron (Interferon beta-1b) for the treatment of ambulatory relapsing-remitting MS is 0.25 mg (8 million IU) injected subcutaneously every other day. Limited data regarding the activity of a lower dose are presented above (see **CLINICAL PHARMACOLOGY, Clinical Trials**).

Evidence of efficacy beyond 2 years is not known since the primary evidence of efficacy derives from a 2-year, double-blind, placebo-controlled clinical trial (see **CLINICAL PHARMACOLOGY, Clinical Trials**). Safety data are not available beyond the third year. Patients were discontinued from this trial due to unremitting disease progression of 6 months or greater.

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

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

Stability: The reconstituted product contains no preservative. Before and after reconstitution with diluent, store at 2° to 8°C (36° to 46°F). Product should be used within 3 hours of reconstitution.

HOW SUPPLIED

Betaseron is supplied as a lyophilized powder containing 0.3 mg (9.6 million IU) of Interferon beta-1b, 15 mg Albumin Human USP, and 15 mg dextrose, USP. Drug is packaged in a clear glass, single-use vial (5 mL capacity); a separate vial containing 2 mL of diluent (Sodium Chloride, 0.54% solution) is included for each vial of drug. Store under refrigeration, between 2° to 8°C (36° to 46°F).

NDC 50419-521-01 0.3 mg (9.6 mIU)/vial
NDC 50419-521-05 5 vials, 0.3 mg (9.6 mIU)/vial

Caution: Federal law prohibits dispensing without prescription.

REFERENCES

1. Ruzicka FJ, et al. J Biol Chem, 1987; 262: 16142-16149.
2. Uze G, et al. Cell, 1990; 60: 225-234.
3. DeMaeyer E, et al. In: Interferons and other regulatory cytokines, NY, Wiley 1988.
4. Colby CB, et al. J Immunol 1984; 133: 3091-3095.
5. Pestka S, et al. Annu Rev Biochem 1987; 56: 727-777.
6. Lengyel P. Annu Rev Biochem 1982; 51: 251-282.
7. Witt PL, et al. J Interferon Res 1990; 10: 393-402.
8. Schiller JH, et al. J Biol Resp Mod 1990; 9: 377-386.
9. Rosenblum MG, et al. J Interferon Res 1990; 10: 141-151.
10. Carlin JM, et al. J Immuno 1987; 130(7): 2414-2418.
11. Witt PI, et al. J Immunotherapy 1993; 13: 191-200.
12. Goldstein D, et al. J Natl Cancer Inst 1989; 81: 1061-1068.
13. Poser CM, et al. Ann Neurol 1983; 13(3): 227-231.
14. Blaschke TF, et al. Clinical Research 1985; 33(1): 19A.

Manufactured by:
CHIRON Corporation
Emeryville, CA 94608

U.S. License No. 1106

Distributed by:
BERLEX Laboratories
Richmond, CA 94804

©1993 Berlex Laboratories

Revised July 28, 1993
Part Number L-1147
Printed in U.S.A.

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