PRODUCT MONOGRAPH

PrBETASERON®

Interferon beta-1b

Lyophilized powder for subcutaneous injection

0.3 mg/vial

Immunomodulator

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PrBETASERON®

Interferon beta-1b

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	Lyophilized powder: 0.3 mg of interferon beta-1b/single-use vial Diluent: 1.2 mL of sodium chloride 0.54% solution/single-use syringe	Albumin human, USP For a complete listing see ***DOSAGE FORMS, COMPOSITION AND PACKAGING*** section.

DESCRIPTION

BETASERON® (interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques and formulated for use by injection.

INDICATIONS AND CLINICAL USE

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

- the treatment of patients with a single demyelinating event accompanied by at least two clinically silent lesions typical of multiple sclerosis (MS) on magnetic resonance imaging, to delay progression to definite MS. Before initiating treatment with BETASERON, alternate diagnoses should first be excluded.
- the reduction of the frequency of clinical exacerbations in ambulatory patients with relapsing-remitting multiple sclerosis. Relapsing-remitting MS is characterized by recurrent attacks of neurologic dysfunction followed by complete or incomplete recovery.
- the slowing of progression in disability and the reduction of the frequency of clinical exacerbations in patients with secondary-progressive multiple sclerosis.

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

Pediatrics (<18 years of age):

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

CONTRAINDICATIONS

- Patients with a history of hypersensitivity to natural or recombinant interferon beta, albumin human or to any other ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Pregnant women.
- Patients with decompensated liver disease (see **WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

General

Patients should be informed of the most common adverse reactions associated with interferon beta, including flu-like syndrome (see **ADVERSE REACTIONS**). These symptoms tend to be most prominent at the initiation of therapy and may decrease in frequency and severity with continued treatment.

Psychiatric

In the RR-MS clinical trial, 1 suicide and 4 attempted suicides were observed among 372 study patients during a 3-year period. All 5 patients received BETASERON (3 in the 0.05 mg [1.6 MIU] group and 2 in the 0.25 mg [8.0 MIU] group). There were no attempted suicides in patients on study who did not receive BETASERON. In the SP-MS study there were 5 suicide attempts in the placebo group and 3 in the BETASERON group including 1 patient in each group who committed suicide.

Suicidal ideation is known to occur with increasing frequency in the MS population. Patients treated with BETASERON should be informed that depression and suicidal ideation may be a side effect of the treatment and should report these symptoms immediately to the prescribing physician. Patients exhibiting depression should be monitored closely and cessation of therapy should be considered.

Cardiovascular

Patients with pre-existing significant cardiac disease such as congestive heart failure, coronary artery disease, or arrhythmias should be monitored closely for worsening of their clinical conditions. While there is no evidence of a direct cardiotoxic potential of BETASERON, flu-like symptoms, which are commonly associated with beta interferons, exert cardiac stress through fever, chills, and tachycardia. This may aggravate cardiac symptoms in patients with pre-existing significant cardiac disease.

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

Dependence/Tolerance

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

Endocrine and Metabolism

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

Exercise caution when administering BETASERON to patients with pre-existing thyroid disorders. Patients treated with BETASERON should be carefully monitored for evidence of thyroid dysfunction (most often presenting as hypothyroidism or hyperthyroidism), and development of thyroid auto-antibodies. Thyroid testing is recommended at baseline and if abnormal, every 6 to 12 months following initiation of therapy. If normal, routing testing is not required but should be performed if clinical findings of thyroid dysfunction appear.

Hepatic/Biliary/Pancreas

Asymptomatic elevations of serum transaminases, in most cases mild and transient, occurred very commonly in patients treated with BETASERON during clinical trials. It is recommended that liver function testing (eg, ASAT [SGOT], ALAT [SGPT], and γ-GT) occur at baseline and then every month for the first 6 months of treatment and at 6-month intervals thereafter. Dose reduction or discontinuation of therapy should be considered if alanine aminotransferase (ALAT) levels increase 5 times above the upper limit of normal.

Postmarket cases of serious hepatic injury, including autoimmune hepatitis, hepatitis, and hepatic failure, have been reported with interferon beta treatment for multiple sclerosis. The most severe events often occurred in patients exposed to other drugs or substances known to be associated with hepatotoxicity or in the presence of comorbid medical conditions (eg, metastasizing malignant disease, severe injection and sepsis, alcohol abuse).

Interferon beta therapy should be initiated with caution in patients with a history of significant liver disease or alcohol abuse and in patients with clinical evidence of acute liver disease.

Caution must be exercised when prescribing drugs with documented hepatotoxicity to patients on interferon beta therapy for multiple sclerosis. Treatment with BETASERON should be stopped if icterus or other clinical symptoms of hepatic dysfunction appear.

Pancreatitis has been observed with BETASERON use, often associated with hypertriglyceridemia.

Pancreatitis should be treated as per appropriate clinical management and in accordance with clinical practice guidelines.

Hypersensitivity

Serious hypersensitivity reactions (severe acute reactions such as bronchospasm, anaphylaxis and urticaria) may occur. Severe reactions should be treated, and BETASERON should be discontinued.

Immune

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

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Serum samples in controlled clinical trials were collected every 3 months for monitoring of development of antibodies to BETASERON.

In the different controlled clinical trials of relapsing-remitting MS (RRMS) and secondary-progressive MS (SPMS) patients, between 23% and 41% of the patients developed serum interferon beta-1b neutralizing activity confirmed by at least two consecutive positive titers; of these patients, between 43% and 55% converted to a stable antibody negative status (based on 2 consecutive negative titers) during the subsequent observational period of the respective study (see **PART II: SCIENTIFIC INFORMATION**: **CLINICAL TRIALS**, **1. Relapsing-Remitting MS** and **2. Secondary-Progressive MS** subsections).

In these studies, the development of neutralizing activity was associated with a reduction in clinical efficacy only with regard to relapse activity. Some analyses suggest that this effect might be larger in patients with higher titre levels of neutralizing activity.

In the study of patients with a single clinical event suggestive of multiple sclerosis, neutralizing antibody titres were measured every 6 months. Neutralizing activity (titre ≥ 20 NU/mL) was observed at least once in 32% (89) of the patients who were initially randomized to BETASERON; of these, 60% (53) returned to negative status based on the last available assessment within the 5-year period. Over this period, the development of neutralizing activity was associated with a significant increase in newly active lesions and T2 lesion volume on magnetic resonance imaging.

It has been demonstrated in vitro that BETASERON cross reacts with natural interferon beta. However, this has not been investigated in vivo and its clinical significance is uncertain.

There are limited, inconclusive data on patients who have developed neutralizing activity and have stopped BETASERON therapy.

The decision to continue or discontinue treatment should be based on all aspects of the patient's disease status rather than on neutralizing activity status.

Nephrotic Syndrome

Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon-beta. Periodic monitoring of early signs or symptoms, e.g. edema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with Betaseron should be considered.

Neurologic

Cases of seizures have been reported with interferon beta therapy. BETASERON should be administered with caution to patients with a history of seizure disorders.

This product contains human albumin and hence carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeld-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

The effect of BETASERON on the ability to drive and use machinery has not been investigated. Central nervous system-related adverse events associated with the use of BETASERON might influence the ability to drive and use machines in susceptible patients.

Sexual Function/Reproduction

No long term studies have been conducted. Studies in female rhesus monkeys with normal menstrual cycles, at doses up to 0.33 mg (10.7 MIU)/kg/day (equivalent to 32 times the recommended human dose based on body surface area comparison), showed no apparent adverse effects on the menstrual cycle or on associated hormonal profiles (progesterone and estradiol) when administered over 3 consecutive menstrual cycles. It is not known if animal doses can be extrapolated to human doses. The effects of BETASERON on women with normal menstrual cycles are not known.

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA), manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur after several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. If clinical features of TMA are observed, testing of blood platelet levels, serum lactate dehydrogenase (LDH), schistocytes (erythrocyte fragmentation) on a blood film with a negative Coombs test and renal function is recommended. Prompt treatment of TTP/HUS is required and immediate discontinuation of treatment with BETASERON is recommended.

Special Populations

Pregnant Women: BETASERON should not be administered to pregnant or lactating women. There are no adequate well-controlled studies in pregnant women. Treatment with BETASERON may be associated with an increased risk of spontaneous abortion. Initiation of treatment is contraindicated during pregnancy. In the event of a pregnancy, please contact Bayer Medical Information at 1-800-265-7382.

BETASERON was not teratogenic at doses up to 0.42 mg (13.3 MIU)/kg/day in rhesus monkeys, but demonstrated dose-related abortifacient activity when administered at doses ranging from 0.028 mg (0.89 MIU)/kg/day (2.8 times the recommended human dose based on body surface area comparison) to 0.42 mg (13.3 MIU)/kg/day (40 times the recommended human dose based on body surface area comparison). It is not known if animal doses can be extrapolated to human doses. Lower doses were not studied in monkeys. 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.

Women of Childbearing Age: Women of childbearing potential who are receiving BETASERON should be advised to take reliable contraceptive measures. It is not known if interferon alters the efficacy of oral contraceptives. Patients who could become pregnant and who do become pregnant should be informed of the potential hazards of interferons to the fetus, including an increased risk of early miscarriage. Discontinuation of therapy should be recommended for patients in whom pregnancy is confirmed, or for patients who are planning to become pregnant (see **CONTRAINDICATIONS** and also **WARNINGS AND PRECAUTIONS**: **Information to be Provided to the Patient**).

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

Pediatrics (< 18 years of age): Safety and efficacy in children under 18 years of age have not been established.

Information to be Provided to the Patient

Patients should be informed of the potential risk of liver injury with interferon beta therapy, and of the requirement for frequent laboratory testing for liver function (see **Monitoring and Laboratory Tests**). Patients should be informed of the symptoms suggesting liver dysfunction, such as jaundice, malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, and pruritus, and advised to consult their physician immediately if such symptoms arise.

Patients should be instructed in injection techniques to assure the safe self-administration of BETASERON (see below and **PART III: CONSUMER INFORMATION**).

Instruction on self-injection technique and procedures: It is recommended that the first injection be administered by, or under the direct supervision of, a physician. Appropriate instructions for reconstitution of BETASERON and self-injection using aseptic techniques should be given to the patient. A careful review of **PART III: CONSUMER INFORMATION** is also recommended.

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

Overall, 80% of patients in the 2 controlled clinical trials reported injection site reactions at 1 or more times during therapy. Postmarketing experience has been consistent with this finding, with infrequent reports of injection site necrosis.

The onset of injection site necrosis usually appears early in therapy with most cases reported to have occurred in the first 2 to 3 months of therapy. The number of sites where necrosis has been observed is variable.

Rarely has the area of necrosis extended to subcutaneous fat or fascia. Response to treatment of injection site necrosis with antibiotics and/or steroids has been variable. In some of these patients elective debridement and, less frequently, skin grafting took place to facilitate healing, which could take from 3 to 6 months.

If the patient has multiple lesions, BETASERON should be discontinued until healing has occurred. Patients with single lesions may continue on BETASERON provided the necrosis is not too extensive, as some patients have experienced healing of injection site necrosis while on BETASERON.

The nature and severity of all reported reactions should be carefully assessed.

To minimize the risk of injection site necrosis, patients should be advised to use an aseptic injection technique and rotate the injection sites with each dose. Patient understanding and use of aseptic self-injection technique and procedures should be periodically re-evaluated.

Flu-like symptoms are not uncommon following initiation of therapy with BETASERON. In the controlled MS clinical trials, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) were permitted for relief of fever or myalgia.

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

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

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

Patients should be advised about the abortifacient potential of BETASERON (see **WARNINGS AND PRECAUTIONS**, **Special Populations – Pregnant Women**).

Monitoring and Laboratory Tests

The following laboratory tests are recommended prior to initiating BETASERON therapy and at periodic intervals thereafter: thyroid function test, hemoglobin, complete and differential white blood cell counts, platelet counts and blood chemistries including liver function tests. It is recommended that liver function testing occur at baseline every month for the first 6 months of treatment and at 6-month intervals thereafter. Dose reduction or discontinuation of therapy should be considered if alanine aminotransferase (ALAT) levels increase 5 times above the upper limit of normal. A pregnancy test, chest roentgenogram and ECG should also be performed prior to initiating BETASERON therapy. Patients with anemia, thrombocytopenia, and leukopenia (alone or in any combination) may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

In the controlled MS trials, patients were monitored every 3 months. The study protocol stipulated that BETASERON therapy be discontinued in the event the absolute neutrophil count fell below 750/mm^3. When the absolute neutrophil count had returned to a value greater than 750/mm^3, therapy could be restarted at a 50% reduced dose. No patients were withdrawn or dose-reduced for neutropenia or lymphopenia. Similarly, if ASAT/ALAT (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, hepatic enzyme abnormalities returned to normal following discontinuation of therapy. When measurements had decreased to below these levels, therapy could be restarted at a 50% dose reduction, if clinically appropriate. Dose was reduced in 2 patients due to increased liver enzymes; 1 continued on treatment and 1 was ultimately withdrawn.

In the placebo-controlled study conducted in patients with a single clinical event suggestive of MS, 5 BETASERON patients (1.7%) were withdrawn due to increased hepatic enzymes (ASAT/ALAT), 2 of them after a dose reduction.

ADVERSE REACTIONS

Adverse Reaction Overview

Adverse event data were collected from 3 phase III randomized, multicenter, double-blind, placebo-controlled studies in patients with multiple sclerosis (1 study evaluated BETASERON in relapsing-remitting MS (RRMS) patients; 1 study assessed BETASERON in secondary-progressive MS (SPMS) patients; and 1 study evaluated BETASERON in patients with a single clinical event suggestive of MS). The most frequently observed adverse reactions were a flu-like symptom complex (fever, chills, arthralgia, malaise, sweating, headache, or myalgia) and injection site reactions (eg, redness, swelling, discoloration, inflammation, pain,

hypersensitivity, necrosis, and nonspecific reactions). The incidence rate of these symptoms decreased over time.

Flu-like symptoms may be reduced by administration of acetaminophen or NSAIDs. Dose titration was used at the start of treatment in the clinically isolated syndrome and secondary-progressive MS studies in order to increase the tolerability of BETASERON (see **DOSAGE AND ADMINISTRATION**).

In the 3 placebo-controlled trials, the most serious adverse reactions with BETASERON were depression, suicidal ideation, and injection site necrosis. Anaphylaxis and other allergic reactions have been reported in patients using BETASERON (see **WARNINGS AND PRECAUTIONS**). The most commonly reported adverse reactions were lymphopenia (lymphocytes < 1500/mm^3), injection site reaction, flu-like symptom complex, asthenia, headache, and pain.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

ADR Data for the Individual Pivotal Trials

1. Relapsing-Remitting MS

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

Flu-like symptom complex was reported in 76% of the patients treated with 0.25 mg (8 MIU) BETASERON. A patient was defined as having a flu-like symptom complex if flu-like syndrome or at least 2 of the following symptoms were concurrently reported: fever, chills, myalgia, malaise, or sweating. Only myalgia, fever, and chills were reported as severe in more than 5% of the patients. The incidence rate for flu-like symptom complex was also calculated over the course of 3 years. The incidence rate of these events decreased over time, with 60% of patients experiencing the event during the first 3 months of treatment compared to 10% during the last 6 months. The median time to the first occurrence of flu-like symptom complex was 3.5 days and the median duration per patient was 7.5 days per year.

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

Mental disorders such as depression, anxiety, emotional lability, depersonalization, suicide attempts, and confusion were observed in this study. Two patients withdrew for confusion. One suicide and 4 attempted suicides were also reported. It is not known whether these symptoms may be related to the underlying neurological basis of MS, to BETASERON treatment, or to a combination of both. Some similar symptoms have been noted in patients receiving interferon alpha and both interferons are thought to act through the same receptor. Patients who experience these symptoms should be monitored closely and cessation of therapy should be considered.

Additional common clinical and laboratory adverse events associated with the use of BETASERON are listed in the following paragraphs. These events occurred at an incidence of 5% or more in the 124 MS patients treated with 0.25 mg (8 MIU) BETASERON every other day for periods of up to 3 years in the controlled trial, and at an incidence that was at least twice that observed in the 123 placebo patients. Common adverse clinical and laboratory events associated with the use of BETASERON were:

- injection site reaction (85%)
- lymphocyte count < 1500/mm^3 (82%)
- ALT (SGPT) > 5 times baseline value (19%)
- absolute neutrophil count < 1500/mm^3 (18%)
- menstrual disorder (17%)
- WBC < 3000/mm^3 (16%)
- palpitation (8%)
- dyspnea (8%)
- cystitis (8%)
- hypertension (7%)
- breast pain (7%)
- tachycardia (6%)
- gastrointestinal disorders (6%)
- total bilirubin > 2.5 times baseline value (6%)
- somnolence (6%)
- laryngitis (6%)
- pelvic pain (6%)
- menorrhagia (6%)
- injection site necrosis (5%)
- peripheral vascular disorders (5%)

A total of 277 MS patients have been treated with BETASERON in doses ranging from 0.025 mg (0.8 MIU) to 0.5 mg (16 MIU). During the first 3 years of treatment, withdrawals due to clinical adverse events or laboratory abnormalities not mentioned above included:

- fatigue (2%, 6 patients)
- cardiac arrhythmia (< 1%, 1 patient)
- allergic urticarial skin reaction to injections (< 1%, 1 patient)
- headache (< 1%, 1 patient)
- unspecified adverse events (< 1%, 1 patient)
- "felt sick" (< 1%, 1 patient)

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

Table 1: Incidence of Adverse Events and Laboratory Abnormalities (Regardless of Causality) ≥ 2% and > 2% Difference (BETASERON vs Placebo) in the Relapsing-Remitting MS Study

System Organ Class Adverse Event	BETASERON 0.25 mg (8 MIU) n=124	Placebo n=123
Infections and Infestations		
Sinusitis	36%	26%
Laryngitis	6%	2%
Neoplasms, Benign, Malignant and Unspecified		
Cyst	4%	2%
Breast neoplasm	2%	0%
Blood and Lymphatic System Disorders		
Lymphadenopathy	14%	11%
Endocrine Disorders		
Goiter	2%	0%
Metabolism and Nutrition Disorders		
Glucose < 55 mg/dL	15%	13%
Weight gain	4%	0%
Weight loss	4%	2%

Table 1: Incidence of Adverse Events and Laboratory Abnormalities (Regardless of Causality) ≥ 2% and > 2% Difference (BETASERON vs Placebo) in the Relapsing-Remitting MS Study

System Organ Class Adverse Event	BETASERON 0.25 mg (8 MIU) n=124	Placebo n=123
Psychiatric Disorders		
Depression	25%	24%
Anxiety	15%	13%
Nervousness	8%	5%
Suicide attempt	2%	0%
Nervous System Disorders		
Dizziness	35%	28%
Hypertonia	26%	24%
Myasthenia	13%	10%
Migraine	12%	7%
Somnolence	6%	3%
Confusion	4%	2%
Speech disorder	3%	1%
Convulsion	2%	0%
Hyperkinesia	2%	0%
Amnesia	2%	0%
Eye Disorders		
Conjunctivitis	12%	10%
Abnormal vision	7%	4%
Cardiac Disorders		
Palpitation[a]	8%	2%
Tachycardia	6%	3%
Vascular Disorders		
Hypertension	7%	2%
Peripheral vascular disorder	5%	2%
Hemorrhage	3%	1%
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea[a]	8%	2%

Table 1: Incidence of Adverse Events and Laboratory Abnormalities (Regardless of Causality) ≥ 2% and > 2% Difference (BETASERON vs Placebo) in the Relapsing-Remitting MS Study

System Organ Class Adverse Event	BETASERON 0.25 mg (8 MIU) n=124	Placebo n=123
Gastrointestinal Disorders		
Diarrhea	35%	29%
Abdominal pain	32%	24%
Constipation	24%	18%
Vomiting	21%	19%
Gastrointestinal disorder	6%	3%
Skin and Subcutaneous Tissue Disorders		
Sweating[a]	23%	11%
Alopecia	4%	2%
Necrosis	2%	0%
Musculoskeletal and Connective Tissue Disorders		
Myalgia[a]	44%	28%
Pelvic pain	6%	3%
Renal and Urinary Disorders		
Cystitis	8%	4%
Urinary urgency	4%	2%
Reproductive System and Breast Disorders		
Dysmenorrhea	18%	11%
Menstrual disorder[a]	17%	8%
Metrorrhagia	15%	8%
Breast pain	7%	3%
Menorrhagia	6%	3%
Fibrocystic breast	3%	1%
General Disorders and Administration Site Conditions		
Injection site reaction[a]	85%	37%
Headache	84%	77%
Flu-like symptom complex[a]	76%	56%
Fever[a]	59%	41%
Pain	52%	48%

Table 1: Incidence of Adverse Events and Laboratory Abnormalities (Regardless of Causality) ≥ 2% and > 2% Difference (BETASERON vs Placebo) in the Relapsing-Remitting MS Study

System Organ Class Adverse Event	BETASERON 0.25 mg (8 MIU) n=124	Placebo n=123
Asthenia[a]	49%	35%
Chills[a]	46%	19%
Malaise[a]	15%	3%
Generalized edema	8%	6%
Injection site necrosis[a]	5%	0%
Investigations		
Lymphocytes < 1500/mm^3	82%	67%
ALAT (SGPT) > 5 times baseline[a]	19%	6%
ANC < 1500/mm^3[a]	18%	6%
WBC < 3000/mm^3[a]	16%	5%
Total bilirubin > 2.5 times baseline	6%	2%
Urine protein > 1+	5%	3%
AST (SGOT) > 5 times baseline[a]	4%	0%

a Significantly associated with BETASERON treatment ($P < 0.05$)

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

2. Secondary-Progressive MS

The incidence of adverse events that occurred in at least 2% of patients treated with 8 MIU BETASERON or placebo for up to 3 years, or where an adverse event was reported at a frequency at least 2% higher with BETASERON than that observed for placebo-treated patients in the secondary-progressive study, is presented in Table 2. Adverse events significantly associated with BETASERON compared to placebo ($P < 0.05$) are also indicated in Table 2.

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

System Organ Class Adverse Event	BETASERON 0.25 mg (8 MIU) n=360	Placebo n=358
Infections and Infestations		
Rhinitis	28%	32%
Urinary tract infection	22%	25%
Pharyngitis	16%	20%
Infection	13%	11%
Bronchitis	9%	12%
Sinusitis	6%	6%
Pneumonia	5%	5%
Abscess[a]	4%	2%
Upper respiratory tract infection	3%	2%
Herpes simplex	3%	2%
Herpes zoster	1%	2%
Blood and Lymphatic System Disorders		
Leukopenia[a]	10%	5%
Lymphadenopathy	3%	1%
Anemia	2%	5%
Ecchymosis	1%	2%
Immune System Disorders		
Allergic reaction	2%	3%
Metabolism and Nutrition Disorders		
Weight loss	2%	3%
Hypercholesterolemia	1%	2%
Psychiatric Disorders		
Depression	27%	31%
Insomnia	12%	8%
Emotional lability	8%	11%
Anxiety	6%	5%
Nervousness	4%	3%

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

System Organ Class Adverse Event	BETASERON 0.25 mg (8 MIU) n=360	Placebo n=358
Nervous System Disorders		
Headache	47%	41%
Hypertonia[a]	41%	31%
Myasthenia	39%	40%
Neuropathy	38%	41%
Paresthesia	35%	39%
Abnormal gait	34%	34%
Ataxia	19%	23%
Dizziness	14%	14%
Incoordination	11%	13%
Vertigo	8%	12%
Paralysis	8%	10%
Somnolence	8%	8%
Tremor	6%	9%
Sleep disorder	6%	5%
Hypesthesia	6%	4%
Neuralgia	5%	7%
Movement disorder	5%	6%
Migraine	4%	3%
Spastic paralysis	3%	1%
Speech disorder	2%	5%
Dysarthria	2%	4%
Convulsion	2%	2%
Hyperesthesia	2%	2%
Optic neuritis	2%	2%
Amnesia	1%	3%
Hemiplegia	1%	2%
Thinking abnormal	1%	2%
Myoclonus	0%	2%

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

System Organ Class Adverse Event	BETASERON 0.25 mg (8 MIU) n=360	Placebo n=358
Eye Disorders		
Abnormal vision	11%	15%
Amblyopia	7%	10%
Diplopia	7%	9%
Eye pain	4%	5%
Eye disorder	3%	2%
Conjunctivitis	2%	3%
Ear and Labyrinth Disorders		
Otitis media	2%	3%
Deafness	1%	3%
Ear disorder	1%	2%
Tinnitus	1%	2%
Cardiac Disorders		
Palpitation	2%	3%
Syncope	2%	3%
Tachycardia	2%	1%
Vascular Disorders		
Vasodilatation	6%	4%
Peripheral vascular disorder	5%	5%
Hypertension[a]	4%	2%
Hypotension	2%	4%
Hemorrhage	2%	2%
Respiratory, Thoracic and Mediastinal Disorders		
Cough increased	5%	10%
Dyspnea	3%	2%
Sore throat	2%	1%
Asthma	1%	2%
Thorax pain	1%	2%
Voice alteration	1%	2%

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

System Organ Class Adverse Event	BETASERON 0.25 mg (8 MIU) n=360	Placebo n=358
Gastrointestinal Disorders		
Nausea	13%	13%
Constipation	12%	12%
Abdominal pain[a]	11%	6%
Diarrhea	7%	10%
Gastroenteritis	6%	5%
Vomiting	4%	6%
Dysphagia	4%	5%
Gastrointestinal disorder	4%	5%
Tooth disorder	4%	4%
Dyspepsia	4%	4%
Anorexia	4%	2%
Flatulence	3%	1%
Fecal incontinence	2%	3%
Gastritis	2%	2%
Gastrointestinal pain	2%	0%
Gingivitis	2%	0%
Dry mouth	1%	2%
Colitis	0%	2%
Skin and Subcutaneous Tissue Disorders		
Rash[a]	20%	12%
Sweating increased	6%	6%
Pruritus	6%	6%
Skin disorder	4%	4%
Eczema	2%	4%
Alopecia	2%	2%
Acne	2%	2%
Dry skin	1%	3%
Subcutaneous hematoma	1%	3%
Seborrhea	1%	2%

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

System Organ Class Adverse Event	BETASERON 0.25 mg (8 MIU) n=360	Placebo n=358
Musculoskeletal and Connective Tissue Disorders		
Back pain	26%	24%
Myalgia[a]	23%	9%
Arthralgia	20%	20%
Pain in extremity	14%	12%
Neck pain	5%	6%
Chest pain	5%	4%
Bone fracture (not spontaneous)	3%	5%
Muscle cramps	3%	3%
Spontaneous bone fracture	3%	3%
Arthritis	2%	1%
Joint disorder	2%	1%
Renal and Urinary Disorders		
Urinary incontinence	8%	15%
Urinary urgency	8%	7%
Urinary tract disorder	7%	10%
Cystitis	7%	9%
Increased urinary frequency	6%	5%
Urinary retention	4%	6%
Dysuria	2%	2%
Nocturia	2%	1%
Pyelonephritis	2%	0%
Kidney pain	0%	2%
Reproductive System and Breast Disorders		
Metrorrhagia	12%	6%
Menstrual disorder	9%	13%
Impotence	7%	4%
Vaginitis	3%	4%
Amenorrhea	3%	4%
Menopause	2%	4%

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

System Organ Class Adverse Event	BETASERON 0.25 mg (8 MIU) n=360	Placebo n=358
Menorrhagia	2%	4%
Vaginal moniliasis	2%	2%
Prostatic disorder	2%	1%
Breast pain	1%	2%
General Disorders and Administration Site Conditions		
Asthenia	63%	58%
Flu syndrome[a]	61%	40%
Injection site inflammation[a]	48%	4%
Injection site reaction[a]	46%	10%
Fever[a]	40%	13%
Pain	31%	25%
Chills[a]	23%	7%
Injection site pain	9%	5%
Malaise	8%	5%
Peripheral edema	7%	7%
Injection site necrosis[a]	5%	0%
Chills and fever[a]	3%	0%
Injection site hemorrhage	2%	2%
Investigations		
Laboratory test abnormal	3%	1%
Liver function test abnormal	3%	1%
SGPT increased	2%	2%
Injury, Poisoning and Procedural Complications		
Accidental injury	14%	17%

a Significantly associated with BETASERON treatment ($P < 0.05$)

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

3. Single Clinical Event Suggestive of MS

The incidence of all adverse events reported during the two-year study duration that occurred in ≥ 1% of patients treated with 8 MIU BETASERON and with a higher frequency versus the placebo group is presented in Table 3. The most frequent adverse events reported for BETASERON were injection site reaction (48.3%), flu syndrome (44.2%), headache (26.7%), and asthenia (21.6%).

Table 3: Incidence of Adverse Events (Regardless of Causality) ≥ 1% Occurring More Frequently in BETASERON (vs Placebo) Patients With a Single Demyelinating Event Suggestive of MS

System Organ Class Adverse Event (Preferred Term, MedDRA Version 9.0)	BETASERON 0.25 mg (8 MIU) (n=292)	Placebo (n=176)
Infections and Infestations		
Infection	5.8%	3.4%
Herpes simplex	1.4%	1.1%
Tooth abscess	1.0%	0.6%
Herpes zoster	1.0%	0%
Blood and Lymphatic System Disorders		
Leukopenia[a]	18.2%	5.7%
Lymphadenopathy	1.4%	0.6%
Thrombocytopenia	1.4%	0.6%
Immune System Disorders		
Hypersensitivity	4.5%	1.7%
Endocrine Disorders		
Hypothyroidism	1.4%	1.1%
Metabolism and Nutrition Disorders		
Hypoglycemia	1.0%	0%
Psychiatric Disorders		
Insomnia	8.2%	4.0%
Affect lability	4.1%	2.3%
Nervousness	1.4%	1.1%
Nervous System Disorders		
Headache[a]	26.7%	17.0%
Optic neuritis	2.7%	2.3%
Migraine	2.4%	1.7%
Hypertonia	2.1%	1.1%
Visual field defect	1.4%	0%

Table 3: Incidence of Adverse Events (Regardless of Causality) ≥ 1% Occurring More Frequently in BETASERON (vs Placebo) Patients With a Single Demyelinating Event Suggestive of MS

System Organ Class Adverse Event (Preferred Term, MedDRA Version 9.0)	BETASERON 0.25 mg (8 MIU) (n=292)	Placebo (n=176)
Hemiplegia	1.0%	0.6%
Myoclonus	1.0%	0%
Eye Disorders		
Visual disturbance[a]	3.4%	0.6%
Eye pain	3.1%	2.8%
Vision blurred	1.7%	0%
Conjunctivitis	1.4%	1.1%
Diplopia	1.0%	0.6%
Cardiac Disorders		
Palpitations	1.4%	0.6%
Tachycardia	1.4%	0%
Vascular Disorders		
Hypertension	2.1%	0%
Hypotension	1.4%	0%
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2.4%	2.3%
Epistaxis	1.4%	0.6%
Gastrointestinal Disorders		
Vomiting[a]	5.1%	1.1%
Abdominal pain	4.8%	2.8%
Diarrhea	4.1%	1.7%
Tooth disorder	2.4%	1.7%
Gastritis	1.7%	0.6%
Aphthous stomatitis	1.4%	0.6%
Constipation	1.0%	0.6%
Glossodynia	1.0%	0%
Skin and Subcutaneous Tissue Disorders		
Rash[a]	11.0%	2.8%
Hyperhidrosis	2.1%	1.1%
Pruritus	2.1%	1.1%

Table 3: Incidence of Adverse Events (Regardless of Causality) ≥ 1% Occurring More Frequently in BETASERON (vs Placebo) Patients With a Single Demyelinating Event Suggestive of MS

System Organ Class Adverse Event (Preferred Term, MedDRA Version 9.0)	BETASERON 0.25 mg (8 MIU) (n=292)	Placebo (n=176)
Urticaria	2.1%	0.6%
Skin disorder	1.4%	0%
Psoriasis	1.0%	0.6%
Eczema	1.0%	0%
Musculoskeletal and Connective Tissue Disorders		
Back pain	9.9%	6.8%
Pain in extremity	6.2%	3.4%
Arthralgia	5.8%	5.7%
Renal and Urinary Disorders		
Proteinuria	2.7%	1.1%
Urinary incontinence	1.0%	0.6%
Micturition urgency	1.0%	0.6%
Nocturia	1.0%	0%
Reproductive System and Breast Disorders		
Dysmenorrhea[b]	2.4%	0%
Ejaculation disorder[c]	2.4%	0%
Metrorraghia[b]	1.9%	0%
Vaginal candidiasis[b]	1.4%	0%
Impotence[c]	1.2%	0%
General Disorders and Administration Site Conditions		
Injection site reaction[a]	48.3%	8.5%
Influenza-like illness[a]	44.2%	18.2%
Asthenia	21.6%	17.0%
Pyrexia[a]	13.0%	4.5%
Injection site pain	5.8%	2.8%
Chills[a]	5.5%	1.1%
Pain	4.1%	4.0%
Gait disturbance	2.1%	0.6%
Malaise	1.0%	0.6%
Chest pain	1.0%	0%

Table 3: Incidence of Adverse Events (Regardless of Causality) ≥ 1% Occurring More Frequently in BETASERON (vs Placebo) Patients With a Single Demyelinating Event Suggestive of MS

System Organ Class Adverse Event (Preferred Term, MedDRA Version 9.0)	BETASERON 0.25 mg (8 MIU) (n=292)	Placebo (n=176)
Injection site inflammation	1.0%	0%
Injection site necrosis	1.0%	0%
Investigations		
Alanine aminotransferase increased[a]	15.4%	4.5%
Aspartate aminotransferase increased[a]	11.0%	2.8%
Liver function test abnormal[a]	5.5%	1.1%
Laboratory test abnormal	2.1%	1.7%
Gamma-glutamyltransferase increased	1.0%	0.6%
Injury, Poisoning and Procedural Complications		
Injury	5.5%	4.0%
Subcutaneous hematoma	3.4%	2.8%
Post-procedural complication	1.4%	0%

a Significantly associated with BETASERON treatment ($P < 0.05$)
b Incidence in females only (n = 207)
c Incidence in males only (n = 85)

The frequency of some adverse events decreased substantially from the first year to the second year of the study. The proportion of BETASERON-treated patients experiencing flu syndrome was reduced from 42% in the first year to 13% in the second year. Also, injection site reactions occurred less frequently during the second year (30%) than during the first year (46%).

Flu-like symptoms and injection site reactions were observed less frequently than in the other pivotal trials. To increase tolerability of BETASERON, dose titration was performed and NSAIDs were administered at start of therapy. Moreover, an autoinjector was used by the majority of patients throughout the study.

A 3-year and 5-year integrated analysis combined safety data from the 2-year placebo-controlled study and the preplanned follow-up study. The incidence of adverse events reported in ≥ 1% of overall patients is presented in Table 4.

Table 4: Incidence of Adverse Events ≥ 1% of Overall Patients in Integrated 3-Year[b] and 5-Year[c] Analyses

System Organ Class Adverse Event (HARTS 2.3, Except[a])	Benefit 3-Year		Benefit 5-Year	
	Initial BETASERON (n=292)	Initial Placebo (n=176)	Initial BETASERON (n=292)	Initial Placebo (n=176)
Abdomen				
Abdominal pain	6.5%	6.8%	7.5%	8.0%
Back				
Back pain	13.0%	10.2%	17.1%	11.4%
Body as a Whole / General, Function and NEC				
Accidental injury	7.5%	6.3%	9.9%	8.5%
Allergic reaction	6.5%	5.7%	8.2%	6.3%
Asthenia	25.7%	26.7%	30.5%	30.1%
Chills	5.5%	2.8%	5.8%	2.8%
Cyst	1.4%	0.0%	1.4%	1.1%
Fever	15.8%	9.7%	16.4%	10.2%
Flu-like symptom complex[a]	51.4%	47.7%	54.1%	51.7%
Ill-defined experience	1.0%	0.6%	1.0%	0.6%
Infection	7.9%	5.7%	9.9%	6.8%
Laboratory test abnormal	2.4%	2.3%	3.4%	2.3%
Pain	7.9%	5.7%	12.3%	8.5%
Pain in extremity	9.6%	8.0%	11.3%	8.5%
Surgery	7.9%	9.1%	11.0%	11.4%
Unevaluable reaction	1.0%	0.0%	3.8%	5.1%
Body as a Whole / Neck				
Neck pain	2.7%	2.8%	3.8%	5.1%
Cardiovascular System / Cardiac Disorders / Arrhythmias				
Tachycardia	2.1%	1.1%	2.4%	1.1%
Cardiovascular System / Cardiac Disorders / General, Functional and NEC				
Palpitation	1.7%	0.6%	2.1%	0.6%
Cardiovascular System / General and NEC				
Chest pain	1.7%	0.0%	1.4%	0.6%
Cardiovascular System / Vascular Disorders / Arterial and Arteriolar Disorders				
Migraine	4.1%	2.8%	4.8%	4.5%

Table 4: Incidence of Adverse Events ≥ 1% of Overall Patients in Integrated 3-Year[b] and 5-Year[c] Analyses

System Organ Class Adverse Event (HARTS 2.3, Except[a])	Benefit 3-Year		Benefit 5-Year	
	Initial BETASERON (n=292)	Initial Placebo (n=176)	Initial BETASERON (n=292)	Initial Placebo (n=176)
Cardiovascular System / Vascular Disorders / Blood Pressure Disorders				
Hypertension	3.1%	2.3%	4.5%	5.1%
Hypotension	1.7%	0.6%	1.7%	1.1%
Cardiovascular System / Vascular Disorders / Venous and Venular Disorders				
Varicose vein	0.3%	0.0%	1.0%	0.0%
Digestive System / Buccal Cavity				
Aphthous stomatitis	1.7%	0.6%	1.7%	0.6%
Gingivitis	0.7%	1.1%	1.7%	1.1%
Periodontal abscess	1.0%	0.6%	1.0%	1.7%
Tongue pain	1.0%	0.0%	1.0%	0.0%
Tooth caries	0.7%	0.0%	1.7%	0.0%
Tooth disorder	3.1%	5.1%	6.5%	5.1%
Digestive System / Colon				
Colitis	1.0%	1.1%	1.4%	1.1%
Digestive System / Entercolon				
Constipation	1.4%	1.7%	1.7%	2.3%
Diarrhea	6.2%	5.1%	7.2%	5.1%
Digestive System / General, Functional and NEC				
Anorexia	1.0%	0.0%	1.7%	0.0%
Dyspepsia	2.1%	2.3%	2.1%	2.3%
Gastroenteritis	4.8%	6.8%	6.5%	8.0%
Gastrointestinal disorder	2.1%	2.3%	3.4%	3.4%
Nausea	6.5%	5.7%	7.2%	6.3%
Vomiting	6.8%	1.7%	7.9%	4.0%
Digestive System / Liver				
Liver function test abnormal	6.5%	2.8%	7.2%	3.4%
Digestive System / Oropharynx				
Sore throat	5.1%	6.3%	6.5%	6.3%
Digestive System / Stomach				
Gastritis	2.1%	2.3%	3.1%	2.8%

Table 4: Incidence of Adverse Events ≥ 1% of Overall Patients in Integrated 3-Year[b] and 5-Year[c] Analyses

System Organ Class Adverse Event (HARTS 2.3, Except[a])	Benefit 3-Year		Benefit 5-Year	
	Initial BETASERON (n=292)	Initial Placebo (n=176)	Initial BETASERON (n=292)	Initial Placebo (n=176)
Endocrine System / Thyroid				
Hypothyroidism	2.1%	2.3%	2.7%	3.4%
Thyroid disorder	0.0%	0.7%	1.0%	1.1%
Hemic and Lymphatic System / Coagulation Disorders / General and NEC				
Ecchymosis	1.4%	2.3%	1.4%	2.3%
Hemic and Lymphatic System / Lymphatic Disorders / Lymphatic Glands (Nodes)				
Lymphadenopathy	1.7%	1.1%	1.7%	1.1%
Hemic and Lymphatic System / Thrombocyte Abnormalities (Platelets and Megakaryocytes) / Decreased				
Thrombocytopenia	1.4%	1.7%	1.4%	1.7%
Hemic and Lymphatic System / Erythrocyte Abnormalities / Erythrocytes Decreased				
Anemia	2.7%	1.1%	2.1%	1.1%
Hemic and Lymphatic System / Erythrocyte Abnormalities / Hemoglobin Disorders				
Decreased Hemoglobin	0.3%	2.3%	1.0%	2.8%
Leukocytes Decreased				
Leukopenia	22.3%	12.5%	25.0%	14.8%
Hemic and Lymphatic System / Leukocyte Abnormalities / Leukocytes Increased				
Leukocytosis	0.7%	0.6%	1.4%	1.1%
Injection Site Reactions				
Injection site reaction complex[a]	57.2%	41.5%	59.6%	43.8%
Post-injection phenomenon	2.4%	1.1%	2.7%	1.7%
Metabolic and Nutritional Disorders / Carbohydrate Disorders NEC				
Hyperglycemia	3.4%	4.0%	4.1%	6.3%
Hypoglycemia	2.4%	0.0%	3.1%	0.0%
Metabolic and Nutritional Enzyme Disorders NEC				
Alkaline phosphatase increased	0.3%	0.0%	1.0%	0.0%
Gamma-GT increased	1.4%	0.6%	2.4%	0.6%
SGOT increased	11.3%	4.5%	11.6%	4.0%
SGPT increased	15.8%	6.8%	17.1%	8.0%

Table 4: Incidence of Adverse Events ≥ 1% of Overall Patients in Integrated 3-Year[b] and 5-Year[c] Analyses

System Organ Class Adverse Event (HARTS 2.3, Except[a])	Benefit 3-Year		Benefit 5-Year	
	Initial BETASERON (n=292)	Initial Placebo (n=176)	Initial BETASERON (n=292)	Initial Placebo (n=176)
Metabolic and Nutritional Disorders / Element and Ion Disorders NEC / Nitrogen Disorders				
Creatinine increased	0.3%	1.7%	1.4%	2.8%
Metabolic and Nutritional Disorders / Lipid Disorders				
Hyperlipemia	0.0%	1.7%	1.4%	2.3%
Metabolic and Nutritional Pigment Disorders				
Bilirubinemia	8.9%	10.2%	9.9%	11.4%
Metabolic and Nutritional Disorders / Water Balance Disorders				
Edema	1.7%	0.6%	1.0%	0.6%
Peripheral edema	0.7%	1.1%	1.0%	1.1%
Metabolic and Nutritional Disorders / Weight Disorders NEC				
Weight gain	0.7%	2.8%	1.0%	3.4%
Weight loss	0.7%	1.1%	1.0%	1.1%
Musculoskeletal System / Bone Disorders / General and NEC				
Bone fracture (not spontaneous)	1.0%	1.1%	1.7%	2.3%
Musculoskeletal System / Joint Disorders				
Arthralgia	7.2%	9.1%	7.5%	8.5%
Arthritis	1.0%	0.6%	2.4%	1.1%
Muscular Disorders				
Muscle cramps	4.5%	3.4%	5.1%	4.5%
Myalgia	9.6%	10.2%	9.9%	11.4%
Myasthenia	3.4%	3.4%	5.5%	5.7%
Twitching	0.7%	0.6%	1.0%	0.6%
Musculoskeletal System / Tendinous Disorders				
Tendon disorder	2.4%	1.7%	3.4%	2.3%
Nervous System / Autonomic Nervous System / Sympathetic Disorder / Sympatholytic				
Sweating increased	2.4%	1.7%	2.7%	1.7%
Brain				
Amnesia	1.7%	1.7%	1.7%	1.7%
Anxiety	7.5%	8.0%	11.3%	10.2%

Table 4: Incidence of Adverse Events ≥ 1% of Overall Patients in Integrated 3-Year[b] and 5-Year[c] Analyses

System Organ Class Adverse Event (HARTS 2.3, Except[a])	Benefit 3-Year		Benefit 5-Year	
	Initial BETASERON (n=292)	Initial Placebo (n=176)	Initial BETASERON (n=292)	Initial Placebo (n=176)
Ataxia	0.7%	2.3%	2.4%	3.4%
Depression	15.4%	20.5%	19.5%	23.3%
Dizziness	4.1%	5.1%	4.8%	5.7%
Emotional lability	4.5%	2.8%	4.5%	2.8%
Hemiplegia	1.0%	0.6%	1.0%	0.6%
Hypertonia	3.1%	2.8%	5.1%	2.8%
Incoordination	0.3%	0.6%	1.0%	0.6%
Insomnia	10.6%	10.2%	12.7%	11.9%
Myoclonus	1.0%	0.0%	1.4%	0.0%
Nervousness	2.1%	1.7%	2.4%	1.7%
Tremor	1.0%	1.7%	1.0%	1.7%
Vertigo	2.4%	5.1%	3.4%	5.7%
Nervous System / General and NEC				
Abnormal Gait	3.1%	0.6%	4.1%	1.1%
Headache	31.8%	27.8%	33.6%	30.7%
Hyperesthesia	0.3%	0.6%	1.0%	0.6%
Hypesthesia	2.7%	4.5%	5.1%	5.7%
Libido decreased	1.0%	0.6%	1.4%	0.6%
Multiple sclerosis	30.1%	43.2%	39.0%	47.2%
Neuropathy	0.7%	0.0%	1.0%	0.6%
Paralysis	1.0%	2.3%	2.1%	2.3%
Peripheral Nervous System				
Neuralgia	1.7%	1.7%	2.7%	1.7%
Paresthesia	25.0%	24.4%	28.1%	30.1%
Respiratory System / General, Functional and NEC				
Cough increased	3.1%	2.8%	4.5%	4.5%
Upper respiratory infection	26.0%	29.5%	32.9%	33.5%
Respiratory System / Larynx				
Laryngitis	1.4%	2.8%	1.4%	2.8%

Table 4: Incidence of Adverse Events ≥ 1% of Overall Patients in Integrated 3-Year[b] and 5-Year[c] Analyses

System Organ Class Adverse Event (HARTS 2.3, Except[a])	Benefit 3-Year		Benefit 5-Year	
	Initial BETASERON (n=292)	Initial Placebo (n=176)	Initial BETASERON (n=292)	Initial Placebo (n=176)
Respiratory System / Lung				
Bronchitis	6.8%	6.3%	9.2%	8.5%
Pneumonia	0.7%	0.6%	1.4%	0.6%
Nasopharynx				
Pharyngitis	12.7%	13.6%	16.1%	14.8%
Respiratory System / Nose				
Epistaxis	2.1%	0.6%	2.7%	0.6%
Rhinitis	4.5%	4.5%	6.2%	5.1%
Respiratory System / Sinus				
Sinusitis	4.8%	7.4%	6.8%	9.7%
Skin and Appendages / Breast Disorders				
Breast neoplasm	0.7%	0.6%	1.0%	1.1%
Breast pain	0.7%	0.6%	1.0%	0.6%
Skin and Appendages / Dermatose / Acneform				
Acne	0.7%	1.1%	1.4%	1.1%
Dermatoses Specified				
Rash	14.4%	8.5%	13.4%	8.5%
Skin and Appendages / Dermatose / Fungal (Mycotic)				
Fungal dermatitis	0.7%	1.1%	1.0%	1.7%
Skin and Appendages / Dermatoses, General and NEC				
Eczema	1.0%	1.1%	2.1%	1.1%
Urticaria	2.7%	1.1%	3.4%	1.1%
Skin and Appendages / Dermatose / Hypertrophic				
Skin benign neoplasm	0.7%	0.0%	1.0%	0.0%
Skin and Appendages / Dermatose / Psoriasiform				
Psoriasis	1.0%	0.6%	1.4%	0.6%
Skin and Appendages / Dermatose / Ulcerative-necrotic				
Skin ulcer	1.0%	0.0%	1.4%	0.0%

Table 4: Incidence of Adverse Events ≥ 1% of Overall Patients in Integrated 3-Year[b] and 5-Year[c] Analyses

System Organ Class Adverse Event (HARTS 2.3, Except[a])	Benefit 3-Year		Benefit 5-Year	
	Initial BETASERON (n=292)	Initial Placebo (n=176)	Initial BETASERON (n=292)	Initial Placebo (n=176)
Skin and Appendages / Dermatose / Vesiculo-bullous				
Herpes simplex	1.4%	2.3%	1.7%	2.8%
Herpes zoster	1.4%	0.0%	1.7%	0.0%
Skin and Appendages / General, Functional and NEC				
Pruritus	3.4%	1.1%	3.8%	2.3%
Skin disorder	2.7%	2.8%	3.4%	4.0%
Skin and Appendages / Hair Disorders				
Alopecia	4.1%	3.4%	4.8%	4.0%
Skin and Appendages / Subcutaneous Disorders				
Subcutaneous hematoma	3.8%	2.8%	3.8%	2.8%
Special Senses / Ear Disorders / General and NEC				
Ear disorder	0.7%	1.7%	1.4%	1.7%
Special Senses / Ear Disorders / Middle Ear				
Otitis media	2.1%	2.8%	2.7%	3.4%
Special Senses / Eye Disorders / Conjunctiva				
Conjunctivitis	2.1%	2.3%	3.1%	2.8%
Special Senses / Eye Disorders / General and NEC				
Dry eye	1.0%	0.6%	0.7%	0.6%
Eye disorder	1.7%	3.4%	2.4%	2.8%
Eye pain	4.5%	3.4%	6.2%	4.0%
Special Senses / Eye Disorders / Optic Nerve				
Optic neuritis	3.4%	3.4%	4.5%	4.0%
Special Senses / Eye Disorders / Vision Disorders NEC				
Abnormal vision	5.1%	3.4%	5.8%	4.5%
Blurred vision	4.1%	2.3%	5.8%	2.3%
Diplopia	1.0%	1.1%	1.4%	1.7%
Visual field defect	1.4%	0.0%	1.7%	0.0%

Table 4: Incidence of Adverse Events ≥ 1% of Overall Patients in Integrated 3-Year[b] and 5-Year[c] Analyses

System Organ Class Adverse Event (HARTS 2.3, Except[a])	Benefit 3-Year		Benefit 5-Year	
	Initial BETASERON (n=292)	Initial Placebo (n=176)	Initial BETASERON (n=292)	Initial Placebo (n=176)
Urogenital System / Female Genital Disorders / Menstrual Disorders				
Dysmenorrhea	2.1%	0.0%	2.4%	0.0%
Hypermenorrhea	0.7%	0.0%	1.0%	0.0%
Menstrual disorder	1.4%	2.8%	2.1%	2.8%
Metrorrhagia	1.7%	0.0%	2.4%	0.0%
Urogenital System / Female Genital Disorders / Ovary (Excluding Endocrine Function)				
Ovarian cyst	1.0%	0.0%	1.4%	1.1%
Urogenital System / Female Genital Disorders / Pregnancy and Puerperal Disorders				
Unintended pregnancy	2.1%	2.8%	5.1%	7.4%
Urogenital System / Female Genital Disorders / Vagina				
Vaginal moniliasis	2.1%	0.0%	2.1%	0.0%
Vaginitis	1.7%	2.3%	2.7%	2.8%
Urogenital System / Urinary Tract Disorders / Bladder / Functional				
Dysuria	0.7%	0.6%	1.0%	0.6%
Urinary incontinence	2.1%	1.7%	2.7%	2.8%
Urinary retention	1.4%	0.6%	1.4%	0.6%
Urinary urgency	2.7%	1.7%	3.4%	2.8%
Urination impaired	1.0%	2.3%	1.4%	2.8%
Urogenital System / Urinary Tract Disorders / Bladder / Morphologic				
Cystitis	1.7%	3.4%	3.1%	4.0%
Urogenital System / Urinary Tract Disorders / General, Functional and NEC				
Urinary tract infection	3.1%	6.3%	4.8%	8.0%
Urogenital System / Urinary Tract Disorders / Kidney Disorders/Functional				
Nocturia	1.0%	0.0%	1.0%	0.0%

Table 4: Incidence of Adverse Events ≥ 1% of Overall Patients in Integrated 3-Year[b] and 5-Year[c] Analyses

System Organ Class Adverse Event (HARTS 2.3, Except[a])	Benefit 3-Year		Benefit 5-Year	
	Initial BETASERON (n=292)	Initial Placebo (n=176)	Initial BETASERON (n=292)	Initial Placebo (n=176)
Urogenital System / Urinary Tract Disorders / Urine Abnormalities				
Hematuria	0.7%	0.0%	1.0%	0.6%
Proteinuria	3.4%	1.1%	4.1%	2.3%
Urine abnormality	1.0%	1.7%	1.7%	2.3%

Abbreviations: ALAT – alanine aminotransferase, SGPT – serum glutamic-pyruvic transaminase, NEC – not elsewhere classified, SGOT – serum glutamic oxaloacetic transaminase, Gamma-GT – Gamma-glutamyl transpeptidase

a "Injection site reaction (various kinds)" comprises all adverse events occurring at the injection site, ie, the terms "injection site edema," "injection site hemorrhage," "injection site hypersensitivity," "injection site inflammation," "injection site mass," "injection site necrosis," "injection site pain," and "injection site reaction."'Flu-like symptom complex" denotes the terms "flu syndrome" and/or a combination of at least two adverse events from "fever," "chills," "myalgia," "malaise," or "sweating."

b The BENEFIT 3-year analysis represents 2 years of double-blind, placebo-controlled phase plus 1 year of open-label follow-up phase; ie, all patients received BETASERON for a minimum of 1 year.

c The BENEFIT 5-year analysis represents 2 years of double-blind, placebo-controlled phase plus 3 years of open-label follow-up phase; ie, all patients received BETASERON for a minimum of 3 years.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

There were no Clinical Trial Adverse Drug Reactions which occurred at a frequency of < 1%.

Other events observed during premarketing evaluation of various doses of BETASERON in 1,440 patients are listed in the paragraphs that follow. Given that most of the events were observed in open and uncontrolled studies, the role of BETASERON in their causation cannot be reliably determined.

Blood and lymphatic system disorders: chronic lymphocytic leukemia, hemoglobin less than 9.4 g/100 mL, petechia, platelets less than 75,000/mm^3, and splenomegaly.

Cardiac disorders: angina pectoris, arrhythmia, atrial fibrillation, cardiomegaly, cardiac arrest, cerebral ischemia, endocarditis, heart failure, myocardial infarct, pericardial effusion, syncope, ventricular extrasystoles, and ventricular fibrillation.

Ear and labyrinth disorders: deafness, ear pain, otitis externa, and otitis media.

Endocrine disorders: Cushing's syndrome, diabetes insipidus, diabetes mellitus, hypothyroidism, and inappropriate ADH.

Eye disorders: blepharitis, blindness, dry eyes, diplopia, iritis, keratoconjunctivitis, mydriasis, photophobia, retinitis, and visual field defect.

Gastrointestinal disorders: aphthous stomatitis, ascites, cardiospasm, cheilitis, cholecystitis, cholelithiasis, duodenal ulcer, dry mouth, enteritis, esophagitis, fecal impaction, fecal incontinence, flatulence, gastritis, gingivitis, glossitis, hematemesis, ileus, increased salivation, intestinal obstruction, melena, nausea, oral leukoplakia, oral moniliasis, pancreatitis, proctitis, salivary gland enlargement, stomach ulcer, taste loss, taste perversion, and tenesmus.

General disorders and administration site conditions: edema, hernia, hypothermia, and photosensitivity.

Hepatobiliary disorders: alkaline phosphatase greater than 5 times baseline value, hepatitis, and hepatomegaly.

Immune system disorders: anaphylactoid reaction.

Infections and infestations: abscess, cellulitis, infection, periodontal abscess, peritonitis, and sepsis.

Metabolism and nutrition disorders: alcohol intolerance, calcium greater than 11.5 mg/dL, glucose greater than 160 mg/dL, glycosuria, hypoglycemic reaction, ketosis, and thirst.

Musculoskeletal and connective tissue disorders: arthritis, arthrosis, bursitis, dystonia, leg cramps, muscle atrophy, myopathy, myositis, ptosis, and tenosynovitis.

Neoplasms, benign, malignant and unspecified: adenoma, carcinoma of the lung, hepatic neoplasia, sarcoma, skin benign neoplasm, skin carcinoma, spider angioma, and uterine neoplasm.

Nervous system disorders: abnormal gait, acute brain syndrome, aphasia, ataxia, brain edema, chronic brain syndrome, coma, delirium, encephalopathy, facial paralysis, foot drop, hemiplegia, hydrocephalus, hypalgesia, hyperesthesia, incoordination, libido decreased, meningitis, neuralgia, neuropathy, nystagmus, oculogyric crisis, ophthalmoplegia, papilledema, paralysis, reflexes decreased, shock, subdural hematoma, torticollis, and tremor.

Psychiatric disorders: agitation, apathy, delusions, dementia, depersonalization, euphoria, hallucinations, manic reaction, neurosis, paranoid reaction, psychosis, and stupor.

Renal and urinary disorders: anuria, BUN greater than 40 mg/dL, hematuria, kidney calculus, kidney failure, kidney tubular disorder, nephritis, nocturia, oliguria, polyuria, urethritis, urinary incontinence, and urinary retention.

Reproductive system and breast disorders: balanitis, breast engorgement, cervicitis, epididymitis, gynecomastia, impotence, leukorrhea, salpingitis, and uterine fibroids enlarged.

Respiratory, thoracic and mediastinal disorders: apnea, asthma, atelectasis, cyanosis, hemoptysis, hiccup, hyperventilation, hypoventilation, hypoxia, interstitial pneumonia, lung edema, parosmia, pleural effusion, pneumonia, and pneumothorax.

Skin and subcutaneous tissue disorders: contact dermatitis, erythema nodosum, exfoliative dermatitis, furunculosis, hirsutism, leukoderma, lichenoid dermatitis, maculopapular rash, psoriasis, seborrhea, skin hypertrophy, skin necrosis, skin ulcer, urticaria, and vesiculobullous rash.

Vascular disorders: cerebral hemorrhage, gastrointestinal hemorrhage, hypotension, intracranial hypertension, postural hypotension, pulmonary embolus, rectal hemorrhage, subarachnoid hemorrhage, thrombophlebitis, thrombosis, vaginal hemorrhage, varicose vein, vasospasm, and venous pressure increased.

Abnormal Hematologic and Clinical Chemistry Findings

1. Relapsing-remitting MS

In the relapsing-remitting MS study, the most common laboratory abnormalities included:

- lymphocyte count < 1500/mm^3 (82%)
- ALT (SGPT) > 5 times baseline value (19%)
- absolute neutrophil count < 1500/mm^3 (18%)
  (no patients had absolute neutrophil counts < 500/mm^3)
- WBC < 3000/mm^3 (16%)
- total bilirubin > 2.5 times baseline value (6%)

Three patients were withdrawn from treatment with 0.25 mg (8 MIU) BETASERON for abnormal liver enzymes including one following dose reduction (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

2. Secondary-progressive MS

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

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

3. Single Clinical Event Suggestive of MS

The following laboratory abnormalities were reported at a significantly higher incidence in the BETASERON group:

- lymphocyte count < 1500/mm^3: BETASERON 79.1% vs placebo 45.5%
- ALT (SGPT) > 5 times baseline value: BETASERON 17.8% vs placebo 4.5%
- absolute neutrophil count < 1500/mm^3: BETASERON 10.6% vs placebo 2.3%
- WBC < 3000/mm^3: BETASERON 10.6% vs placebo 1.7%
- AST (SGOT) > 5 times baseline value: BETASERON 6.2% vs placebo 0.6%

Bilirubin values of Grade 3 or 4 were reported in 5 BETASERON patients and in 1 placebo patient.

Five patients discontinued BETASERON due to elevated liver function tests (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

There were no relevant differences between the BETASERON and placebo groups for lipid profile, thyroid function parameters, other serum chemistry parameters, or urinalysis parameters.

Postmarket Adverse Drug Reactions

Rare postmarketing cases of adverse hepatic reactions have been reported, including autoimmune hepatitis, hepatitis and hepatic failure requiring liver transplantation.

The adverse drug reactions (ADRs) identified during postmarketing surveillance are summarized in Table 5.

Table 5: Postmarketing Experience

System Organ Class	
Blood and Lymphatic System Disorders	Anemia, thrombocytopenia, leukopenia, thrombotic microangiopathy
Immune System Disorders	Anaphylactic reactions Capillary leak syndrome in pre-existing monoclonal gammopathy
Endocrine Disorders	Thyroid disorders: hyperthyroidism, hypothyroidism
Metabolism and Nutrition Disorders	Blood triglycerides increased, anorexia, weight decrease, weight increase
Psychiatric Disorders	Depression, suicide attempt, confusion, anxiety, emotional lability
Nervous System Disorders	Convulsion, dizziness
Cardiac Disorders	Cardiomyopathy, tachycardia, palpitation
Vascular Disorders	Vasodilatation
Respiratory, Thoracic, and Mediastinal Disorders	Bronchospasm, Pulmonary Arterial Hypertension[1]
Gastrointestinal Disorders	Nausea, vomiting, pancreatitis, diarrhea
Hepatobiliary Disorders	Blood bilirubin increased, gamma-glutamyltransferase increased, hepatic injury (including hepatitis), hepatic failure
Skin and Subcutanoeus Tissue Disorders	Urticaria, alopecia, pruritus, skin discoloration
Musculosceletal, Connective Tissue, and Bone Disorders	Arthralgia, Drug-induced lupus erythematosus
Reproductive System and Breast Disorders	Menstrual disorder, menorrhagia
General Disorders and Administration Site Conditions	Sweating
Renal and Urinary Disorders	Nephrotic syndrome

[1] Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products.

DRUG INTERACTIONS

Drug-Drug Interactions

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

BETASERON administered in 3 cancer patients over a dose range of 0.025 mg (0.8 MIU) to 2.2 mg (71 MIU) led to a dose-dependent inhibition of antipyrine elimination. The effect of alternate-day administration of 0.25 mg (8 MIU) BETASERON on drug metabolism in MS patients is unknown.

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

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

FOR SUBCUTANEOUS USE ONLY

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

Recommended Dose and Dosage Adjustment

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

Dose titration was used at the start of treatment in the clinically isolated syndrome and secondary-progressive MS studies in order to increase the tolerability of BETASERON.

In the study in patients with a single clinical event suggestive of MS (clinically isolated syndrome), dosage was increased as shown in Table 6.

Table 6: Schedule for Dose Titration[a]

Treatment Day	Dose	Volume
1, 3, 5	0.0625 mg (2 MIU)	0.25 mL
7, 9, 11	0.125 mg (4 MIU)	0.5 mL
13, 15, 17	0.1875 mg (6 MIU)	0.75 mL
≥ 19	0.250 mg (8 MIU)	1.0 mL

a Titration scheme as used in the study in patients with a single clinical event suggestive of multiple sclerosis. The titration period may be adjusted if any significant adverse reaction occurs.

In the secondary-progressive MS study, patients initiated treatment with half the dose (4 MIU SC every other day) for a period of 2 weeks prior to escalating to the recommended dose of 8 MIU (SC every other day). Efficacy of treatment for longer than 2 years has not been substantially demonstrated in relapsing-remitting multiple sclerosis.

Missed Dose

If an injection is missed, it should be given as soon as feasible. The next injection should be given 2 days later.

Administration

Reconstitution: To reconstitute lyophilized BETASERON for injection, use the vial adapter to inject the entire contents of the prefilled diluent syringe containing 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 diluent, each mL of solution contains 0.25 mg (8 MIU) interferon beta-1b, 13 mg Albumin Human USP, and 13 mg Mannitol USP.

Vial Content	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
0.3 mg interferon beta-1b	1.2 mL	1.2 mL	0.25 mg/mL

In the absence of compatibility studies, BETASERON should not be mixed with other medicinal products except for the supplied diluent.

Subcutaneous injection: Withdraw 1 mL of reconstituted solution from the vial back into the syringe, fitted with a ½-inch needle, and inject the solution subcutaneously. Sites for self-injection include arms, abdomen, buttocks, and thighs. All components are suitable for single use only; unused portions should be discarded (see **PART III: CONSUMER INFORMATION: PROPER USE OF THIS MEDICATION** section for self-injection procedure.)

OVERDOSE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Interferon beta-1b has been given without serious adverse events compromising vital functions to adult cancer patients at individual doses as high as 5.5 mg (176 million IU) intravenously 3 times a week.

Accidental or intentional overdose may increase the likelihood of the occurrence of known adverse reactions, possibly at a greater severity. A compromise of vital functions is not expected to occur. Treatment should be symptomatic.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Interferon beta-1b has been shown to possess both antiviral and immunomodulatory activities. The mechanisms by which BETASERON exerts its actions in multiple sclerosis 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 (eg, 2',5'-oligoadenylate synthetase, protein kinase, and indoleamine 2,3-dioxygenase) that are believed to be the mediators of the biological actions of interferon beta-1b. A number of these interferon-induced products have been readily measured in the serum and cellular fractions of blood collected from patients treated with interferon beta-1b. Interferon beta-1b both decreases the binding affinity and enhances the internalization and degradation of the interferon-γ receptor. Interferon beta-1b also enhances the suppressor activity of peripheral blood mononuclear cells.

Pharmacokinetics

Given that serum concentrations of interferon beta-1b are low or not detectable following subcutaneous administration of 0.25 mg (8 MIU) or less of BETASERON (interferon beta-1b), pharmacokinetic information in MS patients receiving the recommended dose of BETASERON is not available. Following single and multiple daily subcutaneous administrations of 0.5 mg (16 MIU) 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.

After intravenous administration of BETASERON (0.006 mg [0.2 MIU] to 2.0 mg [64 MIU]), 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 MIU) 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.

STORAGE AND STABILITY

Before Reconstitution

Store between 2°C to 25°C. Excursions between 25°C and 30°C are permitted as long as they do not exceed a maximum of 30 days. Do not freeze. Do not use beyond the expiration date indicated on the labels of the BETASERON vial and the prefilled diluent syringe.

After Reconstitution

The reconstituted product contains no preservative. If not used immediately, store under refrigeration between 2ºC and 8ºC (36ºF and 46ºF) **and use within 3 hours of reconstitution.** Do not freeze.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BETASERON (interferon beta-1b) is presented in single-use vials of lyophilized powder containing 0.3 mg (9.6 MIU) interferon beta-1b, 15 mg albumin human USP and 15 mg mannitol USP.

BETASERON is supplied in[a]:

- A carton containing 15 single-use packs; and
- An Initiation Pack of 12 for initial dose titration, containing 4 differently colored and numbered triple packs (containing a total of 12 doses).

[a] Not all presentations may be available in Canada

The single-use pack is supplied in a blister pack or in a carton. Each single-use pack contains the necessary components to prepare and inject a single dose of BETASERON:

Single-use blister pack

1 vial of medication, 1 prefilled diluent syringe (containing 1.2 mL of Sodium Chloride 0.54% solution), 1 vial adapter with attached 27 gauge, ½" needle, and 3 alcohol wipes.

The single-use blister pack can only be used with the BETAJECT® III autoinjector.

Single-use carton

1 vial of medication, 1 prefilled diluent syringe (containing 1.2 mL of Sodium Chloride 0.54% solution), 1 vial adapter with attached 30 gauge, ½" needle, and 2 alcohol wipes.

The single-use carton can only be used with the BETAJECT® Lite, BETACOMFORT® or BETACONNECT® autoinjector.

Initiation Pack

The Initiation Pack contains 4 differently colored and numbered triple packs:

- Yellow with number "1" (for treatment days 1, 3, and 5; 0.25 mL syringe marking)
- Red with number "2" (for treatment days 7, 9, and 11; 0.5 mL syringe marking)
- Green with number "3" (for treatment days 13, 15, and 17; 0.75 mL syringe marking)
- Blue with number "4" (for treatment days 19, 21, and 23; 0.25, 0.5, 0.75, and 1.0 mL syringe markings)

Each **triple** pack contains 3 vials of medication, 3 prefilled diluent syringes (containing 1.2 mL of sodium chloride 0.54% solution), 3 vial adapters with attached 30 gauge, ½" needle, and 6 alcohol wipes.

The Initiation Pack can only be used with the BETAJECT® Lite, BETACOMFORT® or BETACONNECT® autoinjector.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	Interferon beta-1b (USAN)
Molecular mass:	Approximately 18,500 daltons

Reconstituted Drug Product

pH:	Neutral pH range of 7.1-7.8

Product Characteristics

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 per mg (MIU/mg) 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. Prior to 1993, a different analytical standard was used to determine potency. It assigned 54 million IU to 0.3 mg interferon beta-1b.

CLINICAL TRIALS

The efficacy of 8 MIU BETASERON, administered subcutaneously every other day, has been studied in one placebo-controlled clinical trial in relapsing-remitting MS patients (n = 124), a placebo-controlled trial in secondary-progressive MS patients (n = 360), and a placebo-controlled trial in patients with a first clinical demyelinating event suggestive of MS (n = 292), to determine whether BETASERON could delay the onset of definite MS. Patient demographics in these pivotal studies are summarized in Table 7.

Table 7: Summary of Patient Demographics for BETASERON Pivotal Clinical Trials

Indication	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)[a]	Mean Age (Range)	Gender (%)
Relapsing-remitting MS	Double-blind, placebo-controlled, randomized, parallel group	0.25 mg (8 MIU) every other day for up to 2 years	124	35.2 (18-50)	Female: 69.4 Male: 30.6
Secondary-progressive MS	Double-blind, placebo-controlled, randomized, parallel group	0.25 mg (8 MIU) every other day for up to 3 years	360	41.1 (22-56)	Female: 58.1 Male: 41.9
First clinical demyelinating event suggestive of MS	Double-blind, placebo-controlled, randomized, parallel group	0.25 mg (8 MIU) every other day for up to 2 years	292	30.8 (18-45)	Female: 70.9 Male: 29.1
	Open-label, multi-center follow-up study of the preceding double-blind, placebo-controlled, randomized, parallel group study	0.25 mg (8 MIU) every other day for up to 5 years	418[b]	30.7 (18-45)	Female: 70.3 Male: 29.7

a The number of subjects receiving the recommended clinical dose of 8 MIU.
b A total of 418 subjects participated in the follow up phase; 382 of them opted for BETASERON treatment at the recommended clinical dose of 8 MIU.

1. Relapsing-Remitting MS

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

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

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

Patients who required more than three 28-day courses of corticosteroids were withdrawn from the study. Minor analgesics (eg, acetaminophen), antidepressants, and oral baclofen were allowed *ad libitum* but chronic 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 8.

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

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

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

Table 8: 2-Year Study Results - Primary and Secondary Endpoints

Efficacy Parameters		Treatment Groups			Statistical Comparisons *P*-value		
Primary Clinical Endpoints		**Placebo (n=123)**	**0.05 mg (1.6 MIU) (n =125)**	**0.25 mg (8 MIU) (n=124)**	**Placebo vs 0.05 mg (1.6 MIU)**	**0.05 mg (1.6 MIU) vs 0.25 mg (8 MIU)**	**Placebo vs 0.25 mg (8 MIU)**
Annual exacerbation rate		1.31	1.14	0.90	0.005	0.113	0.0001
Proportion of exacerbation-free patients[a]		16%	18%	25%	0.609	0.288	0.094
Exacerbation frequency per patient	**0[a]** **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[b]							
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[c] at endpoint		0.21	0.21	-0.07	0.995	0.108	0.144
Mean change in Scripps score[d] at endpoint		-0.53	-0.50	0.66	0.641	0.051	0.126
Median duration per exacerbation (days)		36	33	35.5	ND	ND	ND
% change in mean MRI lesion area at endpoint		21.4%	9.8%	-0.9%	0.015	0.019	0.0001

Abbreviation: ND = Not done.

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

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

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

d 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 MIU) group was -1.1% which was significantly smaller than the 16.5% observed for the placebo group ($P = 0.0001$).

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

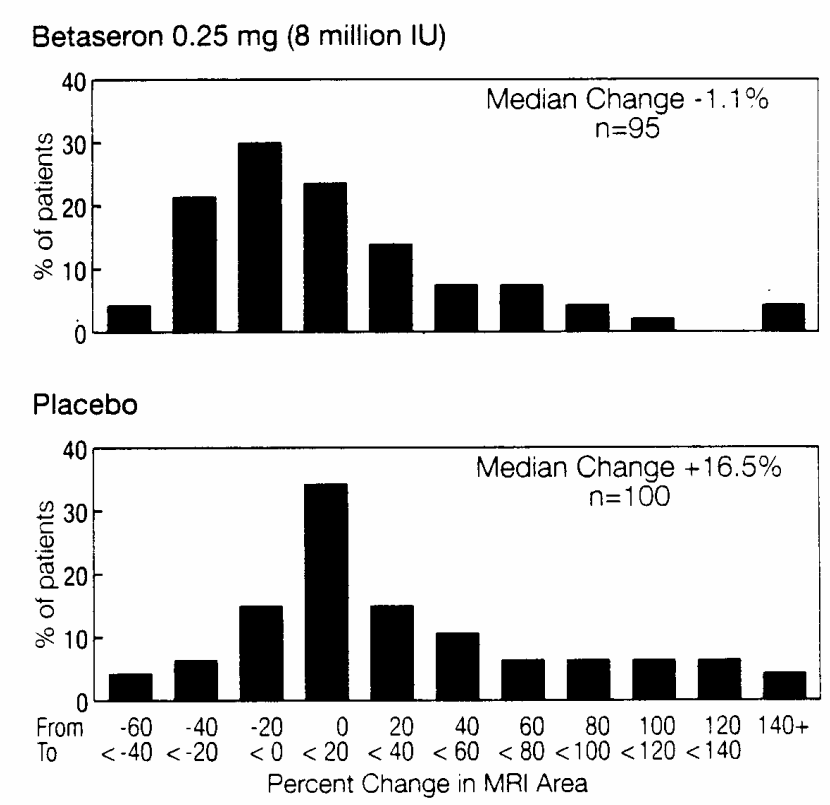


Figure 1: Distribution of Change in MRI Area

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 (ie, classic white matter plaques). The prognostic significance of the MRI findings in this study has not been evaluated.

At the end of 2 years on assigned treatment, patients in the study had the option of continuing on treatment under blinded conditions. Approximately 80% of patients in each treatment group accepted. Although there was a trend toward patient benefit in the BETASERON groups during the third year, particularly in the 0.25 mg (8 MIU) group, there was no statistically significant difference between the BETASERON-treated vs placebo-treated patients in exacerbation rate, or in any of the secondary endpoints described in Table 8. As noted above, in the 2-year analysis, there was a 31% reduction in exacerbation rate in the 0.25 mg (8 MIU) group, compared to

placebo. The *P*-value for this difference was 0.0001. In the analysis of the third year alone, the difference between treatment groups was 28%. The *P*-value was 0.065. The lower number of patients may account for the loss of statistical significance, and lack of direct comparability among the patient groups in this extension study make the interpretation of these results difficult. The third year MRI data did not show a trend toward additional benefit in the BETASERON arm compared with the placebo arm.

Throughout the clinical trial, serum samples from patients were monitored for the development of antibodies to interferon beta-1b. In patients receiving 0.25 mg (8 MIU) BETASERON (n = 124) every other day, 45% were found to have serum neutralizing activity on at least 1 occasion. One-third had neutralizing activity confirmed by at least 2 consecutive positive titers. This development of neutralizing activity may be associated with a reduction in clinical efficacy, although the exact relationship between antibody formation and therapeutic efficacy is not yet known.

2. Secondary-Progressive MS

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

The study included patients between 18 and 55 years of age who had clinically definite or laboratory supported definite MS for not less than 1 year. Disease had to be in the secondary-progressive phase and deterioration could not be exclusively related to incomplete recovery from relapses. EDSS score at study entry was between 3.0 and 6.5 and patients had to have a history of at least 2 clearly identified relapses, or deterioration of at least 1 EDSS point (or 0.5 points between EDSS scores of 6.0 to 7.0) within the preceding 24 months.

The primary efficacy endpoint was time to confirmed progression in disability, as determined by an increase by 1 point on the EDSS from baseline if the entry score was 3.0 to 5.5 or 0.5 points on the EDSS if the baseline score was 6.0 or 6.5. The increased score had to be maintained for 3 months before progression was confirmed. Secondary efficacy endpoints included time to becoming wheelchair-bound (EDSS 7.0) and annual relapse rate.

Although the study was designed with a treatment duration of 3 years, a prospectively planned interim analysis of efficacy was performed after all patients had completed 2 years in the study. This resulted in a decision by an independent Advisory Board to terminate the study early. Approximately 85% of all EDSS data for the 3-year study duration were available for the interim analysis of the primary endpoint. The primary analysis of efficacy was based on all patients randomized to treatment (intent-to-treat). The primary statistical method for the primary endpoint was a nonparametric analysis of covariance with stratification for centre and adjustment for baseline EDSS. Results presented below are for the dataset at study termination.

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

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

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

The treatment effect was consistent across all baseline EDSS levels studied; however, the relative difference in the proportion of patients having confirmed progression in disability between BETASERON and placebo-treated patients was lower for patients with study entry EDSS values of ≥ 6.0, compared to the other EDSS categories, when all patients lost to follow-up were assumed to have progressed (EDSS ≤ 3.5: 27.1%; EDSS 4.0 – 5.5: 17.8%; and EDSS ≥ 6.0: 5.8%). When patients lost to follow-up were assumed not to have progressed, the respective values were 16.6%, 15.5%, and 14.2% (shown in Table 10). Although the proportion of male patients in the BETASERON group with confirmed progression in disability was slightly higher than that of female patients, piecewise logistic regression analysis did not reveal any significant treatment by gender interaction ($P = 0.4335$).

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

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

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

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

In addition to clinical measures, annual MRI was performed. All patients underwent a T2-weighted MRI scanning at baseline and yearly thereafter, while a subgroup of patients (placebo, n = 61; BETASERON, n = 64) underwent monthly scans in months 1 to 6 and 19 to 24 in addition to the annual scans scheduled for the general study population. Results of secondary and tertiary MRI endpoints showed significant differences between treatment groups in favor of BETASERON (see Table 9). The exact relationship between MRI findings and the clinical status of patients is unknown.

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

Table 9: Secondary-Progressive MS Study Results - Summary of Key Efficacy Endpoints

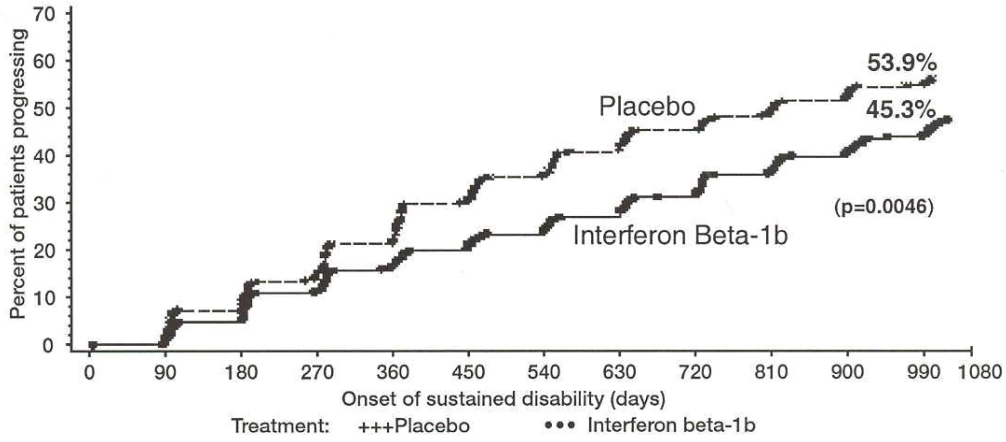
	Treatment Groups		*P*-value
	Placebo (n=358)	**BETASERON 0.25 mg (8 MIU) (n=360)**	
Primary Endpoints			
Time to confirmed progression in disability[a]			0.0046
Year 1	0.70	0.81	0.0032
Year 2	0.53	0.64	0.0013
Month 33	0.44	0.53	0.0066
Secondary Clinical Endpoints			
Time to becoming wheelchair-bound[b]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

a Probability of remaining progression-free during the interval.
b Probability of not becoming wheelchair-bound during the interval.

Table 10: Proportion of Patients With Confirmed Progression Stratified by Baseline EDSS Category

Baseline EDSS	Treatment Group	ITT-A[a] Analysis			ITT-B[b] Analysis		
		% Patients With Confirmed Progression	% Difference vs Placebo		% Patients With Confirmed Progression	% Difference vs Placebo	
			Relative	Absolute		Relative	Absolute
≤ 3.5	Placebo BETASERON	55.3 40.3	-27.1	-15.0	44.7 37.3	-16.6	-7.4
4.0 – 5.5	Placebo BETASERON	63.4 52.1	-17.8	-11.3	54.9 46.4	-15.5	-8.5
≥ 6.0	Placebo BETASERON	60.4 56.9	-5.8	-3.5	55.6 47.7	-14.2	-7.9
Overall	Placebo BETASERON	60.9 51.9	-14.8	-9.0	53.9 45.3	-16.0	-8.6

a ITT-A: Patients lost to follow-up were evaluated as having confirmed progression during the 3 month interval which follows the interval of follow-up loss.
b ITT-B: Patients lost to follow-up were evaluated as not having confirmed progression by the end of the study.



Estimate of the percentage of patients progressing by the end of 3 years

Note: The *P*-value of 0.0046 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given time point.

Figure 2: Onset of Progression in Disability by Time in Study (Kaplan-Meier Methodology: Posthoc Analysis)

3. Single Clinical Event Suggestive of MS

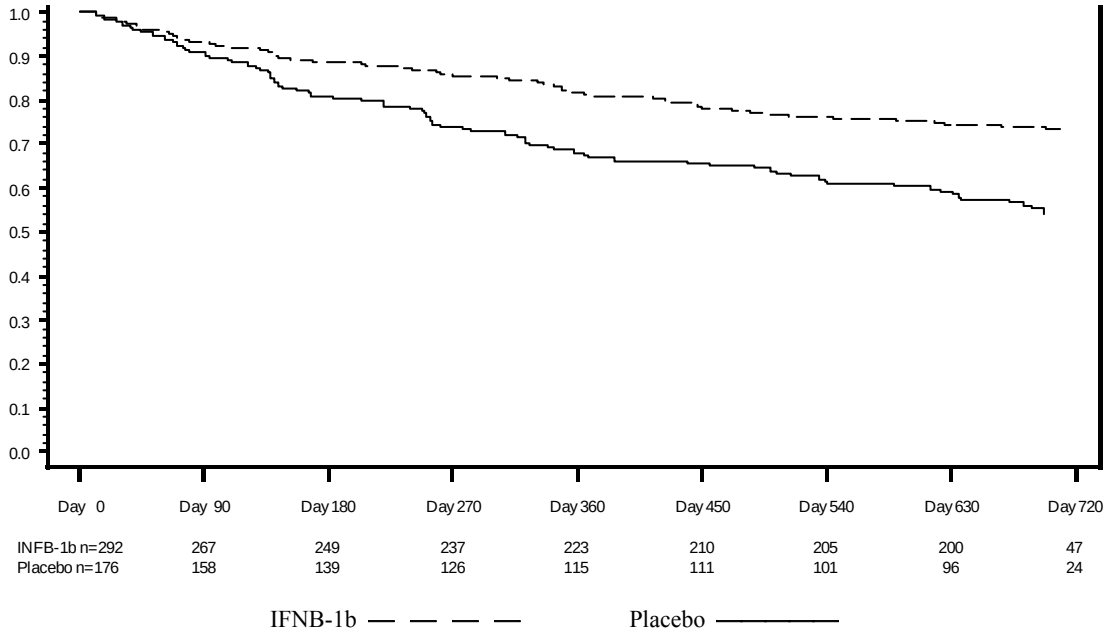
One double-blind, placebo-controlled, randomized, parallel group clinical trial (BENEFIT) was performed in patients with a single clinical demyelinating event suggestive of MS. The study enrolled patients within 60 days after the onset of a single clinical event suggestive of MS (sometimes referred to as "clinically isolated syndrome"), based on the appearance of a new neurological abnormality which had to be present for at least 24 hours. The T2-weighted brain MRI scan had to show at least 2 clinically silent lesions with a size of at least 3 mm, at least 1 of which had to be ovoid or periventricular or infratentorial.

Patients were 18 to 45 years old with an EDSS of ≤ 5.0. Patients with monofocal or multifocal onset of the disease were included (ie, patients with clinical evidence of a single or at least 2 lesions, respectively, of the central nervous system). Any disease other than multiple sclerosis that could better explain the signs and symptoms of the patient had to be excluded. This study consisted of 2 phases, a placebo-controlled phase followed by a pre-planned follow-up phase. The placebo-controlled phase lasted for 2 years or until the patient developed clinically definite multiple sclerosis (CDMS), whichever came first.

Patients selected for the study were randomized to treatment with either 0.25 mg (8 MIU) BETASERON (n = 292) or placebo (n = 176) self administered subcutaneously every other day for a treatment duration of up to 2 years.

Two primary efficacy variables were prespecified in the protocol: time to onset of clinically definite MS (CDMS); and time to onset of MS according to the diagnostic criteria of McDonald et al., 2001. Clinically definite MS was reached if the patient experienced a relapse of the disease and/or a sustained progression of ≥ 1.5 points on the EDSS scale as compared to the lowest EDSS obtained during screening on day 1, with a total EDSS score of ≥ 2.5. Multiple sclerosis according to the McDonald criteria was reached if, in addition to the single clinical demyelinating event, both dissemination in space and dissemination in time had been established.

In the placebo-controlled phase, BETASERON delayed the progression from the first clinical event to clinically definite multiple sclerosis in a highly statistically significant and clinically meaningful manner, corresponding to a risk reduction of 47% (hazard ratio = 0.53; 95% confidence interval [0.39, 0.73], $P < 0.0001$). A posthoc analysis adjusting for the standard baseline covariates of steroid use during single event, type of disease onset (multifocal versus monofocal), age, sex, number of T2 lesions, and number of gadolinium-enhancing lesions, revealed a similar risk reduction of 50%. Within 2 years, CDMS occurred in 45% of the placebo group compared to 28% of the BETASERON group (Kaplan-Meier estimates). BETASERON prolonged the time to CDMS by 363 days, from 255 days in the placebo group to 618 days in the BETASERON group (based on the 25th percentiles).



Ordinate depicts the survival distribution function estimate. Patient numbers at abscissa denote the number of patients at risk.

Figure 3: Kaplan-Meier Curve for Time to CDMS (for Placebo-Controlled Phase of BENEFIT)

The robustness of the treatment effect was also shown by the delay of progression to multiple sclerosis according to the McDonald criteria, corresponding to a risk reduction of 43% (hazard ratio = 0.57; 95% confidence interval [0.46, 0.71], $P < 0.00001$) and 46% based on posthoc analysis adjusting for standard baseline covariates. In the first 6 months, a diagnosis of MS according to the McDonald criteria was made in 51% of placebo and 28% of BETASERON patients, and after 2 years, the respective incidences were 85% and 69%. BETASERON prolonged the time to development of MS according to the McDonald criteria by 78 days, from 92 days in the placebo group to 170 days in the BETASERON group (based on the 25^{th} percentiles) indicating efficacy of the drug at the earliest time point when disease development shows up on the MRI.

Exploratory posthoc subgroup analyses according to baseline factors suggested that BETASERON was efficacious in all subgroups evaluated. These subgroup analyses also included patients with less disseminated and less active disease at the time of the first event, who had risk reductions for progression to CDMS ranging from 55% to 60% (monofocal onset: 55%; without gadolinium enhancement: 57%; or less than nine T2 lesions: 60%) and risk reductions for progression to MS according to the McDonald criteria ranging from 37% to 43% (monofocal onset: 43%; without gadolinium enhancement: 39%; or less than nine T2 lesions: 37%). The results of subgroup analyses should be interpreted with caution since the clinical trial was not designed to evaluate efficacy in subgroups.

Two MRI-derived parameters, the cumulative number of newly active lesions and the change in T2 lesion volume, were analyzed as secondary efficacy variables. The cumulative number of newly active lesions up to end of study was statistically significantly lower in the BETASERON group, irrespective of whether annualized (median number of newly active lesions was 1.34 for BETASERON and 3.16 for placebo) or nonannualized (median number of newly active lesions was 2.0 for BETASERON and 4.0 for placebo) values were considered ($P < 0.0001$ for both analyses). T2-lesion volumes decreased from screening to the end of study in the majority of patients in both treatment groups due to regression of inflammatory changes that had been associated with the first clinical event. For the change in T2 lesion volume, a significant treatment effect of BETASERON was observed for the nonannualized T2 lesion volume change up to the last scan (median change -206.0 mm^3 for BETASERON vs -93.0 mm^3 for placebo; $P = 0.0498$), but not for the annualized values (median change -119.70 mm^3 for BETASERON vs -57.54 mm^3 for placebo; $P = 0.1906$).

Therapy with BETASERON was well accepted as indicated by a high rate of trial completion (92.8% in the BETASERON group).

The BENEFIT Follow-up Phase

The BENEFIT follow-up phase was a preplanned, open-label, multicenter extension of the initial double-blind placebo-controlled BENEFIT phase to obtain long-term follow-up data.

All patients who completed the placebo-controlled phase according to the protocol were eligible to enter the follow-up phase and, after renewing their written informed consent, were offered 0.25 mg (8 MIU) BETASERON for up to five years from randomization. Additionally, a

medical assessment was required stating that there was no objection to the patient's participation in the follow-up phase considering the medical experience from the placebo-controlled phase. Throughout the follow-up phase, patients, investigators, and raters were kept blinded to the original treatment allocation from the placebo-controlled trial.

All efficacy variables were assessed based on the combined data from the double-blind phase and the follow-up phase in all patients who received at least 1 dose of the study drug during the placebo-controlled phase (ITT analysis). The patient group initially randomized to BETASERON was compared with the group initially randomized to placebo with the option of starting with BETASERON after diagnosis of clinical definite MS (CDMS) or after 2 years (whichever came first).

Two preplanned analyses of the integrated data after completion of years 3 and 5 were performed. A nominal 2-sided significance level of 0.0253 was assigned to the analyses of the primary endpoints at both time points, thus allowing for an overall type I error probability of 0.05. Three prespecified primary efficacy measures were tested in a sequential, conditional approach (ie, each could only be tested if the preceding result was statistically significant): 1) time to CDMS; 2) time to confirmed EDSS progression; and 3) FAMS-TOI (Functional Assessment of MS: trial outcome index) score.

For the time-to-event outcomes, differences between the initial BETASERON and the initial placebo group were analyzed by the log-rank test (primary analysis) and by adjusted Cox proportional hazards regression (secondary analysis). Prespecified covariates considered in the Cox regression for time to CDMS were: steroid use during the first clinical event, monofocal vs multifocal disease onset, and number of T2 lesions at screening; and for time to confirmed EDSS progression were: T2 lesion volume at screening. Treatment effects on the FAMS-TOI were analysed by nonparametric and parametric analysis of covariance, with the corresponding baseline assessment as covariate.

Of the 468 patients enrolled in the placebo-controlled phase, 437 patients (93.4%) were eligible for inclusion in the follow-up phase. Out of these, 418 patients (95.7%) gave their informed consent for the follow-up phase, while 19 patients (4.3%) decided not to participate in the follow-up phase of the trial.

More than 90% of all patients entering the open label BENEFIT follow-up phase opted for BETASERON treatment. Of these, 85% of them chose not to take any additional disease-modifying therapies (DMTs) (see Table 11). Less than 10% of patients chose not to take BETASERON; the majority of which also opted not to take any additional DMTs.

Table 11: Choice of Treatments During BENEFIT Follow-up Phase up to Year 3

	Initial BETASERON Total n = 261 (100%)		Initial Placebo Total n = 157 (100%)		Overall Total n = 418 (100%)	
IFNB-1b in any combination	233	(89.3%)	145	(92.4%)	378	(90.4%)
IFNB-1b only	225	(86.2%)	134	(85.4%)	359	(85.9%)
IFNB-1b and other DMT	8	(3.1%)	11	(7.0%)	19	(4.5%)
No IFNB-1b at all	28	(10.7%)	12	(7.6%)	40	(9.6%)
Any other DMT only	5	(1.9%)	2	(1.3%)	7	(1.7%)
No DMT at all	23	(8.8%)	10	(6.4%)	33	(7.9%)

Eighty-four percent (84%) of the 468 patients initially randomized completed 3 years' follow-up for reasons of discontinuation see Table 12).

Table 12: Main Reasons for Premature Discontinuation of Study Participation During the BENEFIT Follow-up Phase up to Year 3

	Initial BETASERON n = 261 (100%)		Initial Placebo n = 157 (100%)		Overall n = 418 (100%)	
Withdrawal of consent	8	(3.1%)	9	(5.7%)	17	(4.1%)
Adverse event	1	(0.4%)	4	(2.5%)	5	(1.2%)
Administration of other DMT	0	-	1	(0.6%)	1	(0.2%)
Other	3	(1.1%)	0	-	3	(0.7%)
Overall	12	(4.6%)	14	(8.9%)	26	(6.2%)

Among all patients enrolled in the BENEFIT follow-up phase, premature permanent discontinuation of study medication at 3 years was recorded for 7.7% of patients in the initial BETASERON group compared to 19.7% in the initial Placebo group (for reasons of discontinuation, see Table 13).

Table 13: Main Reasons for Premature Discontinuation of Study Medication During the BENEFIT Follow-up Phase up to Year 3

	Initial BETASERON n = 261 (100%)		Initial Placebo n = 157 (100%)		Overall n = 418 (100%)	
Adverse event	6	(2.3%)	18	(11.5%)	24	(5.7%)
Withdrawal of consent	7	(2.7%)	7	(4.5%)	14	(3.3%)
Administration of other DMT	3	(1.1%)	3	(1.9%)	6	(1.4%)
Other	4	(1.5%)	3	(1.9%)	7	(1.7%)
Overall	20	(7.7%)	31	(19.7%)	51	(12.2%)

By the third year in the BENEFIT study (placebo-controlled phase plus 1 year in the open label follow-up phase), the majority of patients had been treated with BETASERON for at least a year. By the fifth year, the majority of patients had been treated for at least 3 years. The active treatment duration with IFNB-1b was longer for patients of the initial BETASERON group (median 1793 days; range: 7 – 1963 days) as compared to the initial Placebo group (median 1060 days; range: 0 – 1781 days).

The results of the integrated analysis of the BENEFIT placebo-controlled and follow-up study should be considered in relation to the fact that 4.3% (19) of the patients, although being eligible for the follow-up study, did not give their informed consent and that 9.6% (40) of the patients chose not to receive BETASERON during the follow-up phase up to Year 3.

The results for the efficacy variables time to CDMS and time to EDSS progression for the 3-year analyses are presented in Table 14, and in Figure 4 and Figure 5.

Table 14: Primary Efficacy Endpoints: Time to CDMS and Time to Confirmed EDSS Progression from BENEFIT 3-Year[a] Analyses

	Time to CDMS (Relapse-based efficacy domain)		**Time to Confirmed EDSS Progression** (Disability-based efficacy domain)	
	Initial BETASERON	**Initial Placebo**	**Initial BETASERON**	**Initial Placebo**
Log-rank test	$p = 0.001$		$p = 0.022$	
Cox model	HR[b]: 0.62; 97.47%[d] CI (0.45-0.86), $p = 0.001$		HR[c]: 0.60; 97.47%[d] CI (0.36-0.98), $p = 0.019$	

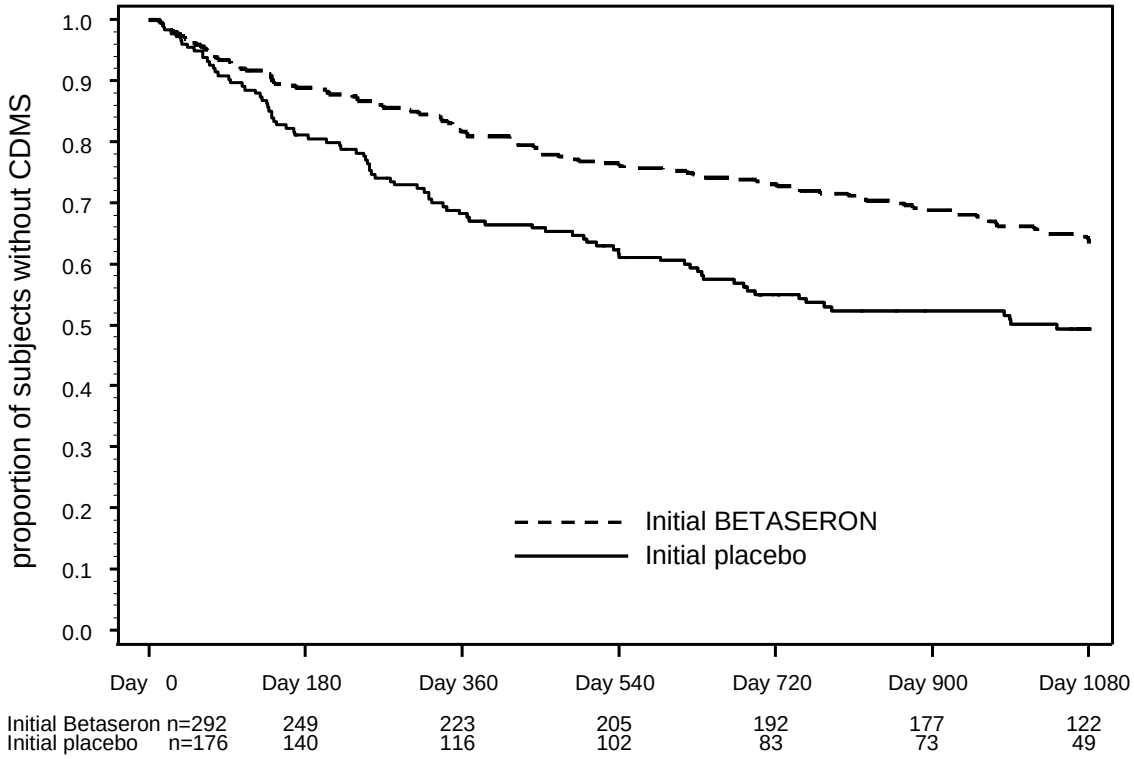
a The BENEFIT 3-year analysis is based on data from the double-blind, placebo-controlled phase with up to 2 years observation and the open-label follow-up phase up to year 3 after randomization, ie, the majority of patients have been on BETASERON for at least 1 or more years.

b Cox proportional hazard regression model with covariates: steroid use during first event, type of disease onset: monofocal vs multifocal, number of T2 lesions at screening.

c Cox proportional hazard regression model with covariates: T2 lesion volume at screening.
Note: The assumption of proportional hazards over 3 years may not be valid.

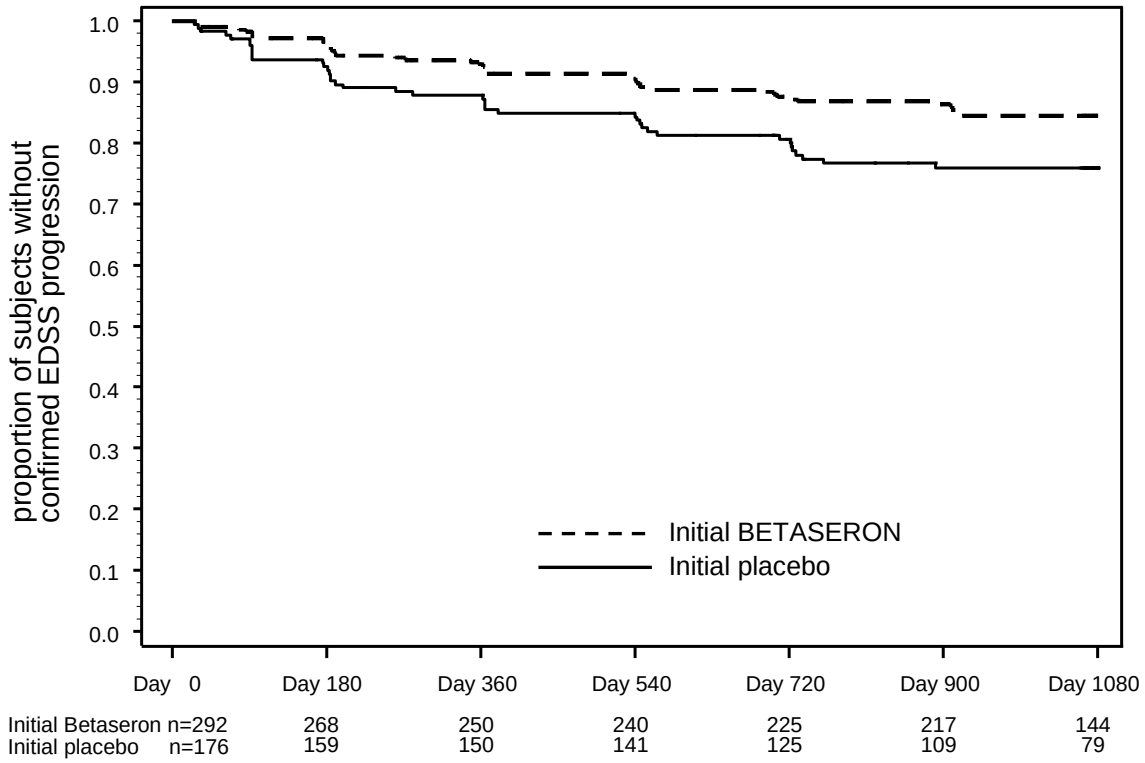
d The 97.47% CI was used according to the Sidak adjustment of the 5% type I error level at 3 and 5 years to 0.0253.

The Kaplan-Meier estimates of the percentages of patients developing CDMS within 36 months were 37% in the initial BETASERON group and 51% in the initial Placebo group; confirmed EDSS progression rates were 16% in the initial BETASERON group and 24% in the initial Placebo group.



Ordinate depicts the estimate for the proportion of subjects without CDMS. Patient numbers at abscissa denote the number of patients at risk.

Figure 4: Kaplan-Meier Estimates for Time to CDMS (3-Year Data)



Ordinate depicts the estimate for the proportion of subjects without confirmed EDSS progression. Patient numbers at abscissa denote the number of patients at risk.

Figure 5: Kaplan-Meier Estimates for Time to confirmed EDSS Progression (3-year Data)

TOXICOLOGY

Carcinogenicity

The carcinogenic potential of BETASERON (interferon beta-1b) 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.

Mutagenicity

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

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PART III: CONSUMER INFORMATION

PrBETASERON®
Interferon beta-1b

This leaflet is part III of a three-part Product Monograph published when BETASERON was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about BETASERON. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
BETASERON (BAY-tah-SEER-on) is used for the treatment of relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations in ambulatory patients (ie, patients who are able to walk without help).

BETASERON is also used for the treatment of secondary-progressive multiple sclerosis to slow the progression of disability and to reduce the frequency of clinical exacerbations.

BETASERON is also approved for use in patients who have symptoms which are likely to be a first sign of multiple sclerosis (single clinical event suggestive of multiple sclerosis). Any other reasons which could explain the symptoms have to be ruled out. Your doctor will perform a test using an imaging machine (magnetic resonance imaging [MRI]). This test has to show at least two signs of inflammation in the central nervous system suggestive of multiple sclerosis.

What it does:
Multiple sclerosis is a life-long disease that affects your nervous system (ie, brain and spinal cord) by destroying the protective covering (myelin) that surrounds your nerve fibers. An abnormal response by the body's immune system is thought to play an important part in the process which damages the nervous system.

BETASERON is a form of protein called interferon beta that occurs naturally in the body. Interferon beta has been shown to modify the immune system response, but the exact way that BETASERON works in MS is unknown. BETASERON will not cure MS but it has been shown to decrease the number of flare-ups and slow the occurrence of some of the physical disabilities that are common in people with MS.

When it should not be used:
You should NOT use BETASERON:
- if you are pregnant; or
- if you have had previous allergic reactions, such as difficulty breathing, itching, flushing or hives, to interferon beta or to any of the nonmedicinal ingredients (see below).

What the medicinal ingredient is:
The active ingredient is interferon beta-1b.

What the nonmedicinal ingredients are:
BETASERON powder: human albumin, mannitol
Diluent: sodium chloride, water for injection

What dosage forms it comes in:
BETASERON is formulated as a sterile, white to off-white powder which must be dissolved using the supplied diluent. Each single-use vial contains 0.3 mg (9.6 million international units [MIU]) of interferon beta-1b. The diluent syringe contains 1.2 mL of sodium chloride 0.54% solution.

The prepared solution for injection contains 0.25 mg (8.0 MIU) of interferon beta-1b per 1 mL and is pH neutral.

WARNINGS AND PRECAUTIONS

BEFORE you use BETASERON, talk to your doctor if you have any of the following conditions:

- Depression, anxiety (feeling uneasy, nervous or fearful for no reason) or trouble sleeping
- Liver problems
- Epilepsy or a history of seizures
- Heart problems
- Problems with your thyroid gland
- Are breast-feeding or are planning to become pregnant

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 or tongue can also happen. If you think you are having an allergic reaction, stop using BETASERON immediately and call your doctor.

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 healthcare 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.

Kidney problems: Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidney (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). This might happen several weeks to several years after starting BETASERON and may cause death. Talk to your doctor if you experience the following symptoms: increased bruising, bleeding, extreme weakness, headache, dizziness or light-headedness. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Liver problems: BETASERON, like other interferon beta products, may cause severe liver problems. Some of the symptoms of liver problems are yellowing of the skin and whites of the eyes, malaise (a vague feeling of discomfort), fatigue, nausea, vomiting, abdominal pain, dark urine and itching of the skin. If you develop these symptoms while taking BETASERON, you should call your doctor right away.

Seizures: Some patients have had seizures while taking interferons. It is not known whether the seizures are related to the effects of MS, to interferons, or to a combination of both. If you have a seizure while taking BETASERON, you should call your doctor right away.

Heart problems: During treatment with BETASERON, cardiomyopathy (a disease of the heart muscle) has been reported in rare cases. If you experience symptoms like irregular heart beat, fluid retention (swelling) in the lower parts of your body (eg, ankles, legs), or shortness of breath, call your doctor immediately.

Thyroid problems: Some people taking BETASERON may develop changes in the function of their thyroid. Symptoms of these changes include feeling hot or cold much of the time or change in your weight (gain or loss) without a change in your diet or the amount of exercise you are getting.

Gastrointestinal problems: In rare cases, an inflammation of the pancreas has been observed with BETASERON use, often associated with an increase of triglycerides (a type of fat in the blood). If you have suffered from increased triglycerides or have had problems with your pancreas, please tell your doctor.

Risk to pregnancy: If you plan to become pregnant or could become pregnant while on BETASERON, advise your doctor. 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. Should you become pregnant, please contact Bayer Medical Information at 1-800-265-7382.

Breast-feeding: You should talk to your doctor if you are breast-feeding an infant. It is not known if BETASERON can be passed to an infant in mother's milk, but because of the potential to cause a serious adverse reaction in an infant, a decision should be made whether to stop breast-feeding or stop taking BETASERON.

Immune system problems: The administration of interferons to patients with a pre-existing rare disturbance of the immune system where abnormal proteins are found in the blood (monoclonal gammopathy) has been associated with problems with small blood vessels leading to shock (collapse) and, in some cases, death.

Human albumin: This product contains a protein (albumin) extracted from human blood and so carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of a disease affecting the nervous system (Creutzfeld-Jakob disease) is also considered extremely remote.

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.

INTERACTIONS WITH THIS MEDICATION

With the exception of steroids or ACTH (anti-inflammatory medicines), the use of BETASERON together with other substances that modify the immune system response was not studied. Caution should be exercised when interferons are given in combination with other drugs which need a certain liver enzyme system (the cytochrome P450 system) for their metabolism. These drugs include some commonly used drugs against fever and pain.

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

PROPER USE OF THIS MEDICATION

BETASERON is intended for use under the guidance and supervision of a physician. Your physician or his/her delegate should instruct you in the preparation and self-injection technique of BETASERON. Do not begin your BETASERON treatment without training.

Usual dose:
BETASERON should be used as prescribed by your doctor. The usual dose is 1 mL of prepared BETASERON solution injected subcutaneously (under the skin) every other day. This is equal to 0.25 mg (8 MIU).

If you have been prescribed BETASERON because you have symptoms likely to be a first sign of multiple sclerosis, your treatment should be started at a low dose of 0.25 mL (0.0625 mg or 2 MIU). Your dose will then be increased slowly until you reach a dose of 1 mL. Your individual tolerability of BETASERON will determine the rate of dose increase. Your doctor will decide this with you. To easily increase the dosage during the first 12 injections, you may be given a special Initiation Pack, containing four differently colored and numbered packs with specially marked syringes.

Your injections should be about 48 hours (two days) apart, so it is best to take them at the same time each day, preferably in the evening before bedtime.

Self-Injection Procedure

SAFETY TIPS

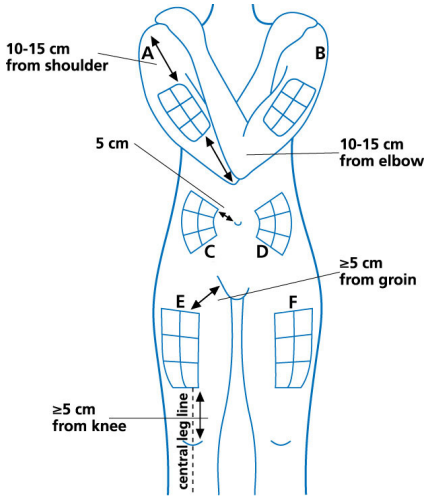
- Use only the supplies that come with your BETASERON package.
- Use only the diluent from the prefilled syringe.
- Wash your hands thoroughly with soap and water before starting.
- Keep the items sterile. Do not touch the needle, the piercing spike of the vial adapter, or the top of the cleaned vial.
- Make sure none of the items in your package have been opened or are damaged.
- Do not reuse opened materials. Throw away any unused portions of BETASERON and diluent.
- Throw away used syringes and needles in the proper disposal container.

STEP 1: CHOOSING AN INJECTION SITE

BETASERON should be injected into subcutaneous tissue (under the skin, between the fat layer and the muscles beneath). The best areas for injection are loose and soft, away from joints.

- Choose an injection site from the following areas (Figure 6):
  - A Right arm, upper back portion (at least 10-15 cm below the shoulder and 10-15 cm above the elbow)
  - B Left arm, upper back portion (at least 10-15 cm below the shoulder and 10-15 cm above the elbow)
  - C-D Abdomen, above the waistline (at least 5 cm on either side of the navel)
  - E Right thigh (at least 5 cm above the knee and 5 cm below the groin)
  - F Left thigh (at least 5 cm above the knee and 5 cm below the groin)
  - G Left buttock (upper, outer portion)
  - H Right buttock (upper, outer portion)
- Change injection areas every time you inject yourself. Give the site time to recover from the last injection. This will help prevent injection site reactions.
- Wait at least one week before reusing an area.
- Do not use any areas where you feel lumps, depressions, pain, or discoloration; talk to your doctor or nurse about anything you find.

Front



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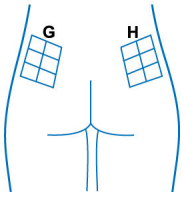

Figure 6

- Keep a record of when and where you are giving yourself injections. Use the BETASERON diary in your training kit.

STEP 2: CHECKING THE CONTENTS OF THE PACK[b]

If you have BETASERON in a single-use blister pack, please follow the blister pack instructions.
If you have BETASERON in a single-use carton, please follow the carton instructions.
If you have BETASERON in an Initiation Pack, please follow the Initiation Pack instructions.

BETASERON Blister Pack
Place the BETASERON single-use blister pack on a clean, flat surface in a well-lighted area. Ensure the pack contains:

- Vial of BETASERON
- Prefilled diluent syringe
- Three (3) alcohol wipes
- Vial adapter with attached 27-gauge, ½" needle in blister pack

BETASERON Carton
Place the BETASERON single-use carton on a clean, flat surface in a well-lighted area. Ensure the pack contains:

- Vial of BETASERON
- Prefilled diluent syringe
- Two (2) alcohol wipes
- Vial adapter with attached 30-gauge, ½" needle in blister pack

NOTE: *Please ensure you have a clean, dry cotton ball or gauze prior to preparing BETASERON for injection.*

BETASERON Initiation Pack
The Initiation Pack contains 4 differently colored and numbered triple packs for the first 12 injections. Ensure each triple pack you open contains:

- Three (3) vials of BETASERON
- Three (3) prefilled syringes
- Three (3) vial adapters with attached 30-gauge, ½" needle in blister pack
- Six (6) alcohol wipes

NOTE: *Please ensure you have a clean, dry cotton ball or gauze prior to preparing BETASERON for injection.*

Each triple pack contains the syringes you will require for preparing **each** dose. The syringes are specially marked accordingly with the appropriate doses (0.25, 0.50, 0.75, or 1.0 mL).

Start by using the **yellow pack** which is clearly marked with a **"1"** on the top right hand side of the box. This first pack should be used for treatment days 1, 3, and 5. It contains specially marked syringes with **0.25 mL** marking. This will help you to inject the required dose only.

After finishing with the yellow pack, start using the **red pack** which is clearly marked with a **"2"** on the top right hand side of the box. This second pack should be used for treatment days 7, 9, and 11. It contains specially marked syringes with **0.50 mL** marking. This will help you to inject the required dose only.

After finishing with the red pack, start using the **green pack** which is clearly marked with a **"3"** on the top right hand side of the box. This third pack should be used for treatment days 13, 15, and 17. It contains specially marked syringes with **0.75 mL** marking. This will help you to inject the required dose only.

Finally, after finishing with the green pack, start using the **blue pack** which is clearly marked with a **"4"** on the top right hand side of the box. This fourth pack should be used for treatment days 19, 21, and 23. It contains specially marked syringes with **0.25, 0.50, 0.75, and 1.0 mL** markings. This will help you to inject the required dose (1.0 mL) and familiarize you with the syringe used in the single-use packs.

STEP 3: INITIAL PREPARATION

1. Wash your hands thoroughly with soap and water.

2. Take out all the contents.
   NOTE: *Be sure the vial adapter blister pack is sealed and the rubber cap is firmly attached to the diluent syringe.*

3. Check the expiry date on the BETASERON vial and the prefilled diluent syringe.

4. Turn the single-use pack over, place the vial in the well (vial holder) in the center of the pack and place the prefilled diluent syringe in the U-shaped trough (if using a blister pack)

STEP 4: RECONSTITUTING BETASERON

1. **Remove** the BETASERON vial from the vial holder (if using a blister pack) and **take** the protective cap off the vial.

2. **Place** the vial back into the vial holder (if using a blister pack).

3. Use an alcohol wipe to **clean** the top of the vial. Move the wipe in one direction only. ***NOTE:*** *Leave the alcohol wipe on top of the vial until Step 4, point 5.*

[b] Not all presentations may be available in Canada.

4. **Peel** off the vial adapter blister pack label but do not remove the vial adapter. ***NOTE:*** *Be sure to avoid touching the vial adapter, in order to maintain its sterility.*

5. **Remove** the alcohol wipe on top of the BETASERON vial. **Place** the vial adapter (still in the blister packaging) on top of the BETASERON vial by pushing it until it pierces the rubber top of the BETASERON vial and snaps in place (Figure 7). Remove the blister packaging from the vial adapter.

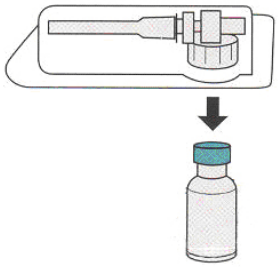

Figure 7

6. **Remove** the rubber cap from the diluent syringe with a twist and pull motion. Discard the rubber cap.

7. **Connect** the syringe with the vial adapter by turning clockwise and tighten carefully. This will form the syringe assembly (Figure 8).

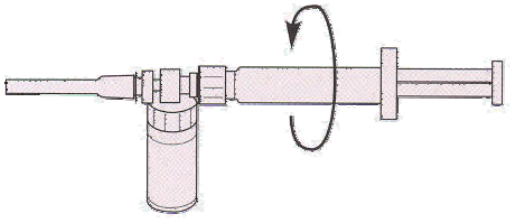

Figure 8

8. It is important to **slowly push** the plunger of the diluent syringe all the way in, keeping the syringe assembly at an angle. This will transfer all of the diluent drop by drop into the BETASERON vial (Figure 9).

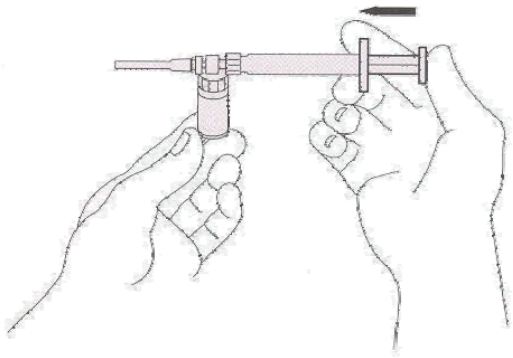

Figure 9

9. Keeping the plunger depressed, with the syringe assembly attached, **swirl** the vial **gently** to completely dissolve the white cake of BETASERON. **(DO NOT SHAKE.)**

10. **Look** closely at the BETASERON solution for particles. It should be clear. **NOTE:** *If the mixture contains particles or is discolored, discard it and start again. Foaming may occur during reconstitution, or if it is swirled or shaken too vigorously. If so, allow the vial to sit undisturbed until the foam settles.*

STEP 5: PREPARING THE INJECTION

1. Keeping the plunger depressed, turn the assembly upside down (ie, 180 degrees) so that the vial is on top. The syringe remains horizontal (Figure 10).

2. **BETASERON Single-use blister or carton:**
   Slowly **pull** the plunger back to withdraw the entire contents of the BETASERON vial into the syringe (Figure 10).
   NOTE: *If 1 mL of clear solution cannot be withdrawn from the vial, discard the vial and syringe and start over.*

   BETASERON Initiation Pack:
   With the Initiation Pack, withdraw the solution from the BETASERON vial **only up to the mark on the syringe**:
   - 0.25 mL for the first three injections (on day 1, 3, and 5 of therapy); or
   - 0.5 mL for the injections on day 7, 9, and 11 of therapy; or
   - 0.75 mL for the injecions on day 13, 15, and 17 of therapy.

   Discard the vial with any remaining solution.

   From day 19 onwards, you are injecting the **full dose 1.0 mL**.

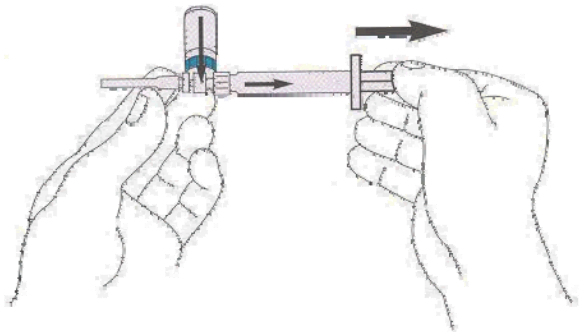

Figure 10

3. **Turn** the syringe assembly so that the needle end is pointing up. Tap the syringe gently so any air bubbles will rise to the top. Tap the syringe with the side of your finger. Do not tap the syringe with a hard object because the glass syringe could break. Push the plunger to the 1 mL mark (or to the amount prescribed by your doctor) to remove any air bubbles.

   If you are injecting less than 1.0 mL with the Initiation Pack, there might not be any air bubbles; however, for the full dose injection, some air bubbles might be seen. Remove them by gently tapping the syringe and pushing the plunger to the respective marking on the syringe.

   NOTE: *If too much solution is expelled into the vial, repeat Step 5, points 1, 2, and 3.*

4. **Remove** the vial adapter and the vial from the syringe by grasping the plastic cap of the vial adapter and twisting it clockwise, as shown in Figure 11. This will release the vial adapter, with the vial, from the syringe but leave the needle on the syringe (Figure 11).

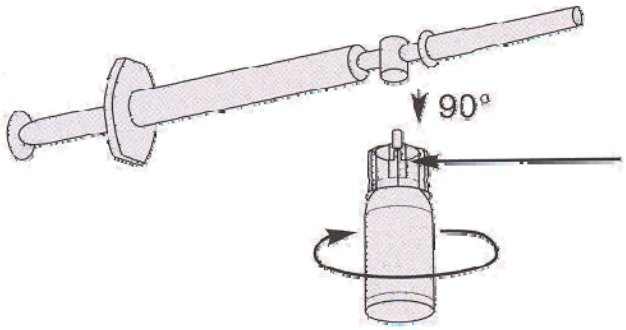

Figure 11

5. **You have now reconstituted your BETASERON and are ready to be injected.**

The injection should be administered immediately after mixing. If you are unable to give the injection immediately, you may refrigerate the medication in the syringe and inject within three hours. Do not freeze.

STEP 6: INJECTING BETASERON

Optional - Autoinjector: If you have been given an autoinjector, you should follow the detailed instructions that are supplied with it.

- **The Single-use blister pack can only be used with the BETAJECT® III autoinjector.**
- **The Single-use carton can only be used with the BETAJECT® Lite, BETACOMFORT® or BETACONNECT® autoinjector.**
- **The Initiation Pack can only be used with the BETAJECT® Lite, BETACOMFORT® or BETACONNECT® autoinjector.**

1. Use a fresh alcohol wipe to **clean** the skin at the injection site. Use a circular motion from the center of the injection site outward. Let the alcohol dry.
2. **Throw away** the wipe.
3. **Remove** the protective needle guard from the needle by pulling it without turning.
4. Gently **pinch** the skin around the site to lift it up a bit.
5. **Stick** the needle straight into the skin at a 90° angle with a quick, firm motion.
6. **Inject** the drug by using a slow, steady push (push the plunger all the way in until the syringe is empty).
7. **Remove** the needle from the skin.
8. Gently **massage** the injection site with a clean, dry cotton ball or gauze (or as directed by your healthcare professional).
9. **Throw away** the syringe in the disposal unit.
10. **Discard** all other components.

Overdose:
If you accidentally take more than your prescribed dose, or take it two days in a row, call your doctor right away.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Center immediately, even if there are no symptoms.

Missed Dose:
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 given about 48 hours (two days) after that dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with any prescription medication, side effects related to therapy can occur. Consult your doctor if you have any problems, whether or not you think they may be related to BETASERON.

Skin reactions: Injection site reactions are common. They include redness, pain, swelling and discoloration. Less frequently, injection site necrosis (skin breakdown and tissue destruction) has been observed. To minimize the chance of a reaction, change injection areas every time you inject yourself and wait at least one week before reusing an area. Do not inject into skin that is tender, red, or hard. Do not use any areas where you feel lumps, depressions, pain, or discoloration. Injection site reactions may occur less frequently if you use an autoinjector. Talk to your doctor or nurse about anything you find. If you experience a break in the skin or drainage of fluid from the injection site, consult your doctor. The occurrence of injection site reactions decreases over time.

Flu-like symptoms: Flu-like symptoms are also common. They include fever, chills, sweating, fatigue, and muscle aches. For many patients, these symptoms will lessen or go away over time. Taking BETASERON at night may help lessen the impact of flu-like symptoms. You should talk to your doctor about whether you should take an over-the-counter medicine for pain or fever reduction (nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) before or after taking your dose of BETASERON.

Liver problems: Your liver function may be affected. Elevations of liver function values occurred very commonly in patients treated with BETASERON in clinical studies and in most cases were mild and transient. Rare cases of severe liver injury have been reported (see **WARNINGS AND PRECAUTIONS** - **Hepatic/Biliary/Pancreas**).

Blood problems: A decrease of infection-fighting white blood cells, red blood cells, or platelets (cells that help you form blood clots) may occur. If decreases are severe, they can lessen your ability to fight infections, make you feel tired or sluggish or cause you to bruise or bleed easily.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical treatment
		Only if severe	In all cases	
Very common	Rash		✓	
Common	Break in skin or drainage of fluid at injection site		✓	
	Lack of coordination in moving arms, fingers or legs, or other muscular movement		✓	
Uncommon	Difficulty breathing or swallowing, swelling of mouth or tongue			✓
	Depression or suicidal thoughts		✓	
	Fluid retention (swelling) in ankles or legs		✓	
	Seizures		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical treatment
		Only if severe	In all cases	
	Symptoms of liver problems: yellowing of the skin and whites of eyes, malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, itching of the skin		✓	
	Symptoms of kidney problems: foamy urine, fatigue, swelling, particularly in the ankles and eyelids, and weight gain		✓	

This is not a complete list of side effects. For any unexpected effects while taking BETASERON, contact your doctor or pharmacist.

HOW TO STORE IT

Before reconstitution: Store BETASERON between 2°C to 25°C. Excursions between 25°C and 30°C are permitted as long as they do not exceed a maximum of 30 days. Do not freeze.

After reconstitution: If not used immediately, reconstituted BETASERON must be refrigerated and used within three hours. Do not freeze.

Keep syringes and needles away from children. Do not reuse needles or syringes. Discard used syringes and needles in a syringe disposal unit.

REPORTING SUSPECTED SIDE EFFECTS

Canada Vigilance Program:

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

Note: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This document plus the full Product Monograph, prepared for health professionals can be found at: http://www.bayer.ca or by contacting the manufacturer at the above-mentioned phone number and email address.

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