HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BETASERON safely and effectively. See full prescribing information for BETASERON.

BETASERON (interferon beta-1b) for injection, for subcutaneous use
Initial U.S. Approval: 1993

----------INDICATIONS AND USAGE----------
Betaseron is an interferon beta indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. (1)

----------DOSAGE AND ADMINISTRATION----------
- For subcutaneous use only (2.1)
- The recommended dose is 0.25 mg every other day. Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a six week period to 0.25 mg (1 mL) every other day. (2.1)
- Reconstitute lyophilized powder with supplied diluent (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 0.3 mg of lyophilized powder in a single-use vial for reconstitution (3)

----------CONTRAINDICATIONS----------
History of hypersensitivity to natural or recombinant interferon beta, albumin or mannitol (4)

----------WARNINGS AND PRECAUTIONS----------
- *Hepatic Injury:* Monitor liver function tests and signs and symptoms of hepatic injury; consider discontinuing Betaseron if serious hepatic injury occurs (5.1, 5.9)
- *Anaphylaxis and Other Allergic Reactions:* Discontinue if anaphylaxis occurs (5.2)
- *Depression and Suicide:* Advise patients to immediately report any symptom of depression and/or suicidal ideation; consider discontinuation of Betaseron if depression occurs (5.3)
- *Congestive Heart Failure (CHF):* Monitor patients with CHF for worsening of cardiac symptoms; consider discontinuation of Betaseron if worsening of CHF occurs (5.4)
- *Injection Site Necrosis and Reactions:* Do not administer Betaseron into affected area until fully healed; if multiple lesions occur, discontinue Betaseron until healing of skin lesions (5.5)
- *Leukopenia*: Monitor complete blood count. (5.6, 5.9)
- *Flu-Like Symptom Complex:* Consider analgesics and/or antipyretics on injection days (5.7)

----------ADVERSE REACTIONS----------
In controlled clinical trials, the most common adverse reactions (at least 5% more frequent on Betaseron than on placebo) were: Injection site reaction, lymphopenia, flu-like symptoms, myalgia,leukopenia, neutropenia, increased liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, and asthenia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling

Revised: October 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Betaseron® (interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose is 0.0625 mg (0.25 mL) subcutaneously every other day, with dose increases over a six week period to the recommended dose of 0.25 mg (1 mL) every other day (see Table 1).

Table 1. Schedule for Dose Titration

	Betaseron Dose[1]	Percentage of recommended dose	Volume
Weeks 1-2	0.0625 mg	25%	0.25 mL
Weeks 3-4	0.125 mg	50%	0.5 mL
Weeks 5-6	0.1875 mg	75%	0.75 mL
Week 7 and thereafter	0.25 mg	100%	1 mL

[1] Dosed every other day, subcutaneously

If a dose of Betaseron is missed, then it should be taken as soon as the patient remembers or is able to take it. The patient should not take Betaseron on two consecutive days. The next injection should be taken about 48 hours (two days) after that dose. If the patient accidentally takes more than their prescribed dose, or takes it on two consecutive days, they should be instructed to call their healthcare provider immediately.

2.2 Reconstitution of the Lyophilized Powder

(a) Prior to reconstitution, verify that the vial containing lyophilized Betaseron is not cracked or damaged. Do not use cracked or damaged vials.

(b) To reconstitute lyophilized Betaseron for injection, attach the prefilled syringe containing the diluent (Sodium Chloride, 0.54% Solution) to the Betaseron vial using the vial adapter.

(c) Slowly inject 1.2 mL of diluent into the Betaseron vial.

(d) Gently swirl the vial to dissolve the lyophilized powder completely; **do not shake**. Foaming may occur during reconstitution or if the vial is swirled or shaken too vigorously. If foaming occurs, allow the vial to sit undisturbed until the foam settles.

(e) 1 mL of reconstituted Betaseron solution contains 0.25 mg of interferon beta-1b.

(f) After reconstitution, if not used immediately, refrigerate the reconstituted Betaseron solution at 2 to 8°C (35 to 46°F) and use within three hours. **Do not freeze**.

2.3 Important Administration Instructions

(a) Perform the first Betaseron injection under the supervision of an appropriately qualified healthcare professional. If patients or caregivers are to administer Betaseron, train them in the proper subcutaneous injection technique and assess their ability to inject subcutaneously to ensure the proper administration of Betaseron.

(b) Visually inspect the reconstituted Betaseron solution before use; discard if it contains particulate matter or is discolored.

(c) Keeping the syringe and vial adapter in place, turn the assembly over so that the vial is on top. Withdraw the appropriate dose of Betaseron solution. Remove the vial from the vial adapter before injecting Betaseron.

(d) Use safe disposal procedures for needles and syringes.

(e) Do not re-use needles or syringes.

(f) Advise patients and caregivers to rotate sites for subcutaneous injections to minimize the likelihood of severe injection site reactions, including necrosis or localized infection.

2.4 Premedication for Flu-like Symptoms

Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Betaseron use *[see Warnings and Precautions (5.7)]*.

3 DOSAGE FORMS AND STRENGTHS

For injection: 0.3 mg lyophilized powder in a single use vial for reconstitution.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

Severe hepatic injury including cases of hepatic failure, some of which have been due to autoimmune hepatitis, has been rarely reported in patients taking Betaseron. In some cases, these events have occurred in the presence of other drugs or comorbid medical conditions that have been associated with hepatic injury. Consider the potential risk of Betaseron used in combination with known hepatotoxic drugs or other products (e.g., alcohol) prior to Betaseron administration, or when adding new agents to the regimen of patients already on Betaseron. Monitor patients for signs and symptoms of hepatic injury. Consider discontinuing Betaseron if serum transaminase levels significantly increase, or if they are associated with clinical symptoms such as jaundice.

Asymptomatic elevation of serum transaminases is common in patients treated with Betaseron. In controlled clinical trials, elevations of SGPT to greater than five times baseline value were reported in 12% of patients receiving Betaseron (compared to 4% on placebo), and increases of SGOT to greater than five times baseline value were reported in 4% of patients receiving Betaseron (compared to 1% on placebo), leading to dose-reduction or discontinuation of treatment in some patients *[see Adverse Reactions (6.1)]*. Monitor liver function tests *[see Warnings and Precautions (5.9)]*.

5.2 Anaphylaxis and Other Allergic-Reactions
Anaphylaxis has been reported as a rare complication of Betaseron use. Other allergic reactions have included dyspnea, bronchospasm, tongue edema, skin rash and urticaria *[see Adverse Reactions (6.1)]*. Discontinue Betaseron if anaphylaxis occurs.

5.3 Depression and Suicide
Depression and suicide have been reported to occur with increased frequency in patients receiving interferon beta products, including Betaseron. Advise patients to report any symptom of depression and/or suicidal ideation to their healthcare provider. If a patient develops depression, discontinuation of Betaseron therapy should be considered.

In randomized controlled clinical trials, there were three suicides and eight suicide attempts among the 1532 patients on Betaseron compared to one suicide and four suicide attempts among 965 patients on placebo.

5.4 Congestive Heart Failure
Monitor patients with pre-existing congestive heart failure (CHF) for worsening of their cardiac condition during initiation of and continued treatment with Betaseron. While beta interferons do not have any known direct-acting cardiac toxicity, cases of CHF, cardiomyopathy, and cardiomyopathy with CHF have been reported in patients without known predisposition to these events, and without other known etiologies being established. In some cases, these events have been temporally related to the administration of Betaseron. Recurrence upon rechallenge was observed in some patients. Consider discontinuation of Betaseron if worsening of CHF occurs with no other etiology.

5.5 Injection Site Necrosis and Reactions
Injection site necrosis (ISN) was reported in 4% of Betaseron-treated patients in controlled clinical trials (compared to 0% on placebo) [*see Adverse Reactions (6.1)]*. Typically, ISN occurs within the first four months of therapy, although postmarketing reports have been received of ISN occurring over one year after initiation of therapy. The necrotic lesions are typically three cm or less in diameter, but larger areas have been reported. Generally the necrosis has extended only to subcutaneous fat, but has extended to the fascia overlying muscle. In some lesions where biopsy results are available, vasculitis has been reported. For some lesions, debridement, and/or skin grafting have been required. In most cases healing was associated with scarring.

Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis. For patients who continue therapy with Betaseron after injection site necrosis has occurred, avoid administration of Betaseron into the affected area until it is fully healed. If multiple lesions occur, discontinue therapy until healing occurs.

Periodically evaluate patient understanding and use of aseptic self-injection techniques and procedures, particularly if injection site necrosis has occurred.

In controlled clinical trials, injection site reactions occurred in 78% of patients receiving Betaseron with injection site necrosis in 4%. Injection site inflammation (42%), injection site pain (16%), injection site hypersensitivity (4%), injection site necrosis (4%), injection site mass (2%), injection site edema (2%) and nonspecific reactions were significantly associated with Betaseron treatment. The incidence of injection site reactions tended to decrease over time. Approximately 69% of patients experienced injection site reactions during the first three months of treatment, compared to approximately 40% at the end of the studies.

5.6 Leukopenia
In controlled clinical trials, leukopenia was reported in 18% of patients receiving Betaseron (compared to 6% on placebo), leading to a reduction of the dose of Betaseron in some patients [*see Adverse Reactions (6.1)*]. Monitoring of complete blood and differential white blood cell counts is recommended. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

5.7 Flu-Like Symptom Complex
In controlled clinical trials, the rate of flu-like symptom complex for patients on Betaseron was 57% [*see Adverse Reactions (6.1)*]. The incidence decreased over time, with 10% of patients reporting flu-like symptom complex at the end of the studies. The median duration of flu-like symptom complex in Study 1 was 7.5 days [see *Clinical Studies (14)*]. Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Betaseron use.

5.8 Seizures
Seizures have been temporally associated with the use of beta interferons in clinical trials and postmarketing safety surveillance. It is not known whether these events were related to a primary seizure disorder, the effects of multiple sclerosis alone, the use of beta interferons, other potential precipitants of seizures (e.g., fever), or to some combination of these.

5.9 Monitoring for Laboratory Abnormalities
In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts and blood chemistries, including liver function tests, are recommended at regular intervals (one, three, and six months) following introduction of Betaseron therapy, and then periodically thereafter in the absence of clinical symptoms.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more details in other sections of labeling:

- Hepatic Injury [see *Warnings and Precautions* (5.1)]
- Anaphylaxis and Other Allergic-Reactions [see *Warnings and Precautions* (5.2)]
- Depression and Suicide [see *Warnings and Precautions* (5.3)]
- Congestive Heart Failure [see *Warnings and Precautions* (5.4)]
- Injection Site Necrosis and Reactions [see *Warnings and Precautions* (5.5)]
- Leukopenia [see *Warnings and Precautions* (5.6)]
- Flu-Like Symptom Complex [see *Warnings and Precautions* (5.7)]
- Seizures [see *Warnings and Precautions* (5.8)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions and over varying lengths of time, adverse reaction rates observed in the clinical trials of Betaseron cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice.

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