

Medication Guide
Betaseron® (bay-ta-seer-on)
Interferon beta-1b
(in-ter-feer-on beta-one-be)

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

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

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

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

What is Betaseron?

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

Who should not take Betaseron?

Do not take Betaseron if you:

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

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

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

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

How should I take Betaseron?

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

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

If you miss a dose, you should take your next dose as soon as you remember or are able to take it. Your next injection should be taken about 48 hours (two days) after that dose. **Do not take Betaseron® on two consecutive days.** If you accidentally take more than your prescribed dose, or take it on two consecutive days, call your doctor right away.

You should always follow your doctor's instructions and advice about how to take this medication. If your doctor feels that you, or a family member or friend may give you the injections, then you and/or the other person should be trained by your doctor or healthcare provider in how to give an injection.

Do not try to give yourself (or have another person give you) injections at home until you (or both of you) understand and are comfortable with how to prepare your dose and give the injection.

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

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

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

What should I avoid while taking Betaseron?

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

What are the possible side effects of Betaseron?

- **Flu-like symptoms.** Most patients have flu-like symptoms (fever, chills, sweating, muscle aches and tiredness). For many patients, these symptoms will lessen or go away over time. You should talk to your doctor about whether you should take an over the counter medication for pain or fever reduction before or after taking your dose of Betaseron.
- **Skin reactions.** Soreness, redness, pain, bruising or swelling may occur at the place of injection. (see: "*What is the most important information I should know about Betaseron?*").
- **Depression and anxiety.** Some patients taking interferons have become very depressed and/or anxious. There have been patients taking interferons who have had thoughts about killing themselves. If you feel sad or hopeless you should tell a friend or family member right away and call your doctor immediately. (see: "*What is the most important information I should know about Betaseron?*").
- **Liver problems.** Your liver function may be affected. Symptoms of changes in your liver include yellowing of the skin and whites of the eyes and easy bruising.
- **Blood problems.** You may have a drop in the levels of infection-fighting white blood cells, red blood cells, or cells that help you form blood clots. If drops in levels are severe, they can lessen your ability to fight infections, make you feel tired or sluggish or cause you to bruise or bleed easily.

- **Thyroid problems.** Your thyroid function may change. Symptoms of changes in the function of your thyroid include feeling cold or hot much of the time or change in your weight (gain or loss) without a change in your diet or amount of exercise you are getting.
- **Allergic reaction.** Some patients have had hives, rash, skin bumps or itching while they were taking Betaseron. There is also a rare possibility that you can have a life-threatening allergic reaction. (see “What is the most important information I should know about Betaseron”)

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

General Information About Prescription Medicines

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

Instructions for Preparing and Giving Yourself an Injection of Betaseron

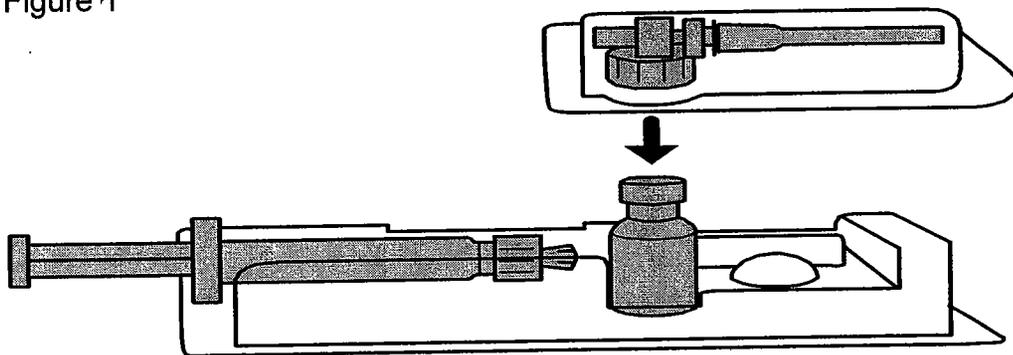
1. Find a clean, flat working surface that is well-lit and collect all the supplies you will need to give yourself an injection. You will need:
 - One tray containing Betaseron. Make sure the tray contains: A prefilled diluent syringe
 - A vial of Betaseron
 - Two (2) alcohol prep pads
 - A vial adapter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

Reconstituting Betaseron

1. Remove the Betaseron vial from the well and take the cap off the vial.
2. Place the vial back into the vial holder. Use an alcohol prep pad to clean the top of the vial. Move the prep pad in one direction. Leave the alcohol prep pad on top of the vial until step 5.

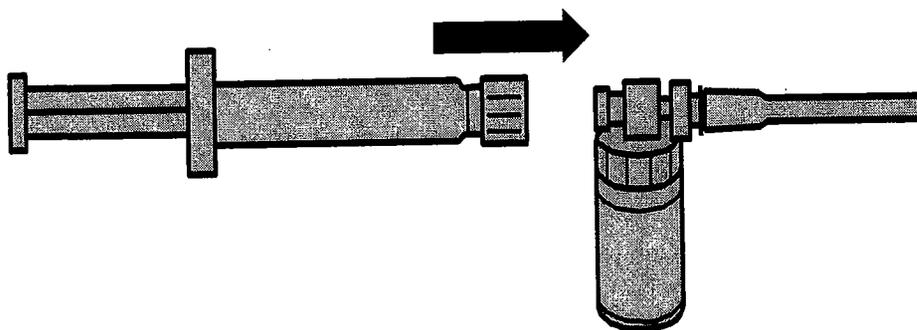
3. Peel the label off the blister pack with the vial adapter in it, but do not remove the vial adapter. The vial adapter is sterile; avoid touching the vial adapter.
4. Remove the alcohol prep pad from the top of the Betaseron vial. Keeping the vial adapter in the blister pack, place the adapter on top of the Betaseron vial and push down on the adapter until it pierces the rubber top of the Betaseron vial and snaps in place (Figure 1). Remove the blister packaging from the vial adapter.

Figure 1



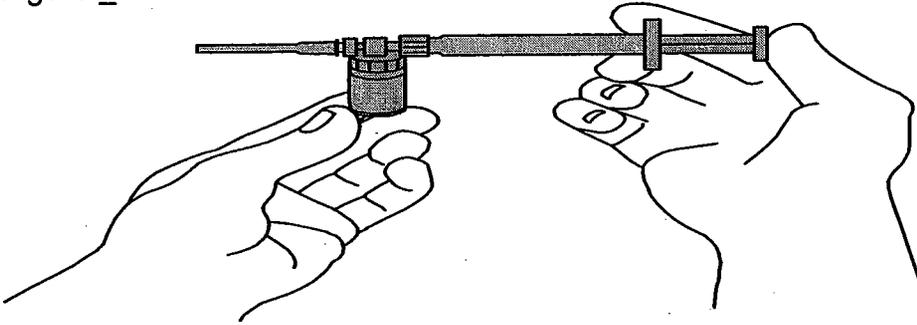
5. Remove the rubber cap from the diluent syringe using a twist and pull motion. Discard the rubber cap.
6. Keeping the syringe assembly attached to the vial, remove the vial from the tray. Be careful not to pull the vial adapter off the top of the vial.
7. Connect the syringe to the vial adapter by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

Figure 2



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

Figure 3



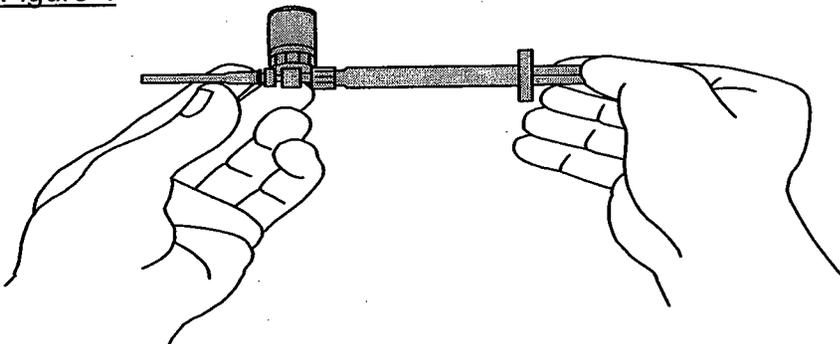
9. Gently swirl the vial to completely dissolve the white cake of Betaseron. Do not shake. Shaking can cause Betaseron to foam; even gently mixing the solution can cause foaming. If there is foam, allow the vial to sit undisturbed until the foam settles.
10. After the cake is dissolved, look closely at the solution to make sure the solution is clear and colorless and does not contain particles. If the mixture contains particles, or is discolored, do not use. Repeat the steps to prepare your dose using a new tray of Betaseron, prefilled syringe, vial adapter, and alcohol prep pads. Contact Berlex at 1-888-237-5394 to obtain replacement product.

Preparing the Injection

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

1. Push the plunger in and hold it there; then turn the syringe assembly so that the vial is on top. (The syringe is horizontal.) (Figure 4).
2. Slowly pull the plunger back to withdraw the entire contents of the Betaseron vial into the syringe

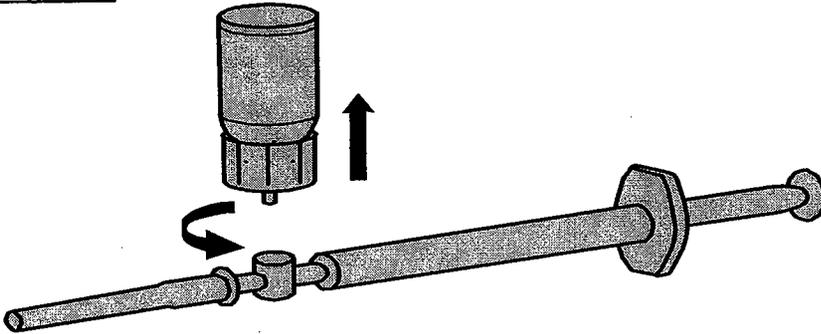
Figure 4



NOTE: The syringe barrel is marked with numbers from 0.25 to 1.0. If the solution in the vial cannot be drawn up to the 1.0 mark, discard the vial and syringe and start over with a new tray containing a Betaseron vial, prefilled diluent syringe, vial adapter and alcohol prep pads.

3. Turn the syringe assembly so that the needle end is pointing up. Remove any air bubbles by tapping the outer wall of the syringe with your fingers. Slowly push the plunger to the 1 mL mark on the syringe (or to the amount prescribed by your doctor).
NOTE: If too much solution is pushed into the vial, repeat steps 1, 2, and 3.
4. Remove the vial adapter and the vial from the syringe by twisting the vial adapter as shown in Figure 5. This will remove the vial adapter and the vial from the syringe, but will leave the needle on the syringe (Figure 5).

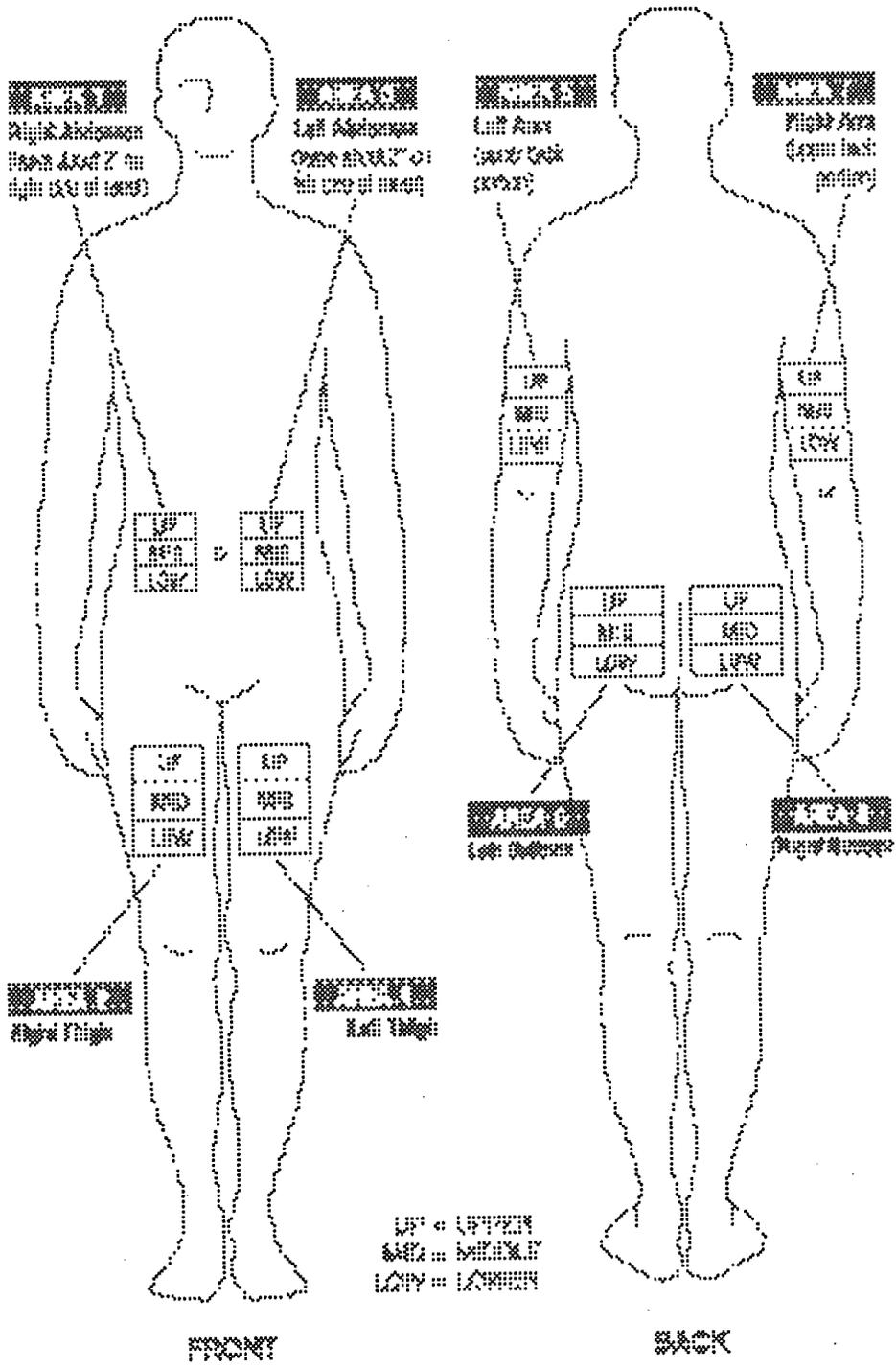
Figure 5



Picking an Injection Site

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

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

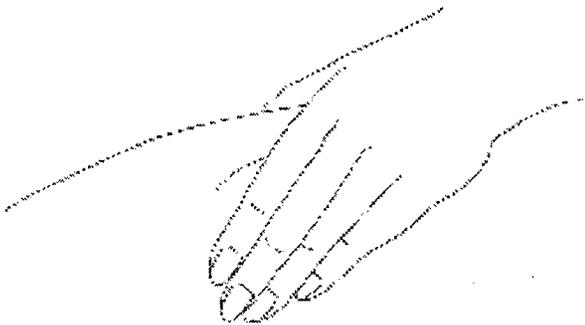


Do not inject in a site where the skin is red, bruised, infected, or scabbed, has broken open, or has lumps, bumps, or pain. Tell your doctor or healthcare provider if you find skin conditions like the ones mentioned here or any other unusual looking areas where you have been given injections.

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

Remove the cap from the needle.

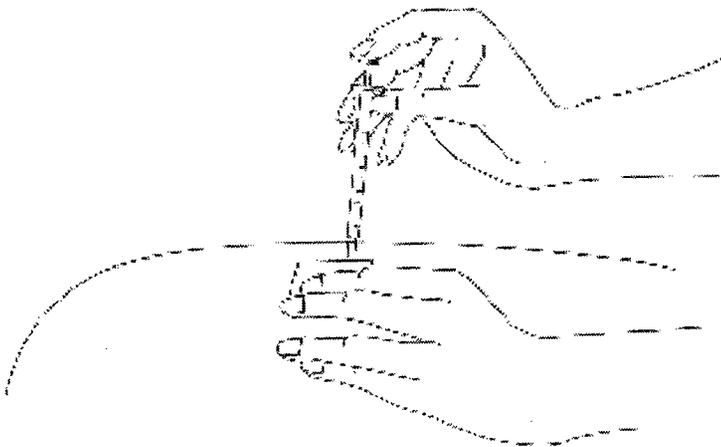
Hold the syringe like a pencil or dart in one hand.
Gently pinch the skin around the site with the thumb and forefinger of the other hand.



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

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

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



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

Throw away the 1 mL syringe in the disposal container.

Disposing of syringes and needles

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

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

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

How Should I Store Betaseron?

Betaseron should be stored at room temperature 77°F, but may be stored between 58° and 86°F. Avoid freezing.

This Medication Guide has been approved by the U.S. Food and Drug Administration
Manufactured by: Chiron Corporation, Emeryville, CA 94608
Distributed by: Berlex Laboratories, Montville, NJ 07045

October 2003

Physician Insert Labeling

DESCRIPTION

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

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

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

CLINICAL PHARMACOLOGY

General

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

Biologic Activities

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

Pharmacokinetics

Because serum concentrations of Interferon beta-1b are low or not detectable following subcutaneous administration of 0.25 mg or less of Betaseron, pharmacokinetic information in patients with MS receiving the recommended dose of Betaseron is not available. Following single and multiple daily

51 subcutaneous administrations of 0.5 mg Betaseron to healthy volunteers (N=12), serum Interferon beta-1b
52 concentrations were generally below 100 IU/mL. Peak serum Interferon beta-1b concentrations occurred
53 between one to eight hours, with a mean peak serum interferon concentration of 40 IU/mL.
54 Bioavailability, based on a total dose of 0.5 mg Betaseron given as two subcutaneous injections at
55 different sites, was approximately 50%.

56
57 After intravenous administration of Betaseron (0.006 mg to 2.0 mg), similar pharmacokinetic profiles
58 were obtained from healthy volunteers (N=12) and from patients with diseases other than MS (N=142).
59 In patients receiving single intravenous doses up to 2.0 mg, increases in serum concentrations were dose
60 proportional. Mean serum clearance values ranged from 9.4 mL/min•kg⁻¹ to 28.9 mL/min•kg⁻¹ and were
61 independent of dose. Mean terminal elimination half-life values ranged from 8.0 minutes to 4.3 hours and
62 mean steady-state volume of distribution values ranged from 0.25 L/kg to 2.88 L/kg. Three-times-a-week
63 intravenous dosing for two weeks resulted in no accumulation of Interferon beta-1b in sera of patients.
64 Pharmacokinetic parameters after single and multiple intravenous doses of Betaseron were comparable.

65
66 Following every other day subcutaneous administration of 0.25 mg Betaseron in healthy volunteers,
67 biologic response marker levels (neopterin, β_2 -microglobulin, MxA protein, and the immunosuppressive
68 cytokine, IL-10) increased significantly above baseline six-twelve hours after the first Betaseron dose.
69 Biologic response marker levels peaked between 40 and 124 hours and remained elevated above baseline
70 throughout the seven-day (168-hour) study. The relationship between serum Interferon beta-1b levels or
71 induced biologic response marker levels and the clinical effects of Interferon beta-1b in multiple sclerosis
72 is unknown.

73 74 **CLINICAL STUDIES**

75
76 The safety and efficacy of Betaseron have been assessed in three multicenter trials. Study 1 evaluated
77 Betaseron in relapsing-remitting MS (RRMS) patients and Studies 2 and 3 assessed Betaseron in
78 secondary progressive MS (SPMS) patients.

79
80 The effectiveness of Betaseron in relapsing-remitting MS (Study 1) was evaluated in a double blind,
81 multiclinic, randomized, parallel, placebo controlled clinical investigation of two years duration. The
82 study enrolled MS patients, aged 18 to 50, who were ambulatory (EDSS of ≤ 5.5), exhibited a relapsing-
83 remitting clinical course, met Poser's criteria¹ for clinically definite and/or laboratory supported definite
84 MS and had experienced at least two exacerbations over two years preceding the trial without
85 exacerbation in the preceding month. Patients who had received prior immunosuppressant therapy were
86 excluded.

87
88 An exacerbation was defined as the appearance of a new clinical sign/symptom or the clinical worsening
89 of a previous sign/symptom (one that had been stable for at least 30 days) that persisted for a minimum of
90 24 hours.

91
92 Patients selected for study were randomized to treatment with either placebo (N=123), 0.05 mg of
93 Betaseron (N=125), or 0.25 mg of Betaseron (N=124) self-administered subcutaneously every other day.
94 Outcome based on the 372 randomized patients was evaluated after two years.

95
96 Patients who required more than three 28-day courses of corticosteroids were removed from the study.
97 Minor analgesics (acetaminophen, codeine), antidepressants, and oral baclofen were allowed ad libitum,
98 but chronic nonsteroidal anti-inflammatory drug (NSAID) use was not allowed.

99
100 The primary protocol-defined outcome measures were 1) frequency of exacerbations per patient and 2)

101 proportion of exacerbation free patients. A number of secondary clinical and magnetic resonance imaging
 102 (MRI) measures were also employed. All patients underwent annual T2 MRI imaging and a subset of 52
 103 patients at one site had MRIs performed every six weeks for assessment of new or expanding lesions.
 104

105 The study results are shown in Table 1.
 106
 107

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

Efficacy Parameters		Treatment Groups			Statistical Comparisons p-value		
		Placebo (N=123)	0.05 mg (N=125)	0.25 mg (N=124)	Placebo vs 0.05 mg	0.05 mg vs 0.25 mg	Placebo vs 0.25 mg
Primary End Points							
Annual exacerbation rate		1.31	1.14	0.90	0.005	0.113	0.0001
Proportion of exacerbation-free patients†		16%	18%	25%	0.609	0.288	0.094
Exacerbation frequency per patient	0†	20	22	29	0.151	0.077	0.001
	1	32	31	39			
	2	20	28	17			
	3	15	15	14			
	4	15	7	9			
	≥5	21	16	8			
Secondary Endpoints††							
Median number of months to first on-study exacerbation		5	6	9	0.299	0.097	0.010
Rate of moderate or severe exacerbations per year		0.47	0.29	0.23	0.020	0.257	0.001
Mean number of moderate or severe exacerbation days per patient		44.1	33.2	19.5	0.229	0.064	0.001
Mean change in EDSS score‡ at endpoint		0.21	0.21	-0.07	0.995	0.108	0.144
Mean change in Scripps score‡‡ at endpoint		-0.53	-0.50	0.66	0.641	0.051	0.126
Median duration in days per exacerbation		36	33	35.5	ND	ND	ND
% change in mean MRI lesion area at endpoint		21.4%	9.8%	-0.9%	0.015	0.019	0.0001

ND Not done

† 14 exacerbation free patients (0 from placebo, six from 0.05 mg, and eight from 0.25 mg) dropped out of the study before completing six months of therapy. These patients are excluded from this analysis.

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

‡ EDSS scores range from 1-10, with higher scores reflecting greater disability

‡‡ Scripps neurologic rating scores range from 0-100, with smaller scores reflecting greater disability.

108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126

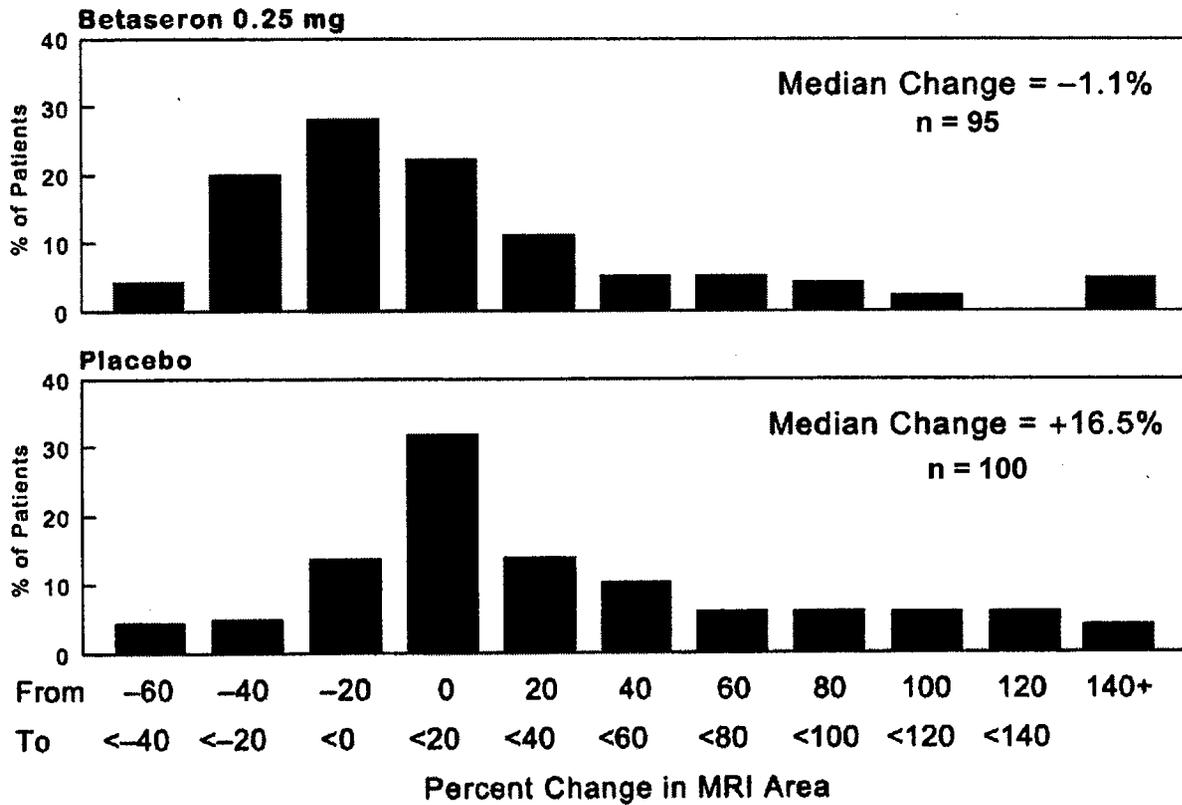
Of the 372 RRMS patients randomized, 72 (19%) failed to complete two full years on their assigned treatments.

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

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

Distribution of Change in MRI Area

Figure 1



127
128
129
130
131
132
133

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

The exact relationship between MRI findings and clinical status of patients is unknown. Changes in

134 lesion area often do not correlate with changes in disability progression. The prognostic significance of
135 the MRI findings in this study has not been evaluated.

136
137 Studies 2 and 3 were multicenter, randomized, double-blind, placebo controlled trials conducted to assess
138 the effect of Betaseron in patients with SPMS. Study 2 was conducted in Europe and Study 3 was
139 conducted in North America. Both studies enrolled patients with clinically definite or laboratory-
140 supported MS in the secondary progressive phase, and who had evidence of disability progression (both
141 Study 2 and 3) or two relapses (Study 2 only) within the previous two years. Baseline Kurtzke expanded
142 disability status scale (EDSS) scores ranged from 3.0 to 6.5.² Patients in Study 2 were randomized to
143 receive Betaseron 0.25 mg (n=360) or placebo (n=358). Patients in Study 3 were randomized to
144 Betaseron 0.25 mg (n=317), Betaseron 0.16 mg/m² of body surface area (n=314, mean assigned dose 0.30
145 mg), or placebo (n=308). Test agents were administered subcutaneously, every other day for three years.

146
147 The primary outcome measure was progression of disability, defined as a 1.0 point increase in the EDSS
148 score, or a 0.5 point increase for patients with baseline EDSS \geq 6.0. In Study 2, time to progression in
149 EDSS was longer in the Betaseron treatment group (p=0.005), with estimated annualized rates of
150 progression of 16% and 19% in the Betaseron and placebo groups, respectively. In Study 3, the rates of
151 progression did not differ significantly between treatment groups, with estimated annualized rates of
152 progression of 12%, 14%, and 12% in the Betaseron fixed dose, surface area-adjusted dose, and placebo
153 groups, respectively.

154
155 Multiple analyses, including covariate and subset analyses based on sex, age, disease duration, clinical
156 disease activity prior to study enrollment, MRI measures at baseline and early changes in MRI following
157 treatment were evaluated in order to interpret the discordant study results. No demographic or disease-
158 related factors enabled identification of a patient subset where Betaseron treatment was predictably
159 associated with delayed progression of disability.

160
161 In Studies 2 and 3, like Study 1, a statistically significant decrease in the incidence of relapses associated
162 with Betaseron treatment was demonstrated. In Study 2, the mean annual relapse rates were 0.42 and 0.63
163 in the Betaseron and placebo groups, respectively (p<0.001). In Study 3, the mean annual relapse rates
164 were 0.16, 0.20, and 0.28, for the fixed dose, surface area-adjusted dose, and placebo groups, respectively
165 (p<0.02).

166
167 MRI endpoints in both Study 2 and Study 3 showed lesser increases in T2 MRI lesion area and decreased
168 number of active MRI lesions in patients in the Betaseron groups. The exact relationship between MRI
169 findings and the clinical status of patients is unknown. Changes in MRI findings often do not correlate
170 with changes in disability progression. The prognostic significance of the MRI findings in these studies is
171 not known.

172
173 Safety and efficacy of treatment with Betaseron beyond three years are not known.

174 175 **INDICATIONS AND USAGE**

176
177 Betaseron (Interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to
178 reduce the frequency of clinical exacerbations.

179 180 **CONTRAINDICATIONS**

181
182 Betaseron is contraindicated in patients with a history of hypersensitivity to natural or recombinant
183 interferon beta, Albumin (Human), USP, or any other component of the formulation.

184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233

WARNINGS

Depression and Suicide

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

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

Injection Site Necrosis

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

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

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

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

Anaphylaxis

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

Albumin (Human), USP

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote.

234 No cases of transmission of viral diseases or CJD have ever been identified for albumin.

235

236 **PRECAUTIONS**

237

238 **Information for Patients**

239

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

242

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

248

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

252

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

257

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

260

261 **Instruction on Self-injection Technique and Procedures**

262

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

267

268 Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal
269 procedures. A puncture resistant container for disposal of used needles and syringes should be supplied to
270 the patient along with instructions for safe disposal of full containers.

271

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

275

276 **Laboratory Tests**

277

278 In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis,
279 complete blood and differential white blood cell counts, platelet counts and blood chemistries, including
280 liver function tests, are recommended at regular intervals (one, three, and six months) following
281 introduction of Betaseron therapy, and then periodically thereafter in the absence of clinical symptoms.
282 Thyroid function tests are recommended every six months in patients with a history of thyroid
283 dysfunction or as clinically indicated. Patients with myelosuppression may require more intensive

284 monitoring of complete blood cell counts, with differential and platelet counts.

285

286 **Drug Interactions**

287

288 No formal drug interaction studies have been conducted with Betaseron. In the placebo controlled studies
289 in MS, corticosteroids or ACTH were administered for treatment of relapses for periods of up to 28 days
290 in patients (N=664) receiving Betaseron.

291

292 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

293

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

295

296 *Mutagenesis:* Betaseron was not mutagenic when assayed for genotoxicity in the Ames bacterial test in
297 the presence or absence of metabolic activation. Interferon beta-1b was not mutagenic to human
298 peripheral blood lymphocytes *in vitro*, in the presence or absence of metabolic inactivation. Betaseron
299 treatment of mouse BALBc-3T3 cells did not result in increased transformation frequency in an *in vitro*
300 model of tumor transformation.

301

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

308

309 **Pregnancy – Teratogenic Effects**

310

311 *Pregnancy Category C:* Betaseron was not teratogenic at doses up to 0.42 mg/kg/day when given to
312 pregnant female rhesus monkeys on gestation days 20 to 70. However, a dose related abortifacient
313 activity was observed in these monkeys when Interferon beta-1b was administered at doses ranging from
314 0.028 mg/kg/day to 0.42 mg/kg/day (2.8 to 40 times the recommended human dose based on body surface
315 area comparison). The validity of extrapolating doses used in animal studies to human doses is not
316 known. Lower doses were not studied in monkeys. Spontaneous abortions while on treatment were
317 reported in patients (n=4) who participated in the Betaseron RRMS clinical trial. Betaseron given to
318 rhesus monkeys on gestation days 20 to 70 did not cause teratogenic effects; however, it is not known if
319 teratogenic effects exist in humans. There are no adequate and well-controlled studies in pregnant
320 women. If the patient becomes pregnant or plans to become pregnant while taking Betaseron, the patient
321 should be apprised of the potential hazard to the fetus and it should be recommended that the patient
322 discontinue therapy.

323

324 **Nursing Mothers**

325

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

330

331 **Pediatric Use**

332

333 Safety and efficacy in pediatric patients have not been established.

334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382

Geriatric Use

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

ADVERSE REACTIONS

In all studies, the most serious adverse reactions with Betaseron were depression, suicidal ideation and injection site necrosis (see **WARNINGS**). The incidence of depression of any severity was approximately 34% in both Betaseron-treated patients and placebo-treated patients. Anaphylaxis and other allergic reactions have been reported in patients using Betaseron (see **WARNINGS**). The most commonly reported adverse reactions were lymphopenia (lymphocytes < 1500/mm³), injection site reaction, asthenia, flu-like symptom complex, headache, and pain. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Betaseron, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were depression, flu-like symptom complex, injection site reactions, leukopenia, increased liver enzymes, asthenia, hypertonia, and myasthenia.

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

The data described below reflect exposure to Betaseron in the three placebo controlled trials of 1115 patients with MS treated with 0.25 mg or 0.16 mg/m², including 1041 exposed for greater than one year. The population encompassed an age range from 18 – 65 years. Sixty-five percent (65%) of the patients were female. The percentages of Caucasian, Black, Asian, and Hispanic patients were 94.0%, 4.3%, 0.2%, and 0.8%, respectively.

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

Injection Site Reactions

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

Flu-Like Symptom Complex

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

383 was 7.5 days.

384

385 **Laboratory Abnormalities**

386

387 In the three clinical trials, leukopenia was reported in 18% and 5% of patients in Betaseron- and placebo-
388 treated groups, respectively. No patients were withdrawn or dose reduced for neutropenia in Study 1.
389 Three percent (3%) of patients in Studies 2 and 3 experienced leukopenia and were dose-reduced. Other
390 laboratory abnormalities included SGPT greater than five times baseline value (10%), and SGOT greater
391 than five times baseline value (3%). In Study 1, two patients were dose reduced for increased liver
392 enzymes; one continued on treatment and one was ultimately withdrawn. In Studies 2 and 3, 1.5% of
393 Betaseron patients were dose-reduced or interrupted treatment for increased liver enzymes. Three (0.3%)
394 patients were withdrawn from treatment with Betaseron for any laboratory abnormality including two
395 (0.2%) patients following dose reduction (see **PRECAUTIONS, Laboratory Tests**).

396

397 **Menstrual Irregularities**

398

399 In the three clinical trials, 82 (14%) of the 577 pre-menopausal females treated with Betaseron and 74
400 (18%) of the 405 pre-menopausal females treated with placebo reported menstrual disorders. One event
401 was reported as severe, all other reports were mild to moderate severity. No patients withdrew from the
402 studies due to menstrual irregularities.

403

404 Table 2 enumerates adverse events and laboratory abnormalities that occurred among all patients treated
405 with 0.25 mg or 0.16 mg/m² Betaseron every other day for periods of up to three years in the controlled
406 trials at an incidence that was at least 2% more than that observed in the placebo patients.

407

Table 2
Adverse Reactions and Laboratory Abnormalities

Adverse Reaction	Placebo (n=789)	Betaseron (n=1115)
Body as a Whole		
Injection site reaction	29%	85%
Asthenia	54%	61%
Flu-like symptom complex	41%	60%
Headache	48%	57%
Pain	42%	51%
Fever	22%	36%
Chills	11%	25%
Abdominal pain	13%	19%
Chest pain	7%	11%
Malaise	4%	8%
Injection site necrosis	0%	5%
Cardiovascular System		
Peripheral edema	12%	15%
Vasodilation	6%	8%
Hypertension	4%	7%
Peripheral vascular disorder	4%	6%
Palpitation	2%	4%
Tachycardia	2%	4%
Digestive System		
Nausea	25%	27%
Constipation	18%	20%

Diarrhea	16%	19%
Dyspepsia	12%	14%
Hemic and Lymphatic System		
Lymphocytes < 1500/mm ³	70%	88%
ANC < 1500/mm ³	5%	14%
WBC < 3000/mm ³	4%	14%
Lymphadenopathy	4%	8%
Metabolic and Nutritional Disorders		
SGPT > 5 times baseline	4%	10%
SGOT > 5 times baseline	1%	3%
Weight gain	5%	7%
Musculoskeletal System		
Myasthenia	43%	46%
Arthralgia	29%	31%
Myalgia	16%	27%
Leg cramps	2%	4%

408
409
410

Adverse Reaction	Placebo (n=789)	Betaseron (n=1115)
Nervous System		
Hypertonia	40%	50%
Dizziness	21%	24%
Insomnia	19%	24%
Incoordination	18%	21%
Anxiety	8%	10%
Nervousness	5%	7%
Respiratory System		
Dyspnea	4%	7%
Skin and Appendages		
Rash	18%	24%
Skin disorder	10%	12%
Sweating	6%	8%
Alopecia	2%	4%
Urogenital System		
Urinary urgency	10%	13%
Metrorrhagia*	8%	11%
Menorrhagia*	6%	8%
Impotence**	7%	9%
Urinary frequency	5%	7%
Dysmenorrhea*	5%	7%
Prostatic disorder**	1%	3%
*pre-menopausal women		
**male patients		

411
412
413
414

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

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

422 *The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been
423 associated with the development of this syndrome.
424

425 **Immunogenicity**

426
427 As with all therapeutic proteins, there is a potential for immunogenicity. Serum samples were monitored
428 for the development of antibodies to Betaseron during the RRMS study. In patients receiving 0.25 mg
429 every other day 56/124 (45%) were found to have serum neutralizing activity at one or more of the time
430 points tested. The relationship between antibody formation and clinical safety or efficacy is not known.
431

432 These data reflect the percentage of patients whose test results were considered positive for antibodies to
433 Betaseron using a biological neutralization assay that measures the ability of immune sera to inhibit the
434 production of the interferon-inducible protein, MxA. Neutralization assays are highly dependent on the
435 sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an
436 assay may be influenced by several factors including sample handling, timing of sample collection,
437 concomitant medications, and underlying disease. For these reasons, comparison of the incidence of
438 antibodies to Betaseron with the incidence of antibodies to other products may be misleading.
439

440 Anaphylactic reactions have rarely been reported with the use of Betaseron.
441

442 **DRUG ABUSE AND DEPENDENCE**

443
444 No evidence or experience suggests that abuse or dependence occurs with Betaseron therapy; however,
445 the risk of dependence has not been systematically evaluated.
446

447 **OVERDOSAGE**

448
449 Safety of doses higher than 0.25 mg every other day has not been adequately evaluated. The maximum
450 amount of Betaseron that can be safely administered has not been determined.
451

452 **DOSAGE AND ADMINISTRATION**

453
454 The recommended dose of Betaseron is 0.25 mg injected subcutaneously every other day.
455 Generally, patients should be started at 0.0625 mg (0.25 mL) subcutaneously every other day, and
456 increased over a six-week period to 0.25 mg (1.0 mL) every other day (see Table 3).
457

458 Table 3. Schedule for Dose Titration
459

	Recommended Titration	Betaseron Dose	Volume
Weeks 1-2	25%	0.0625 mg	0.25 mL
Weeks 3-4	50%	0.125 mg	0.50 mL

Weeks 5-6	75%	0.1875 mg	0.75 mL
Week 7+	100%	0.25 mg	1.0 mL

460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506

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

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

Stability and Storage

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

HOW SUPPLIED

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

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

Rx Only.

REFERENCES

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

Manufactured by: CHIRON Corporation Emeryville, CA 94608

U.S. License No. 1106

507 Distributed by: BERLEX Laboratories Montville, NJ 07045
508
509 U.S. Patent No. 4,588,585; 4,959,314; 4,737,462; 4,450,103
510
511 © 2003 Berlex Laboratories All rights reserved.
512 Printed in U.S.A. on recycled paper
513 Part Number XXXX October 2003