Rebif® (interferon beta-1a)

DESCRIPTION

Rebif® (interferon beta-1a) is a purified 166 amino acid glycoprotein with a molecular weight of approximately 22,500 daltons. It is produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of Rebif® is identical to that of natural fibroblast derived human interferon beta. Natural interferon beta and interferon beta-1a (Rebif®) are glycosylated with each containing a single N-linked complex carbohydrate moiety.

Using a reference standard calibrated against the World Health Organization natural interferon beta standard (Second International Standard for Interferon, Human Fibroblast GB 23 902 531), Rebif® has a specific activity of approximately 270 million international units (MIU) of antiviral activity per mg of interferon beta-1a determined specifically by an in vitro cytopathic effect bioassay using WISH cells and Vesicular Stomatitis virus. Rebif® 8.8 mcg, 22 mcg and 44 mcg contains approximately 2.4 million international units , 6 million international units or 12 million international units, respectively, of antiviral activity using this method.

Rebif® (interferon beta-1a) is formulated as a sterile solution in a pre-filled syringe or Rebif® Rebidose® autoinjector intended for subcutaneous (sc) injection. Each 0.5 ml (0.5 cc) of Rebif® contain either 22 mcg or 44 mcg of interferon beta-1a, 2 mg or 4 mg albumin (human) USP, 27.3 mg mannitol USP, 0.4 mg sodium acetate, Water for Injection USP. Each 0.2 ml (0.2 cc) of Rebif® contains 8.8 mcg of interferon beta-1a, 0.8 mg albumin (human) USP, 10.9 mg mannitol USP, 0.16 mg sodium acetate, and Water for Injection USP.

CLINICAL PHARMACOLOGY

General

Interferons are a family of naturally occurring proteins that are produced by eukaryotic cells in response to viral infection and other biological inducers. Interferons possess immunomodulatory, antiviral and antiproliferative biological activities. They exert their biological effects by binding to specific receptors on the surface of cells. Three major groups of interferons have been distinguished: alpha, beta, and gamma. Interferons alpha and beta form the Type I interferons and interferon gamma is a Type II interferon. Type I interferons have considerably overlapping but also distinct biological activities. Interferon beta is produced naturally by various cell types including fibroblasts and macrophages. Binding of interferon beta to its receptors initiates a complex cascade of intracellular events that leads to the expression of numerous interferon-induced gene products and markers, including 2', 5'-oligoadenylate synthetase, beta 2-microglobulin and neopterin, which may mediate some of the biological activities. The specific interferon-induced proteins and mechanisms by which interferon beta-1a exerts its effects in multiple sclerosis have not been fully defined.

Pharmacokinetics

The pharmacokinetics of Rebif® (interferon beta-1a) in people with multiple sclerosis have not been evaluated. In healthy volunteer subjects, a single subcutaneous (sc) injection of 60 mcg of Rebif® (liquid formulation), resulted in a peak serum concentration (C_{max}) of 5.1 ± 1.7 IU/mL (mean ± SD), with a median time of peak serum concentration (T_{max}) of 16 hours. The serum elimination half-life ($t_{1/2}$) was 69 ± 37 hours, and the area under the serum concentration versus time curve (AUC) from zero to 96 hours was 294 ± 81 IU·h/mL. Following every other day sc injections in healthy volunteer subjects, an increase in AUC of approximately 240% was

observed, suggesting that accumulation of interferon beta-1a occurs after repeat administration. Total clearance is approximately 33-55 L/hour. There have been no observed gender-related effects on pharmacokinetic parameters. Pharmacokinetics of Rebif® in pediatric and geriatric patients or patients with renal or hepatic insufficiency have not been established.

Pharmacodynamics

Biological response markers (e.g., 2',5'-OAS activity, neopterin and beta 2-microglobulin) are induced by interferon beta-1a following parenteral doses administered to healthy volunteer subjects and to patients with multiple sclerosis. Following a single sc administration of 60 mcg of Rebif® intracellular 2',5'-OAS activity peaked between 12 to 24 hours and beta-2-microglobulin and neopterin serum concentrations showed a maximum at approximately 24 to 48 hours. All three markers remained elevated for up to four days. Administration of Rebif® 22 mcg three times per week (tiw) inhibited mitogen-induced release of pro-inflammatory cytokines (IFN-γ, IL-1, IL-6, TNF-α and TNF-β) by peripheral blood mononuclear cells that, on average, was near double that observed with Rebif® administered once per week (qw) at either 22 or 66 mcg.

The relationships between serum interferon beta-1a levels and measurable pharmacodynamic activities to the mechanism(s) by which Rebif® exerts its effects in multiple sclerosis are unknown. No gender-related effects on pharmacodynamic parameters have been observed.

CLINICAL STUDIES

Two multicenter studies evaluated the safety and efficacy of Rebif® in patients with relapsing-remitting multiple sclerosis.

Study 1 was a randomized, double-blind, placebo controlled study in patients with multiple sclerosis for at least one year, Kurtzke Expanded Disability Status Scale (EDSS) scores ranging from 0 to 5, and at least 2 acute exacerbations in the previous 2 years.[(1)] Patients with secondary progressive multiple sclerosis were excluded from the study. Patients received sc injections of either placebo (n = 187), Rebif® 22 mcg (n = 189), or Rebif® 44 mcg (n = 184) administered three times per week for two years. Doses of study agents were progressively increased to their target doses during the first 4 to 8 weeks for each patient in the study (see **DOSAGE AND ADMINISTRATION**).

The primary efficacy endpoint was the number of clinical exacerbations. Numerous secondary efficacy endpoints were also evaluated and included exacerbation-related parameters, effects of treatment on progression of disability and magnetic resonance imaging (MRI)-related parameters. Progression of disability was defined as an increase in the EDSS score of at least 1 point sustained for at least 3 months. Neurological examinations were completed every 3 months, during suspected exacerbations, and coincident with MRI scans. All patients underwent proton density T2-weighted (PD/T2) MRI scans at baseline and every 6 months. A subset of 198 patients underwent PD/T2 and T1-weighted gadolinium-enhanced (Gd)-MRI scans monthly for the first 9 months. Of the 560 patients enrolled, 533 (95%) provided 2 years of data and 502 (90%) received 2 years of study agent.

Study results are shown in Table 1 and Figure 1. Rebif® at doses of 22 mcg and 44 mcg administered sc three times per week significantly reduced the number of exacerbations per patient as compared to placebo. Differences between the 22 mcg and 44 mcg groups were not significant ($p > 0.05$).

The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in lesion area often do not correlate with changes in disability progression. The prognostic significance of the MRI findings in these studies has not been evaluated.

Table 1: Clinical and MRI Endpoints from Study 1

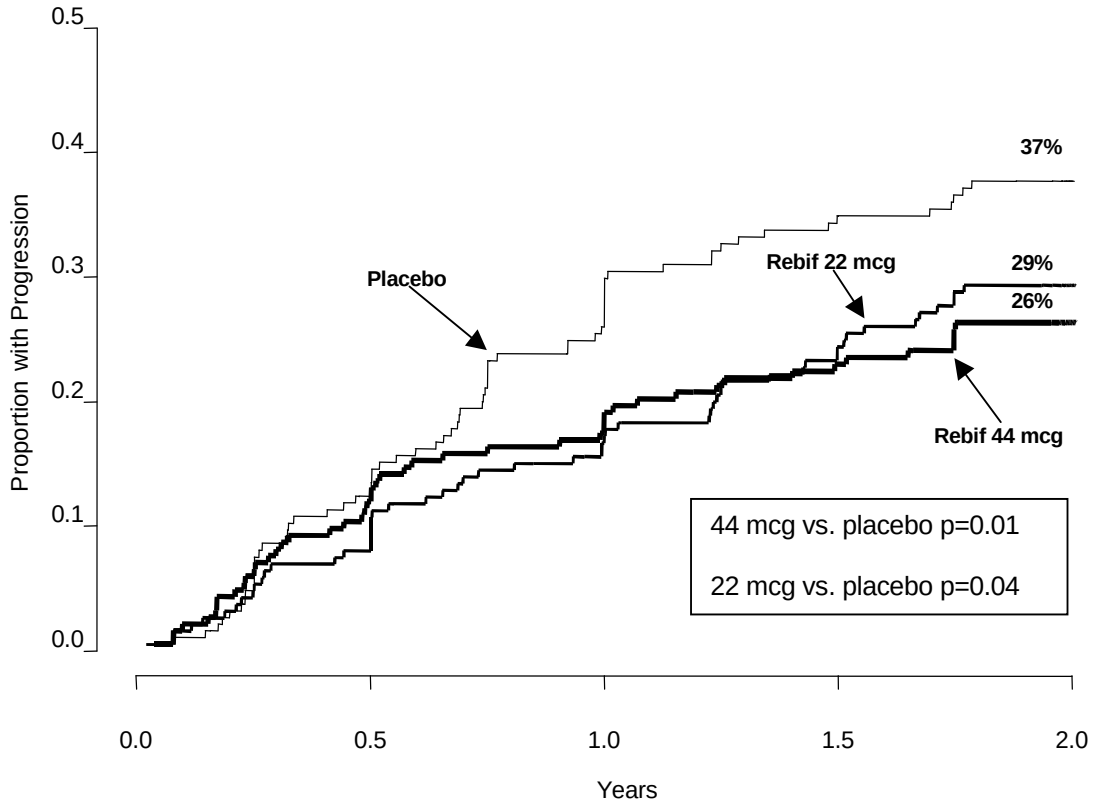
	Placebo	22 mcg tiw	44 mcg tiw
	n = 187	n = 189	n = 184
Exacerbation-related			
Mean number of exacerbations per patient over 2 years[1,2]	2.56	1.82**	1.73***
(Percent reduction)		(29%)	(32%)
Percent (%) of patients exacerbation-free at 2 years[3]	15%	25%*	32%***
Median time to first exacerbation (months)[1,4]	4.5	7.6**	9.6***
MRI	n = 172	n = 171	n = 171
Median percent (%) change of MRI PD-T2 lesion area at 2 years[5]	11.0	-1.2***	-3.8***
Median number of active lesions per patient per scan (PD/T2; 6 monthly)[5]	2.25	0.75***	0.5***

* p<0.05 compared to placebo ** p<0.001 compared to placebo *** p<0.0001 compared to placebo

(1) Intent-to-treat analysis
(2) Poisson regression model adjusted for center and time on study
(3) Logistic regression adjusted for center. Patients lost to follow-up prior to an exacerbation were excluded from this analysis (n = 185, 183, and 184 for the placebo, 22 mcg tiw, and 44 mcg tiw groups, respectively)
(4) Cox proportional hazard model adjusted for center
(5) ANOVA on ranks adjusted for center. Patients with missing scans were excluded from this analysis

The time to onset of progression in disability sustained for three months was significantly longer in patients treated with Rebif® than in placebo-treated patients. The Kaplan-Meier estimates of the proportions of patients with sustained disability are depicted in Figure 1.

Figure 1: Proportions of Patients with Sustained Disability Progression



The safety and efficacy of treatment with Rebif® beyond 2 years have not been established.

Study 2 was a randomized, open-label, evaluator-blinded, active comparator study.[(2)] Patients with relapsing-remitting multiple sclerosis with EDSS scores ranging from 0 to 5.5, and at least 2 exacerbations in the previous 2 years were eligible for inclusion. Patients with secondary progressive multiple sclerosis were excluded from the study. Patients were randomized to treatment with Rebif® 44 mcg tiw by sc injection (n=339) or Avonex® 30 mcg qw by intramuscular (im) injection (n=338). Study duration was 48 weeks.

The primary efficacy endpoint was the proportion of patients who remained exacerbation-free at 24 weeks. The principal secondary endpoint was the mean number per patient per scan of combined unique active MRI lesions through 24 weeks, defined as any lesion that was T1 active or T2 active. Neurological examinations were performed every three months by a neurologist

blinded to treatment assignment. Patient visits were conducted monthly, and mid-month telephone contacts were made to inquire about potential exacerbations. If an exacerbation was suspected, the patient was evaluated with a neurological examination. MRI scans were performed monthly and analyzed in a treatment–blinded manner.

Patients treated with Rebif® 44 mcg sc three times per week were more likely to remain relapse-free at 24 and 48 weeks than were patients treated with Avonex® 30 mcg im qw (Table 2). This study does not support any conclusion regarding effects on the accumulation of physical disability.

Table 2: Clinical and MRI Results from Study 2

	Rebif®	Avonex®	Absolute Difference	Risk of relapse on Rebif® relative to Avonex®
Relapses	N=339	N=338		
Proportion of patients relapse-free at 24 weeks[1]	75%*	63%	12% (95% CI: 5%, 19%)	0.68 (95% CI: 0.54, 0.86)
Proportion of patients relapse-free at 48 weeks	62%**	52%	10% (95%CI: 2%, 17%)	0.81 (95%CI: 0.68, 0.96)
MRI (through 24 weeks)	N=325	N=325		
Median of the mean number of combined unique MRI lesions per patient per scan[2](25th, 75th percentiles)	0.17* (0.00, 0.67)	0.33 (0.00, 1.25)		

* p <0.001, and ** p = 0.009, Rebif® compared to Avonex®
(1) Logistic regression model adjusted for treatment and center, intent to treat analysis
(2) Nonparametric ANCOVA model adjusted for treatment and center, with baseline combined unique lesions as the single covariate.

The adverse reactions over 48 weeks were generally similar between the two treatment groups.

Exceptions included injection site disorders (83% of patients on Rebif® vs. 28% of patients on Avonex®), hepatic function disorders (18% on Rebif® vs. 10% on Avonex®), and leukopenia (6% on Rebif® vs. <1% on Avonex®), which were observed with greater frequency in the Rebif® group compared to the Avonex® group.

INDICATIONS AND USAGE

Rebif® (interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Efficacy of Rebif® in chronic progressive multiple sclerosis has not been established.

CONTRAINDICATIONS

Rebif® (interferon beta-1a) is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon, human albumin, or any other component of the formulation.

WARNINGS

Depression and Suicide

Rebif® (interferon beta-1a) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including Rebif®. In addition, there have been postmarketing reports of suicide in patients treated with Rebif®. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to the prescribing physician. If a patient develops depression, cessation of treatment with Rebif® should be considered.

Hepatic Injury

Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has been reported rarely in patients taking Rebif®. Symptoms of liver dysfunction began from one to six months following the initiation of Rebif®. If jaundice or other symptoms of liver dysfunction appear, treatment with Rebif® should be discontinued immediately due to the potential for rapid progression to liver failure.

Asymptomatic elevation of hepatic transaminases (particularly SGPT) is common with interferon therapy (see **ADVERSE REACTIONS**). Rebif® should be initiated with caution in patients with active liver disease, alcohol abuse, increased serum SGPT (> 2.5 times ULN), or a history of significant liver disease. Also, the potential risk of Rebif® used in combination with known hepatotoxic products should be considered prior to Rebif® administration, or when adding new agents to the regimen of patients already on Rebif®. Reduction of Rebif® dose should be considered if SGPT rises above 5 times the upper limit of normal. The dose may be gradually re-escalated when enzyme levels have normalized. (See **PRECAUTIONS:** Laboratory Tests and Drug Interactions; and **DOSAGE AND ADMINISTRATION)**

Anaphylaxis

Anaphylaxis has been reported as a rare complication of Rebif® use. Other allergic reactions have included skin rash and urticaria, and have ranged from mild to severe without a clear relationship to dose or duration of exposure. Several allergic reactions, some severe, have occurred after prolonged use.

Albumin (Human)

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

PRECAUTIONS

General

Caution should be exercised when administering Rebif® to patients with pre-existing seizure disorders. Seizures have been associated with the use of beta interferons. A relationship between occurrence of seizures and the use of Rebif® has not been established. Leukopenia and new or worsening thyroid abnormalities have developed in some patients treated with Rebif® (see **ADVERSE REACTIONS**). Regular monitoring for these conditions is recommended (see **PRECAUTIONS**: Laboratory Tests).

Information for Patients

All patients should be instructed to read the Rebif® Medication Guide supplied to them. Patients should be cautioned not to change the dosage or the schedule of administration without medical consultation.

Patients should be informed of the most common and the most severe adverse reactions associated with the use of Rebif® (see **WARNINGS and ADVERSE REACTIONS**). Patients should be advised of the symptoms associated with these conditions, and to report them to their physician.

Female patients should be cautioned about the abortifacient potential of Rebif® (see **PRECAUTIONS**: Pregnancy).

Patients should be instructed in the use of aseptic technique when administering Rebif®. Appropriate instruction for self-injection or injection by another person should be provided to the patient or their caregiver, including careful review of the Rebif® Medication Guide and the Rebif® Rebidose® autoinjector Instructions for Use that accompanies the product. Users should demonstrate competency in all aspects of the injection prior to independent use. If a patient is to self-administer Rebif®, the physical and cognitive ability of that patient to self-administer and properly dispose of pre-filled syringes or the Rebif® Rebidose® autoinjectors should be assessed. Patients with severe neurological deficits should not self administer injections without assistance from a trained caregiver. The initial injection should be performed under the supervision of an appropriately qualified health care provider. Patients can remove the pre-filled syringes or the Rebif® Rebidose® autoinjector from the refrigerator at least 30 minutes prior to use so it can warm to room temperature. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of severe injection site reactions or necrosis and whether or not to pinch the skin prior to injection. A puncture-resistant container for disposal of used needles, pre-filled syringes and Rebif® Rebidose® autoinjectors should be supplied to the patient along with instructions for safe disposal of full containers. Patients should be instructed in the importance of proper disposal of pre-filled syringes and Rebif® Rebidose® autoinjectors and be cautioned against reuse of these items.

Laboratory Tests

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) following introduction of Rebif® therapy and then periodically thereafter in the

absence of clinical symptoms. Thyroid function tests are recommended every 6 months in patients with a history of thyroid dysfunction or as clinically indicated. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Drug Interactions

No formal drug interaction studies have been conducted with Rebif®. Due to its potential to cause neutropenia and lymphopenia, proper monitoring of patients is required if Rebif® is given in combination with myelosuppressive agents.

Also, the potential for hepatic injury should be considered when Rebif® is used in combination with other products associated with hepatic injury, or when new agents are added to the regimen of patients already on Rebif® (see **WARNINGS:** Hepatic injury).

Immunization

In a nonrandomized prospective clinical study, 86 multiple sclerosis (MS) patients on Rebif® 44 mcg three times per week for at least 6 months and 77 patients not receiving interferon received influenza vaccination. The proportion of patients achieving a positive antibody response (defined as a titer > 1:40 measured by a hemagglutination inhibition assay) was similar in the two groups (93% and 91%, respectively). The exact relationship of antibody titers to vaccine efficacy was not studied and is not known in patients receiving Rebif®. Therefore, while patients receiving Rebif® may receive concomitant vaccination, the overall effectiveness of such vaccination is unknown.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: No carcinogenicity data for Rebif® are available in animals or humans.

Mutagenesis: Rebif® was not mutagenic when tested in the Ames bacterial test and in an *in vitro* cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation.

Impairment of Fertility: No studies have been conducted to evaluate the effects of Rebif® on fertility in humans. In studies in normally cycling female cynomolgus monkeys given daily sc injections of Rebif® for six months at doses of up to 9 times the recommended weekly human dose (based on body surface area), no effects were observed on either menstrual cycling or serum estradiol levels. The validity of extrapolating doses used in animal studies to human doses is not established. In male monkeys, the same doses of Rebif® had no demonstrable adverse effects on sperm count, motility, morphology, or function.

Pregnancy Category C

Rebif® treatment has been associated with significant increases in embryolethal or abortifacient effects in cynomolgus monkeys administered doses approximately 2 times the cumulative weekly human dose (based on either body weight or surface area) either during the period of organogenesis (gestation day 21-89) or later in pregnancy. There were no fetal malformations or other evidence of teratogenesis noted in these studies. These effects are consistent with the abortifacient effects of other type I interferons. There are no adequate and well-controlled studies of Rebif® in pregnant women. However, in Studies 1 and 2, there were 2 spontaneous abortions observed and 5 fetuses carried to term among 7 women in the Rebif® groups. If a woman becomes pregnant or plans to become pregnant while taking Rebif®, she should be informed about the potential hazards to the fetus, and discontinuation of Rebif® should be considered.

Nursing Mothers

It is not known whether Rebif® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Rebif® is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Rebif® in pediatric patients have not been studied.

Geriatric Use: Clinical studies of Rebif® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The most frequently reported serious adverse reactions with Rebif® were psychiatric disorders including depression and suicidal ideation or attempt (see **WARNINGS**). The incidence of depression of any severity in the Rebif®-treated groups and placebo-treated group was approximately 25%. In post-marketing experience, Rebif® administration has been rarely associated with severe liver dysfunction, including hepatic failure requiring liver transplantation (see **WARNINGS:** Hepatic Injury).

The most commonly reported adverse reactions were injection site disorders, influenza-like symptoms (headache, fatigue, fever, rigors, chest pain, back pain, myalgia), abdominal pain, depression, elevation of liver enzymes and hematologic abnormalities. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Rebif®, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were injection site disorders, influenza-like symptoms, depression and elevation of liver enzymes (see **WARNINGS**).

In Study 1, 6 patients randomized to Rebif® 44 mcg three times per week (3%), and 2 patients who received Rebif® 22 mcg three times per week (1%) developed injection site necrosis during two years of therapy. Rebif® was continued in 7 patients and interrupted briefly in one patient. There was one report of injection site necrosis in Study 2 during 48 weeks of Rebif® treatment. All events resolved with conservative management; none required skin debridement or grafting.

The rates of adverse reactions and association with Rebif® in patients with relapsing-remitting multiple sclerosis are drawn from the placebo-controlled study (n = 560) and the active comparator-controlled study (n = 339).

The population encompassed an age range from 18 to 55 years. Nearly three-fourths of the patients were female, and more than 90% were Caucasian, largely reflecting the general demographics of the population of patients with multiple sclerosis.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Rebif® cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

Table 3 enumerates adverse events and laboratory abnormalities that occurred at an incidence that was at least 2% more in either Rebif®-treated group than was observed in the placebo group.

Table 3. Adverse Reactions and Laboratory Abnormalities in Study 1

Body System **Preferred Term**	**Placebo tiw (n=187)**	**Rebif® 22 mcg tiw (n=189)**	**Rebif® 44 mcg tiw (n=184)**
BODY AS A WHOLE			
Influenza-like symptoms	51%	56%	59%
Headache	63%	65%	70%

Fatigue	36%	33%	41%
Fever	16%	25%	28%
Rigors	5%	6%	13%
Chest Pain	5%	6%	8%
Malaise	1%	4%	5%
INJECTION SITE DISORDERS			
Injection Site Reaction	39%	89%	92%
Injection Site Necrosis	0%	1%	3%
CENTRAL & PERIPH NERVOUS SYSTEM DISORDERS			
Hypertonia	5%	7%	6%
Coordination Abnormal	2%	5%	4%
Convulsions	2%	5%	4%
ENDOCRINE DISORDERS			
Thyroid Disorder	3%	4%	6%
GASTROINTESTINAL SYSTEM DISORDERS			
Abdominal Pain	17%	22%	20%
Dry Mouth	1%	1%	5%
LIVER AND BILIARY SYSTEM DISORDERS			
SGPT Increased	4%	20%	27%
SGOT Increased	4%	10%	17%
Hepatic Function Abnormal	2%	4%	9%
Bilirubinaemia	1%	3%	2%
MUSCULO-SKELETAL SYSTEM DISORDERS			
Myalgia	20%	25%	25%
Back Pain	20%	23%	25%
Skeletal Pain	10%	15%	10%
HEMATOLOGIC DISORDERS			
Leukopenia	14%	28%	36%
Lymphadenopathy	8%	11%	12%
Thrombocytopenia	2%	2%	8%
Anemia	3%	3%	5%
PSYCHIATRIC DISORDERS			
Somnolence	1%	4%	5%
SKIN DISORDERS			
Rash Erythematous	3%	7%	5%
Rash Maculo-Papular	2%	5%	4%
URINARY SYSTEM DISORDERS			
Micturition Frequency	4%	2%	7%
Urinary Incontinence	2%	4%	2%
VISION DISORDERS			
Vision Abnormal	7%	7%	13%
Xerophthalmia	0%	3%	1%

The adverse reactions were generally similar in Studies 1 and 2, taking into account the disparity in study durations.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. In study 1, the presence of neutralizing antibodies (NAb) to Rebif® was determined by collecting and analyzing serum pre-study and at 6 month time intervals during the 2 years of the clinical trial. Serum NAb were detected in 59/189 (31%) and 45/184 (24%) of Rebif®-treated patients at the 22 mcg and 44 mcg three times per week doses, respectively, at one or more times during the study. The clinical significance of the presence of NAb to Rebif® is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to Rebif® using an antiviral cytopathic effect assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of NAb positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Rebif® with the incidence of antibodies to other products may be misleading.

Anaphylaxis and other allergic reactions have been observed with the use of Rebif® (see **WARNINGS:** Anaphylaxis).

DRUG ABUSE AND DEPENDENCE

There is no evidence that abuse or dependence occurs with Rebif® therapy. However, the risk of dependence has not been systematically evaluated.

OVERDOSAGE

Safety of doses higher than 44 mcg sc three times per week has not been adequately evaluated. The maximum amount of Rebif® that can be safely administered has not been determined.

DOSAGE AND ADMINISTRATION

Dosages of Rebif® shown to be safe and effective are 22 mcg and 44 mcg injected subcutaneously three times per week. Rebif® should be administered, if possible, at the same time (preferably in the late afternoon or evening) on the same three days (e.g., Monday, Wednesday, and Friday) at least 48 hours apart each week (see **CLINICAL STUDIES**). Generally, patients should be started at 20% of the prescribed dose three times per week and increased over a 4-week period to the targeted dose, either 22 mcg three times per week (see Table 4) or 44 mcg three times per week (see Table 5). Patients prescribed a targeted dose of 22 mcg three times per week should use the pre-filled syringes for titration. Following the administration of each dose, any residual product remaining in the syringe should be discarded in a safe and proper manner.

A Titration Pack containing 6 doses of 8.8 mcg (0.2 mL) and 6 doses of 22 mcg (0.5 mL) is available for use during the titration period in both Rebif® pre-filled syringes and Rebif® Rebidose® autoinjectors.

Table 4: Titration Schedule for a 22 mcg Prescribed Dose*

Week of Use	Dose	Syringe to Use	Amount of syringe
Week 1 Titration	4.4 mcg	8.8 mcg syringe	Use half of syringe
Week 2 Titration	4.4 mcg	8.8 mcg syringe	Use half of syringe
Week 3 Titration	11 mcg	22 mcg syringe	Use half of syringe
Week 4 Titration	11 mcg	22 mcg syringe	Use half of syringe
Week 5 and on	22 mcg	22 mcg syringe or autoinjector	Use full syringe or autoinjector

*Only pre-filled syringes can be used to titrate to 22 mcg Prescribed Dose

Table 5: Titration Schedule for a 44 mcg Prescribed Dose**

Week of Use	Dose	Syringe or Autoinjector to Use	Amount of syringe or autoinjector
Week 1 Titration	8.8 mcg	8.8 mcg syringe or autoinjector	Use full syringe or autoinjector
Week 2 Titration	8.8 mcg	8.8 mcg syringe or autoinjector	Use full syringe or autoinjector

Week 3 Titration	22 mcg	22 mcg syringe or autoinjector	Use full syringe or autoinjector
Week 4 Titration	22 mcg	22 mcg syringe or autoinjector	Use full syringe or autoinjector
Week 5 and on	44 mcg	44 mcg syringe or autoinjector	Use full syringe or autoinjector

**Pre-filled syringes or autoinjectors can be used to titrate to 44 mcg Prescribed Dose

Leukopenia or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif® administration until toxicity is resolved (see **WARNINGS:** Hepatic Injury**,** **PRECAUTIONS**: General and **ADVERSE REACTIONS**).

Rebif® 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 (sc) injections using the pre-filled syringe or injection device approved for use with Rebif®. Injection depth of the Rebif® Rebidose® autoinjector is fixed at 8 mm; the health care provider should determine the injection technique. Patients should be advised to rotate sites for sc injections (see **PRECAUTIONS:** Information for Patients). Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days. Rebif® should be inspected visually for particulate matter and discoloration prior to administration**.**

Stability and Storage

Rebif® should be stored refrigerated between 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. If a refrigerator is not available, Rebif® may be stored between 36°F to 77°F (2°C to 25°C) for up to 30 days and away from heat and light.

Do not use beyond the expiration date printed on packages. Rebif® contains no preservatives. Each pre-filled syringe and Rebif® Rebidose® autoinjector is intended for single use. Unused portions should be discarded.

HOW SUPPLIED

Rebif® is supplied as a sterile, preservative-free solution packaged in two different delivery options:

- Pre-filled Syringes: graduated, ready to use in 0.2 mL or 0.5 mL with 29-gauge 0.5 inch needle for subcutaneous injections.

- Rebif® Rebidose® Autoinjectors: pre-assembled, ready to use in 0.2 mL or 0.5 mL with 29-gauge, 0.5 inch needle for subcutaneous injections.

The following package presentations are available:

Pre-Filled Syringes:

Rebif® (interferon beta -1a) Titration Pack, NDC 44087-8822-1

- Six Rebif® 8.8 mcg pre-filled syringes and Six Rebif® 22 mcg pre-filled syringe

Rebif® (interferon beta -1a) 22 mcg Pre-filled syringe

- One Rebif® 22 mcg pre-filled syringe, NDC 44087-0022-1

- Twelve Rebif® 22 mcg pre-filled syringes, NDC 44087-0022-3

Rebif® (interferon beta -1a) 44 mcg Pre-filled syringe

- One Rebif® 44 mcg pre-filled syringe, NDC 44087-0044-1

- Twelve Rebif® 44 mcg pre-filled syringes, NDC 44087-0044-3

Rebif® Rebidose® Autoinjectors:

Rebif® (interferon beta-1a) Titration Pack, NDC 44087-0188-1

- Six Rebif® 8.8 mcg autoinjectors with lime-green injector buttons and Six Rebif® 22 mcg with yellow injector buttons.

Rebif® (interferon beta-1a) 22 mcg Rebif® Rebidose® Autoinjector

- Twelve Rebif® 22 mcg autoinjectors with yellow injector buttons, NDC 44087-3322-1

Rebif® (interferon beta-1a) 44 mcg Rebif® Rebidose® Autoinjector

- Twelve Rebif® 44 mcg autoinjectors with teal-blue injector buttons, NDC 44087-3344-1

Rx only

References

1. PRISMS Study Group. Randomized double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. Lancet 1998; 352: 1498-1504.
2. Panitch H. Goodin DS, Francis G, et al. Randomized, comparative study of interferon β-1a treatment regimens in MS. The EVIDENCE Trial. Neurology 2002 59:1496-1506.

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