

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REBIF safely and effectively. See full prescribing information for REBIF.

REBIF (interferon beta-1a), for subcutaneous injection

Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

Warnings and Precautions, Thrombotic Microangiopathy (5.6) 10/2015

INDICATIONS AND USAGE

REBIF is an interferon beta 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 (1)

DOSAGE AND ADMINISTRATION

- For subcutaneous injection only (2.1)
- The recommended dose is either 22 mcg or 44 mcg injected subcutaneously three times per week (2.1)
- Titration: Generally, the starting dose should be 20% of the prescribed dose three times per week, and increased over a 4 week period to the targeted recommended dose of either 22 mcg or 44 mcg injected subcutaneously three times per week (2.1)
- Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms (2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 8.8 mcg in 0.2 mL, and 22 mcg or 44 mcg in 0.5 mL in single-dose prefilled syringe (3)
- Injection: 8.8 mcg in 0.2 mL, and 22 mcg or 44 mcg in 0.5 mL in single-dose autoinjector (3)

CONTRAINDICATIONS

- History of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation (4)

WARNINGS AND PRECAUTIONS

- Depression and Suicide: Advise patients to immediately report any symptoms of depression and/or suicidal ideation; consider discontinuation of REBIF if depression occurs (5.1)
- Hepatic Injury: Monitor liver function tests; monitor patients for signs and symptoms of hepatic injury; consider discontinuing REBIF if hepatic injury occurs (5.2)
- Anaphylaxis and Other Allergic Reactions: Discontinue REBIF if anaphylaxis occurs (5.3)
- Injection Site Reactions including Necrosis: Do not administer REBIF into affected area until fully healed; if multiple lesions occur, discontinue REBIF until healing of skin lesions (5.4)
- Decreased Peripheral Blood Counts: Monitor complete blood counts (5.5)
- Thrombotic Microangiopathy: Cases of thrombotic microangiopathy have been reported. Discontinue REBIF if clinical symptoms and laboratory findings consistent with TMA occur (5.6)
- Seizures: Monitor for seizures when administering REBIF to patients, particularly those with pre-existing seizure disorders (5.7)

ADVERSE REACTIONS

The most common adverse reactions in controlled clinical trials were injection site disorders, influenza-like symptoms, abdominal pain, depression, elevation of liver enzymes and hematologic abnormalities (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext. 5563 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 Medication Guide.

Revised: 10/2015

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FULL PRESCRIBING INFORMATION

1 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of REBIF is either 22 mcg or 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.

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 1) or 44 mcg three times per week (see Table 2). Patients prescribed a targeted dose of 22 mcg three times per week should use the prefilled syringes for titration.

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 prefilled syringes and REBIF Rebidose autoinjectors.

Table 1: 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 after	22 mcg	22 mcg syringe or autoinjector	Use full syringe or autoinjector

*Use only prefilled syringes, not autoinjectors, to titrate to the 22 mcg Prescribed Dose

Table 2: 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 after	44 mcg	44 mcg syringe or autoinjector	Use full syringe or autoinjector

**Prefilled syringes or autoinjectors can be used to titrate to the 44 mcg Prescribed Dose

Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of REBIF administration until toxicity is resolved [see *Warnings and Precautions (5.2, 5.5) and Adverse Reactions (6)*].

2.2 Important Administration Instructions

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 injections using the prefilled syringe or injection device approved for use with REBIF. Injection depth of the REBIF Rebidose autoinjector is fixed at 8 mm; the healthcare provider should determine the injection technique.

The initial injection should be performed under the supervision of an appropriately qualified healthcare provider.

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 prefilled 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.

Advise patients and caregivers to:

- visually inspect REBIF for particulate matter and discoloration prior to administration
- use aseptic technique when administering REBIF
- rotate site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis [see *Warnings and Precautions, (5.4)*]
- use a puncture-resistant container for safe disposal of used needles, prefilled syringes and REBIF Rebidose autoinjectors
- do not re-use needles, syringes or REBIF Rebidose autoinjectors

2.3 Premedication for Flu-like Symptoms

Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with REBIF use on treatment days.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 8.8 mcg per 0.2 mL in a graduated, single-dose REBIF prefilled syringe
- Injection: 22 mcg per 0.5 mL in a graduated, single-dose REBIF prefilled syringe
- Injection: 44 mcg per 0.5 mL in a graduated, single-dose REBIF prefilled syringe
- Injection: 8.8 mcg per 0.2 mL in a single-dose prefilled REBIF Rebidose autoinjector
- Injection: 22 mcg per 0.5 mL in a single-dose prefilled REBIF Rebidose autoinjector
- Injection: 44 mcg per 0.5 mL in a single-dose prefilled REBIF Rebidose autoinjector

4 CONTRAINDICATIONS

REBIF is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 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.

5.2 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 (6.1)*]. 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 *Warnings and Precautions (5.8)*; and *Dosage and Administration (2.1)*].

5.3 Anaphylaxis and Other Allergic Reactions

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. Discontinue REBIF if anaphylaxis occurs.

5.4 Injection Site Reactions including Necrosis

In controlled clinical trials, injection site reactions occurred more frequently in REBIF-treated patients (92% in the 44 mcg group and 89% in the 22 mcg group) than in placebo-treated patients (39%) and at a higher frequency in REBIF treated patients (83%) than in AVONEX-treated patients (28%). Injection site necrosis also occurred more frequently in REBIF-treated patients (3% in the 44 mcg group and 1% in the 22 mcg group) than in placebo-treated patients (0) during the two years of therapy. All events resolved with conservative management.

Injection site reactions including injection site pain, erythema, edema, cellulitis, abscess, and necrosis have been reported in the postmarketing setting. Some occurred more than 2 years after initiation of REBIF. Necrosis occurred at single and at multiple injection sites. Some cases of injection site necrosis required treatment with intravenous antibiotics and surgical intervention (debridement and skin grafting).

Patient understanding and use of aseptic self-injection techniques and procedures should be periodically evaluated, particularly if injection site necrosis has occurred. Patients should be advised of the importance of rotating sites of injection with each dose and not reusing syringes. Patients should be advised against injecting an area which is inflamed, edematous, erythematous, ecchymotic, or has any other signs of infection. These signs should be reported to a healthcare professional immediately.

5.5 Decreased Peripheral Blood Counts

Decreased peripheral blood counts in all cell lines, including pancytopenia, have been reported in REBIF-treated patients. In controlled clinical trials, leukopenia occurred at a higher frequency in REBIF-treated patients (36% in 44 mcg group and 28% in 22 mcg group) than in placebo-treated patients (14%) and at a higher frequency in REBIF-treated patients (6%) compared to the AVONEX-treated patients (<1%). Thrombocytopenia and anemia occurred more frequently in 44 mcg REBIF-treated patients (8% and 5%, respectively) than in placebo-treated patients (2% and 3%, respectively). In a pooled analysis of 7 placebo controlled trials with REBIF doses of 22 mcg or 44 mcg, the rate of pancytopenia (in subjects with normal baseline values who developed laboratory values less than the lower limit of normal for all 3 hematology parameters simultaneously) was higher in the total REBIF group (5.5 per 1000 subject-year) than in the placebo group (1.2 per 1000 subject-year). Patients should be monitored for symptoms or signs of decreased blood counts. Monitoring of complete blood and differential white blood cell counts is also recommended [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.8)*].

5.6 Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, some fatal, have been reported with interferon beta products, including REBIF. Cases have been reported several weeks to years after starting interferon beta products. Discontinue REBIF if clinical symptoms and laboratory findings consistent with TMA occur, and manage as clinically indicated.

5.7 Seizures

Caution should be exercised when administering REBIF to patients with pre-existing seizure disorders. Seizures have been temporally associated with the use of beta interferons, including REBIF, in clinical trials and in postmarketing reports.

5.8 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. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.5)*]. New or worsening thyroid abnormalities have developed in some patients treated with REBIF. Thyroid function tests are recommended every 6 months in patients with a history of thyroid dysfunction or as clinically indicated.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in the *Warnings and Precautions* section of the label:

- Depression and Suicide [see *Warnings and Precautions (5.1)*]
- Hepatic Injury [see *Warnings and Precautions (5.2)*]
- Anaphylaxis and Other Allergic Reactions [see *Warnings and Precautions (5.3)*]
- Injection Site Reactions including Necrosis [see *Warnings and Precautions (5.4)*]
- Decreased Peripheral Blood Counts [see *Warnings and Precautions (5.5)*]
- Thrombotic Microangiopathy [see *Warnings and Precautions (5.6)*]
- Seizures [see *Warnings and Precautions (5.7)*]
- Laboratory Tests [see *Warnings and Precautions (5.8)*]

6.1 Clinical Trial Experience

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.

A total of 712 patients with relapsing-remitting multiple sclerosis (RRMS) in two controlled clinical trials took REBIF (22 mcg or 44 mcg given three times per week) [see *Clinical Studies (14)*]. Ages ranged 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.

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) were injection site disorders, influenza-like symptoms, depression, and elevation of liver enzymes [see *Warnings and Precautions (5)*].

Study 1 was a 2-year placebo-controlled study in RRMS patients treated with REBIF 22 mcg (n=189), 44 mcg (n=184), or placebo (n=187). Table 3 enumerates adverse reactions 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	Placebo tiw (n=187)	REBIF 22 mcg tiw (n=189)	REBIF 44 mcg tiw (n=184)
Preferred Term	%	%	%
BODY AS A WHOLE			
Influenza-like symptoms	51	56	59
Headache	63	65	70

Body System	Placebo tiw (n=187)	REBIF 22 mcg tiw (n=189)	REBIF 44 mcg tiw (n=184)
Preferred Term	%	%	%
Fatigue	36	33	41
Fever	16	25	28
Rigors	5	6	13
Chest pain	5	6	8
Malaise	1	4	5

Body System	Placebo tiw (n=187)	REBIF 22 mcg tiw (n=189)	REBIF 44 mcg tiw (n=184)
Preferred Term	%	%	%
INJECTION SITE DISORDERS			
Injection Site Reaction	39	89	92
Injection Site Necrosis	0	1	3
NERVOUS SYSTEM DISORDERS			
Hypertonia	5	7	6
Coordination Abnormal	2	5	4
Convulsions	2	5	4
Somnolence	1	4	5
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
Bilirubinemia	1	3	2
MUSCULO-SKELETAL SYSTEM DISORDERS			
Myalgia	20	25	25
Back Pain	20	23	25
Skeletal Pain	10	15	10

Body System Preferred Term	Placebo tiw (n=187)	REBIF 22 mcg tiw (n=189)	REBIF 44 mcg tiw (n=184)
	%	%	%
HEMATOLOGIC DISORDERS			
Leukopenia	14	28	36
Lymphadenopathy	8	11	12
Thrombocytopenia	2	2	8
Anemia	3	3	5
SKIN DISORDERS			
Rash Erythematous	3	7	5
Rash Maculo-Papular	2	5	4
Hyperhidrosis	2	4	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

Adverse reactions in Study 2, a 1-year active-controlled (vs. interferon beta-1a, 30 mcg once weekly intramuscular injection, n=338) study including 339 patients with MS treated with REBIF were generally similar to those in Study 1, taking into account the disparity in study durations.

6.2 Immunogenicity

Anaphylaxis and other allergic reactions have been observed with the use of REBIF [see *Warnings and Precautions (5.3)*]. 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 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.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of REBIF. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Autoimmune Disorders: Drug-induced lupus erythematosus, autoimmune hepatitis

Eye Disorders: Retinal vascular disorders (i.e. retinopathy, cotton wool spots or obstruction of retinal artery or vein)

Skin and Subcutaneous Tissue Disorders: Erythema multiforme, Stevens-Johnson syndrome

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. REBIF should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a study in pregnant cynomolgus monkeys, interferon beta was administered daily (intramuscular doses approximately 1, 2, and 7 times the maximum recommended cumulative weekly human dose, based on body surface area) either throughout the period of organogenesis or later in pregnancy (gestation day 90 to term). No adverse effects on embryofetal development were observed; however, the possibility of adverse effects cannot be ruled out because of the small number of animals tested (six per dose group at each developmental period).

8.3 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.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 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.

11 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 prefilled syringe or REBIF Rebidose autoinjector intended for subcutaneous (sc) injection. Each 0.5 mL (0.5 cc) of REBIF contains either 22 mcg or 44 mcg of interferon beta-1a, 2 mg or 4 mg albumin (human), 27.3 mg mannitol, 0.4 mg sodium acetate, and water for injection. Each 0.2 mL (0.2 cc) of REBIF contains 8.8 mcg of interferon beta-1a, 0.8 mg albumin (human), 10.9 mg mannitol, 0.16 mg sodium acetate, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism(s) by which REBIF (interferon beta-1a) exerts its therapeutic effects in patients with multiple sclerosis is unknown.

12.2 Pharmacodynamics

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.

12.3 Pharmacokinetics

The pharmacokinetics of REBIF (interferon beta-1a) in people with multiple sclerosis have not been evaluated. In healthy 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 \pm 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 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: REBIF has not been tested for carcinogenic potential in animals.

Mutagenesis: Interferon beta was negative in an *in vitro* bacterial reverse mutation (Ames) assay and an *in vitro* cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation.

Impairment of Fertility: In studies in normally cycling female cynomolgus monkeys given daily subcutaneous injections of interferon beta 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. In male monkeys, the same doses of interferon beta had no demonstrable adverse effects on sperm count, motility, morphology, or function.

14 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. Patients with secondary progressive multiple sclerosis were excluded from the study. Patients received subcutaneous 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 (2.1)*].

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 one 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 4 and Figure 1. REBIF at doses of 22 mcg and 44 mcg administered 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 4: Clinical and MRI Endpoints from Study 1

	Placebo	REBIF 22 mcg	REBIF 44 mcg
	n = 187	n = 189	n = 184
Exacerbation-related			
Mean number of exacerbations per patient over 2 years ^{1,2} (Percent reduction)	2.56	1.82** (29%)	1.73*** (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			
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

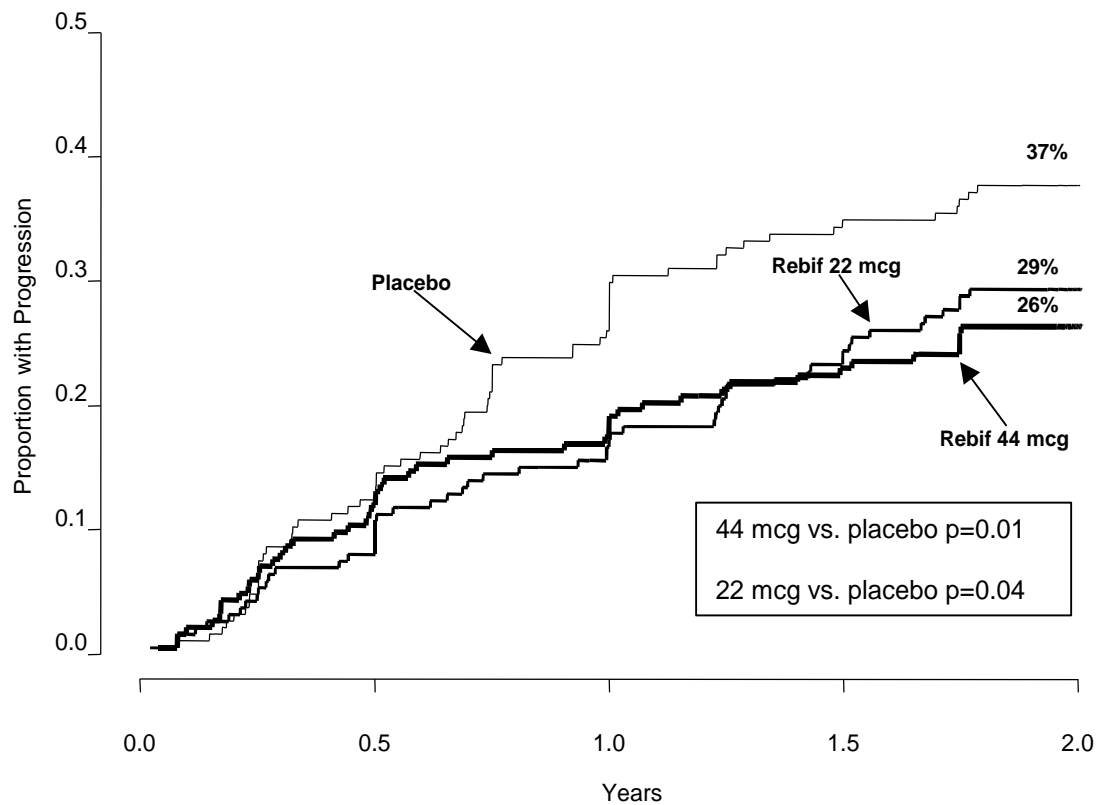
(3) Logistic regression adjusted for center. Patients lost to follow-up prior to an exacerbation were excluded from this analysis. (Analysis included 185, 183, and 184 patients for three times per week placebo, 22 mcg REBIF, and 44 mcg REBIF, respectively).

(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. 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 three times per week subcutaneous injections of REBIF 44 mcg (n=339) or once weekly intramuscular injections of 30 mcg AVONEX (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 three times per week were more likely to remain relapse-free at 24 and 48 weeks than were patients treated with AVONEX 30 mcg once per week (Table 5). This study does not support any conclusion regarding effects on the accumulation of physical disability.

Table 5: Clinical and MRI Results from Study 2

	REBIF 44 mcg	AVONEX 30 mcg	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 (25 th , 75 th percentiles)	0.17* (0.00, 0.67)	0.33 (0.00, 1.25)		

* p < 0.001 (REBIF compared to AVONEX)

** 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

16 HOW SUPPLIED/STORAGE AND HANDLING

REBIF is supplied as a sterile solution containing no preservative available in the following package presentations:

Prefilled Syringes:

REBIF (interferon beta -1a) Titration Pack, NDC 44087-8822-1- Six REBIF 8.8 mcg prefilled syringes and Six REBIF 22 mcg prefilled syringes

REBIF (interferon beta -1a) 22 mcg Prefilled syringe

- One REBIF 22 mcg prefilled syringe, NDC 44087-0022-1- Twelve REBIF 22 mcg prefilled syringes, NDC 44087-0022-3

REBIF (interferon beta -1a) 44 mcg Prefilled syringe

- One REBIF 44 mcg prefilled syringe, NDC 44087-0044-1
- Twelve REBIF 44 mcg prefilled syringes, NDC 44087-0044-3

REBIF Rebidose Autoinjectors:

REBIF Rebidose (interferon beta-1a) Titration Pack, NDC 44087-0188-1

- Six REBIF Rebidose 8.8 mcg autoinjectors with lime-green injector buttons and Six REBIF Rebidose 22 mcg with yellow injector buttons.

REBIF Rebidose (interferon beta-1a) 22 mcg Autoinjector

- Twelve REBIF Rebidose 22 mcg autoinjectors with yellow injector buttons, NDC 44087-3322-1

REBIF Rebidose (interferon beta-1a) 44 mcg Autoinjector

- Twelve REBIF Rebidose 44 mcg autoinjectors with teal-green injector buttons, NDC 44087-3344-1

REBIF should be stored refrigerated between 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. If needed, 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, but refrigeration is preferred.

Do not use beyond the expiration date printed on packages. REBIF contains no preservatives. Each prefilled syringe and REBIF Rebidose autoinjector is intended for a single dose. Unused portions should be discarded.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Inform patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking REBIF. Instruct patients to take REBIF only as prescribed.

Depression and Suicide

Advise patients that depression, suicidal ideation, and suicide have been reported during the use of REBIF. Inform patients of the symptoms of depression and suicidal ideation and instruct patients to immediately report any of these symptoms to their healthcare provider [*see Warnings and Precautions (5.1)*].

Hepatic Injury

Advise patients that severe liver injury, including hepatic failure, has been reported with the use of REBIF. Educate patients about the symptoms of hepatic injury and instruct patients to report them immediately to their healthcare provider [*see Warnings and Precautions (5.2)*].

Anaphylaxis and Other Allergic Reactions

Advise patients of the symptoms of allergic reactions and anaphylaxis, and instruct patients to seek immediate medical attention if these symptoms occur [*see Warnings and Precautions (5.3)*].

Injection Site Reactions including Necrosis

Advise patients that injection site reactions occur in most patients treated with REBIF and that injection site necrosis may occur [*see Warnings and Precautions (5.4)*]. Instruct patients to promptly report any break in the skin, which may be associated with blue-black discoloration, swelling, or drainage of fluid from the injection site, prior to continuing their REBIF therapy.

To minimize the likelihood of injection site reactions, inform patients of the importance of rotating injection sites with each dose and the use of aseptic injection technique [*see Dosage and Administration (2.2)*]. Advise patients not to re-use needles or syringes and instruct patients on safe disposal procedures. Provide appropriate instruction for self-injection of REBIF and REBIF Rebidose, including careful review of the REBIF Medication Guide.

Decreased Peripheral Blood Counts

Advise patients that they may develop a lowering of their peripheral blood counts, including their white blood counts, red blood counts, and platelets, and that their blood counts will be checked during therapy with REBIF. Inform patients that they may be more likely to get infections, anemia, or be at risk for bleeding, and that they should contact their healthcare provider if they develop symptoms of these adverse reactions [*see Warnings and Precautions (5.5)*].

Seizures

Instruct patients to report seizures immediately to their healthcare provider [*see Warnings and Precautions (5.7)*].

Flu-like Symptoms

Inform patients that flu-like symptoms are common following initiation of therapy with REBIF. Advise patients that concurrent use of analgesics and/or antipyretics may help reduce flu-like symptoms on treatment days [*see Dosage and Administration (2.3)*].

Risk in Pregnancy

Advise patients that REBIF should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus [*see Use in Specific Populations (8.1)*]. Therefore, inform patients that if a pregnancy is considered, or does occur, the risks and benefits of continuing REBIF should be discussed with their healthcare provider.

Manufactured by EMD Serono, Inc. Rockland, MA 02370 U.S. License # 1773

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Rockland, MA 02370	New York, NY 10017

Revised: 10/2015

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