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

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)
- Seizures: Monitor for seizures when administering REBIF to patients, particularly those with pre-existing seizure disorders (5.6)

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: 04/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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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 health care provider should determine the injection technique.

The initial injection should be performed under the supervision of an appropriately qualified health care 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 (5.7); 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.

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