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 contain approximately 2.4 MIU, 6 MIU or 12 MIU, respectively, of antiviral activity using this method.

Rebif® (interferon beta-1a) is formulated as a sterile solution in a prefilled syringe 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, and 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 tiw 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 tiw 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

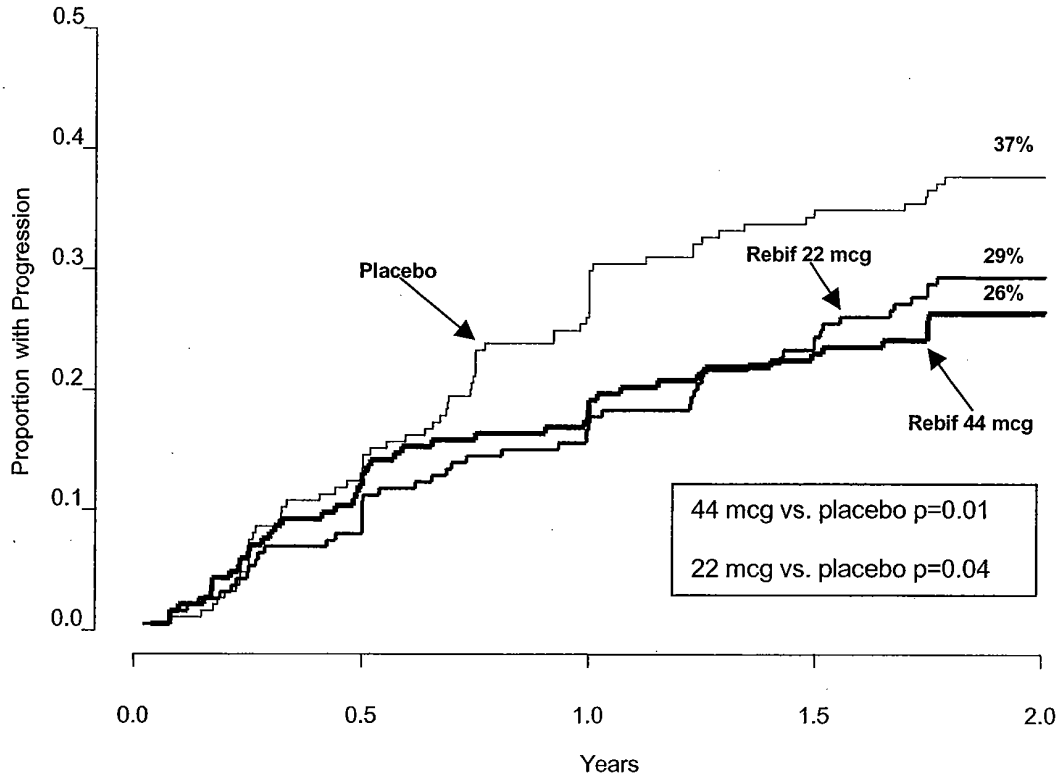
(3) Logistic regression adjusted for center. Patients lost to follow-up prior to an exacerbation were excluded from this analysis (n = 185, 183, and 184 for the placebo, 22 mcg tiw, and 44 mcg tiw groups, respectively)

(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.

104 **Figure 1: Proportions of Patients with Sustained Disability Progression**



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

107

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

114

115 The primary efficacy endpoint was the proportion of patients who remained exacerbation-free at
116 24 weeks. The principal secondary endpoint was the mean number per patient per scan of
117 combined unique active MRI lesions through 24 weeks, defined as any lesion that was T1 active
118 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 tiw 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

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®. 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 dysfunction, leading to hepatic failure requiring liver transplantation, has been reported very rarely in patients taking Rebif®. Symptomatic hepatic dysfunction, including hepatitis, primarily presenting as jaundice, has been reported as a rare complication of Rebif use. 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. Dose reduction 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. Treatment with Rebif® should be stopped if jaundice or other clinical symptoms of liver dysfunction appear.

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, including careful review of the Rebif® Medication Guide. If a patient is to self-administer Rebif®, the physical and cognitive ability of that patient to self-administer and properly dispose

of syringes should be assessed. The initial injection should be performed under the supervision of an appropriately qualified health care professional. 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. A puncture-resistant container for disposal of used needles and syringes should be supplied to the patient along with instructions for safe disposal of full containers. Patients should be instructed in the technique and importance of proper syringe disposal 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

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.

A pregnancy registry has been established to monitor pregnancy outcomes of women exposed to Rebif® while pregnant. Health care providers are encouraged to register patients on line at rebifpregnancyregistry.com or by calling MS LifeLines at 1-877-44-REBIF (1-877-447-3243).

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%. 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 tiw (3%), and 2 patients who received Rebif® 22 mcg tiw (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 tiw 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 tiw 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 tiw and increased over a 4-week period to the targeted dose, either 22 mcg or 44 mcg tiw (see **Table 4**). Following the administration of each dose, any residual product remaining in the syringe should be discarded in a safe and proper manner.

A Rebif® 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.

Table 4: Schedule for Patient Titration

	Recommended Titration (% of final dose)	Titration dose for Rebif® 22 mcg	Titration dose for Rebif® 44 mcg
Weeks 1-2	20 %	4.4 mcg	8.8 mcg
Weeks 3–4	50 %	11 mcg	22 mcg
Weeks 5+	100 %	22 mcg	44 mcg

Leukopenia or elevated liver function tests may necessitate dose reductions of 20-50% until toxicity is resolved (see **WARNINGS: Hepatic Injury, PRECAUTIONS: General**).

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 pre-filled syringe. 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 2-8°C (36-46°F). DO NOT FREEZE. If a refrigerator is not available, Rebif® may be stored at or below 25° C/77° F 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 syringe is intended for single use. Unused portions should be discarded.

HOW SUPPLIED

Rebif® is supplied as a sterile, preservative-free solution packaged in graduated, ready to use in 0.2 mL or 0.5 mL pre-filled syringes with 29-gauge, 0.5 inch needle for subcutaneous injection. The following package presentations are available.

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 syringes

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

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. Data on file.

Manufacturer: Serono, Inc. Rockland, MA 02370 U.S. License # 1574

Co-Marketed by:
Serono, Inc.
Rockland, MA 02370
Pfizer Inc.
New York, NY 10017

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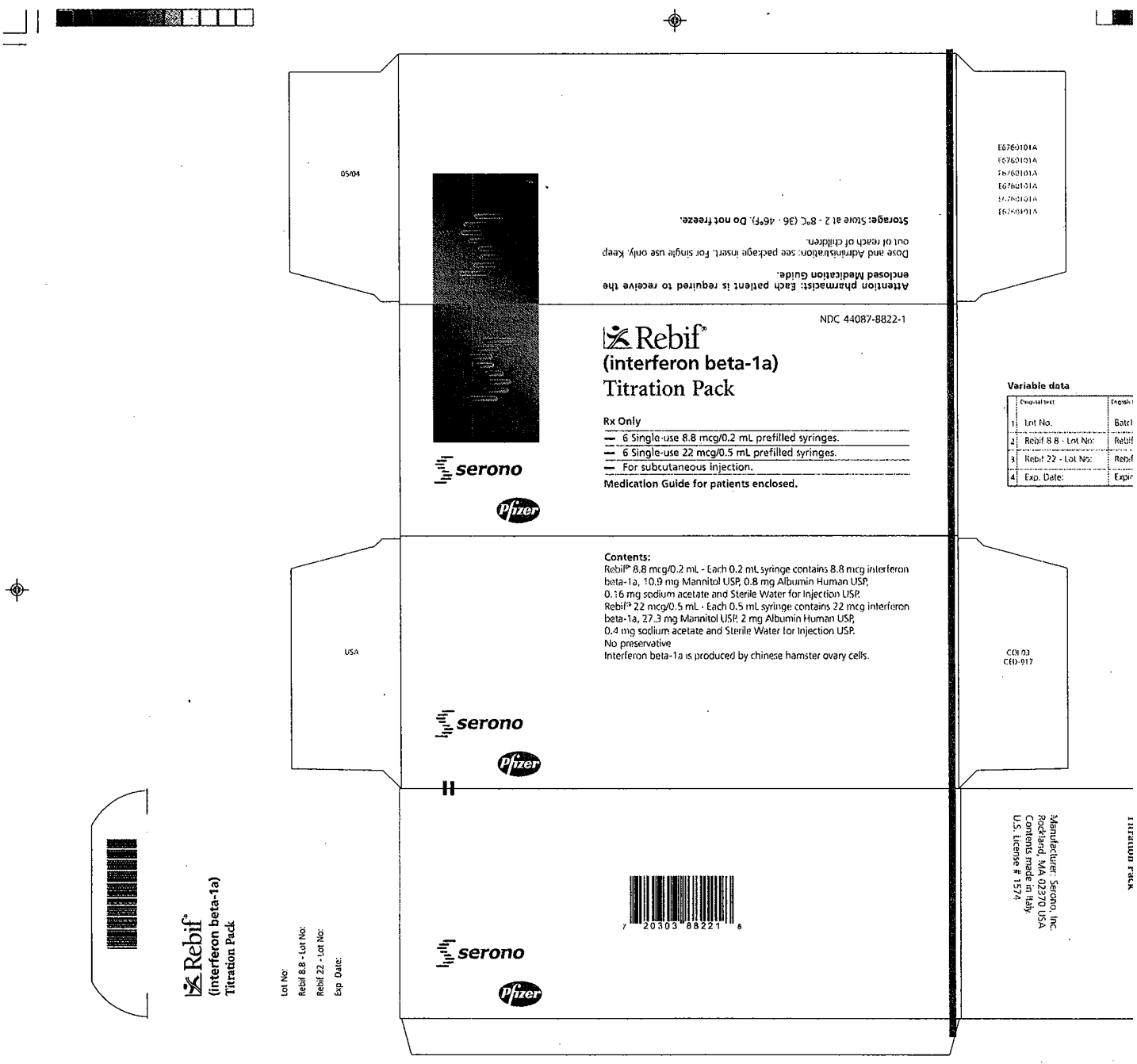

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Peel Here

Rebif®
(interferon beta-1a)
8.8 mcg/0.2 mL
For subcutaneous injection.
Dose and Administration: see package insert.
Manufacturer: Serono Inc., Rockland, MA 02370 U.S. Lic. 1574

1 Single-Use Prefilled Syringe
Store at 2°-8°C (36°-46°F). **Do not freeze.**
Rx Only

serono

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1 Single-Use Prefilled Syringe
Store at 2°-8°C (36°-46°F). **Do not freeze.**
Rx Only

serono

Peel Here

Rebif®
(interferon beta-1a)
8.8 mcg/0.2 mL
For subcutaneous injection.
Dose and Administration: see package insert.
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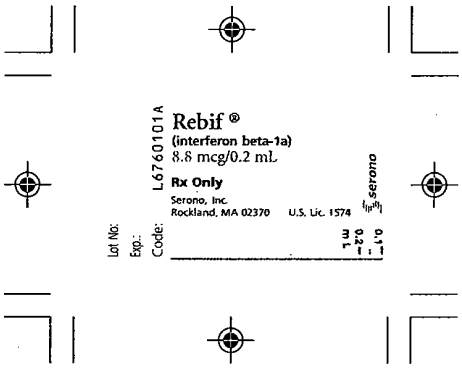

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Crystal Clear - Noir - CET-572
Crystal Clear - 293 - CET-572

Variable data

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2	Exp.:	Expiry date	Signature: 02.11.04, 16:28
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Medication Guide
Rebif® (Re-bif)
Interferon beta-1a
(in-ter-feer-on beta-one-â)

Please read this leaflet carefully before you start to use Rebif® 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 regularly talking with your doctor or healthcare professional.

What is the most important information I should know about Rebif®?

Rebif® will not cure multiple sclerosis (MS) but it has been shown to decrease the number of flare-ups and slow the occurrence of some of the physical disability that is common in people with MS. Rebif® can cause serious side effects, so before you start taking Rebif®, you should talk with your doctor about the possible benefits of Rebif® and its possible side effects to decide if Rebif® is right for you. Potential serious side effects include:

- **Depression.** Some patients treated with interferons, including Rebif®, 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 as soon as possible. Your doctor may ask that you stop using Rebif®. You should also tell your doctor if you have ever had any mental illness, including depression, and if you take any medications for depression.

- **Liver problems.** Your liver may be affected by taking Rebif® and a few patients have developed severe liver injury. Your healthcare provider may ask you to have regular blood tests to make sure that your liver is working properly. If your skin or the whites of your eyes become yellow or if you are bruising easily you should call your doctor right away.

- **Risk to pregnancy**. If you become pregnant while taking Rebif® you should stop using Rebif® immediately and call your doctor. Rebif® 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 Rebif® is greater than the risks are to your unborn child.

  A pregnancy registry has been established to monitor pregnancy outcomes of women exposed to Rebif® while pregnant. Patients are encouraged to have their health care provider register them at rebifpregnancyregistry.com or by calling MS LifeLines at 1-877-44-REBIF (1-877-447-3243).

- **Allergic reactions.** Some patients taking Rebif® have had severe allergic reactions leading to difficulty breathing, and loss of consciousness. Allergic reactions can happen after your first dose or may not happen until after you have taken Rebif® many times. Less severe allergic reactions such as itching, flushing or skin bumps can also happen at any time. If you think you are having an allergic reaction, stop using Rebif® immediately and call your doctor.

- **Injection site problems.** Rebif® 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 Rebif®?

Rebif® 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 and slow the occurrence of some of the physical disability that is common in people with MS. MS is a life-long disease that affects your nervous system by destroying the protective covering (myelin) that surrounds your nerve fibers. The way Rebif® works in MS is not known.

Who should not take Rebif®?

Do not take Rebif® if you:

- have had an allergic reaction 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 Rebif®:

- Depression (a sinking feeling or sadness), anxiety (feeling uneasy 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 planning to become pregnant

Tell your doctor about all medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Rebif® and other medicines may affect each other causing serious side effects. Talk to your doctor before you take any new medicines.

How should I take Rebif®?

Rebif® is given by injection under the skin (subcutaneous injection) on the same three days a week (for example, Monday, Wednesday and Friday). Your injections should be at least 48 hours apart so it is best to take them the same time each day. Your doctor will tell you what dose of Rebif® to use, and may change the dose based on how your body responds. You should not change the 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, then skip the following day. **Do not take Rebif® on two consecutive days.** You should return to your regular schedule the following week. 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 injections.

Always use a new, unopened, prefilled syringe of Rebif® for each injection. Never reuse syringes.

It is important that you change your injection site each time Rebif® is injected. This will lessen the chance of your having a serious skin reaction at the spot where you inject Rebif®. You should always avoid injecting Rebif® 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 Rebif®. You should become familiar with these instructions and follow your doctor's orders before injecting Rebif®.

What should I avoid while taking Rebif®?

- **Pregnancy.** You should avoid becoming pregnant while taking Rebif® until you have talked with your doctor. Rebif® can cause you to lose your baby (miscarry).

- **Breast feeding.** You should talk to your doctor if you are breast feeding an infant. It is not known if the interferon in Rebif® 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.

- Rebif® and other medicines may affect each other causing serious side effects. Talk to your doctor before you take any new medicines.

What are the possible side effects of Rebif®?

- **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 Rebif®.

- **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 Rebif®?*")

- **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 Rebif®?*")

- **Liver problems.** Your liver function may be affected. If you develop symptoms of changes in your liver, including yellowing of the skin and whites of the eyes and easy bruising, call

your doctor immediately. (see: "*What is the most important information I should know about Rebif®?*")

- **Blood problems.** You may have a drop in the levels of infection-fighting blood cells, red blood cells or cells that help to form blood clots. If the drop 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 all the time, change in your weight (gain or loss) without a change in your diet or amount of exercise you are getting.

- **Allergic reactions:** Some patients have had hives, rash, skin bumps or itching while they were taking Rebif®. Other patients have had more serious allergic reactions such as difficulty breathing, or feeling light-headed. You should tell your doctor if you think you are having an allergic reaction. (see: "*What is the most important information I should know about Rebif®?*")

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.

Storage Conditions

Rebif® is packaged in prefilled syringes with needles already attached to the syringe.
Rebif® should be stored refrigerated between 2-8°C (36-46°F). DO NOT FREEZE. If a refrigerator is not available, Rebif® may be stored at or below 25° C/77° F for up to 30 days and away from heat and light.

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 Rebif®

Before you begin, gather all of the supplies listed below:

- Rebif® prefilled syringe with 29 gauge needle. You may wish to remove your syringe from the refrigerator at least 30 minutes prior to use and let it adjust to room temperature so the liquid is not cold. Do not heat or microwave a syringe.
- Alcohol swabs (wipes) or cotton balls and rubbing alcohol
- Small adhesive bandage strip (if desired)
- Puncture resistant safety container for disposal of used syringes
- Antibacterial soap

- An over-the-counter pain or fever reducing medication, if your doctor has recommended that you take this prior to, at the same time, or after you give yourself Rebif® to help minimize the fever, chills, sweating and muscle aches (flu-like symptoms) that may occur.

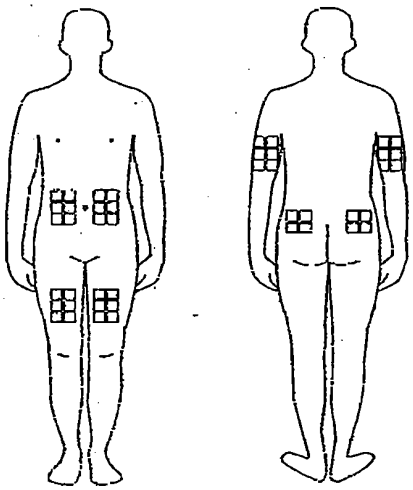
When first starting treatment with Rebif®, your doctor may prescribe either the 22 mcg or 44 mcg dose of Rebif®. You should gradually increase the dose over 4 weeks, starting at 20% of the prescribed dose for the first 2 weeks, half-dose for the second 2 weeks (weeks 3 and 4), and then the full dose prescribed by your doctor.
A Rebif® Titration Pack containing 6 syringes with 8.8 mcg (0.2 mL) and 6 syringes with 22 mcg (0.5 mL) is available for use during the titration period. The following table explains how to use the Rebif® Titration Pack during the first four weeks to gradually increase your dose to 22 or 44 mcg.

		Your Prescribed Dose	
Week of Use	**Syringe to Use**	**22 mcg**	**44 mcg**
Weeks 1 and 2	8.8 mcg syringe	Use half of syringe	Use full syringe
Weeks 3 and 4	22 mcg syringe	Use half of syringe	Use full syringe
Weeks 5 and On	22 or 44 mcg syringe	Use a full syringe depending on your prescribed dose: 22 or 44 mcg	

Preparing for an injection:

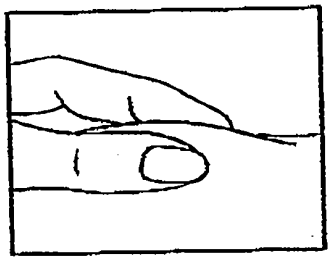
- Check the expiration date; **do not use if the medication is expired.** The expiration date is printed on the syringe, plastic syringe packaging and carton.
- Be sure that the dose, either, 8.8 mcg 22 mcg or 44 mcg, described on the carton is the same as the dose prescribed by your doctor.
- Remove the Rebif® syringe from the plastic packaging. Keep the needle capped.
- Examine the contents of the syringe carefully. The liquid should be clear to slightly yellow. **Do not use if the liquid is cloudy, discolored or contains particles.**
- Choose the injection site. The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, your stomach or buttocks. 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. Use a different site each time you inject (thigh, hip, stomach or upper arm, see Figure below). Do not inject Rebif® into an area of your body where the skin is irritated, reddened, bruised, infected or abnormal in any way.
- Keep a record of the date and location of each injection.
- Wash your hands thoroughly with antibacterial soap before preparing to inject the medication.

- Clean the injection site with an alcohol swab (wipe) or cotton ball with rubbing alcohol using a circular motion. To avoid stinging, you should let your skin dry before you inject Rebif®.

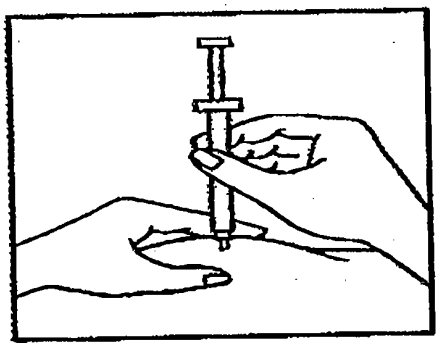


Giving yourself an injection of Rebif®

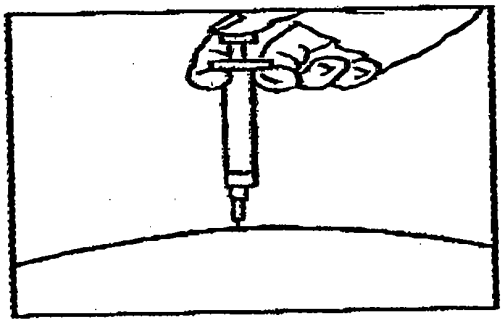
- Remove the needle cap from the syringe needle.
- If your doctor has told you to use less than the full 0.5ml dose, slowly push the plunger in until the amount of medication left in the syringe is the amount your doctor told you to use.
- Use your thumb and forefinger to pinch a pad of skin surrounding the cleaned injection site (see figure below). Hold the syringe like a pencil with your other hand.



- While still pinching the skin, swiftly insert the needle like a dart at about a 90 degree angle (just under the skin) into the pad of tissue as shown.



- After the needle is in, remove the hand that you used to pinch your skin and inject the drug using a slow, steady push on the plunger until all the medication is injected and the syringe is empty.



- Withdraw the needle and apply gentle pressure to the injection site with a dry cotton ball or sterile gauze. Applying a cold compress or ice pack to the injection site after injection may help reduce local skin reactions.

- Put a small adhesive bandage strip over the injection site, if desired.

- After 2 hours, check the injection site for redness, swelling, or tenderness. If you have a skin reaction and it doesn't clear up in a few days, contact your doctor or nurse.

Disposing of Needles and Syringes

There are special state or local laws for properly disposing used needles and syringes. Your doctor or health care professional will instruct you on how to discard your used syringe and needle and may provide you with a puncture resistant syringe disposal container called a Sharps container.

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

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Serono, Inc.
Rockland, MA 02370
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