

Rebif® (interferon beta-1a)**DESCRIPTION**

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

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

24 **General**

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

38 **Pharmacokinetics**

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

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

50 **Pharmacodynamics**

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

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

64 **CLINICAL STUDIES**

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

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

74 The primary efficacy endpoint was the number of clinical exacerbations. Numerous secondary
75 efficacy endpoints were also evaluated and included exacerbation-related parameters, effects of
76 treatment on progression of disability and magnetic resonance imaging (MRI)-related
77 parameters. Progression of disability was defined as an increase in the EDSS score of at least 1
78 point sustained for at least 3 months. Neurological examinations were completed every
79 3 months, during suspected exacerbations, and coincident with MRI scans. All patients
80 underwent proton density T2-weighted (PD/T2) MRI scans at baseline and every 6 months. A
81 subset of 198 patients underwent PD/T2 and T1-weighted gadolinium-enhanced (Gd)-MRI scans
82 monthly for the first 9 months. Of the 560 patients enrolled, 533 (95%) provided 2 years of data
83 and 502 (90%) received 2 years of study agent.

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

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

90 **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} (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*** |
| <u>MRI</u> | 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*** |

91

92

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

94 (1) Intent-to-treat analysis

95 (2) Poisson regression model adjusted for center and time on study

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

99 (4) Cox proportional hazard model adjusted for center

100 (5) ANOVA on ranks adjusted for center. Patients with missing scans were excluded from this analysis

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

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