

1 **Rebif<sup>®</sup>** (interferon beta-1a)

## 2 **DESCRIPTION**

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

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

16 Rebif<sup>®</sup> (interferon beta-1a) is formulated as a sterile solution in a pre-filled syringe or Rebif<sup>®</sup>  
17 Rebidose<sup>®</sup> autoinjector intended for subcutaneous (sc) injection. Each 0.5 ml (0.5 cc) of Rebif<sup>®</sup>  
18 contain either 22 mcg or 44 mcg of interferon beta-1a, 2 mg or 4 mg albumin (human) USP,  
19 27.3 mg mannitol USP, 0.4 mg sodium acetate, Water for Injection USP. Each 0.2 ml (0.2 cc) of  
20 Rebif<sup>®</sup> contains 8.8 mcg of interferon beta-1a, 0.8 mg albumin (human) USP, 10.9 mg mannitol  
21 USP, 0.16 mg sodium acetate, and Water for Injection USP.

22

## 23 CLINICAL PHARMACOLOGY

### 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<sup>®</sup> (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<sup>®</sup> (liquid formulation), resulted in a peak serum concentration ( $C_{max}$ ) of  $5.1 \pm 1.7$  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  $69 \pm 37$  hours, and the area under the serum concentration versus  
44 time curve (AUC) from zero to 96 hours was  $294 \pm 81$  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  
56 48 hours. All three markers remained elevated for up to four days. Administration of Rebif®  
57 22 mcg three times per week (tiw) inhibited mitogen-induced release of pro-inflammatory  
58 cytokines (IFN- $\gamma$ , IL-1, IL-6, TNF- $\alpha$  and TNF- $\beta$ ) by peripheral blood mononuclear cells that, on  
59 average, was near double that observed with Rebif® administered once per week (qw) at either  
60 22 or 66 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.<sup>(1)</sup> Patients with secondary  
70 progressive multiple sclerosis were excluded from the study. Patients received sc injections of  
71 either placebo (n = 187), Rebif<sup>®</sup> 22 mcg (n = 189), or Rebif<sup>®</sup> 44 mcg (n = 184) administered  
72 three times per week for two years. Doses of study agents were progressively increased to their  
73 target doses during the first 4 to 8 weeks for each patient in the study (see **DOSAGE AND**  
74 **ADMINISTRATION**).

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

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

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

92 **Table 1: Clinical and MRI Endpoints from Study 1**

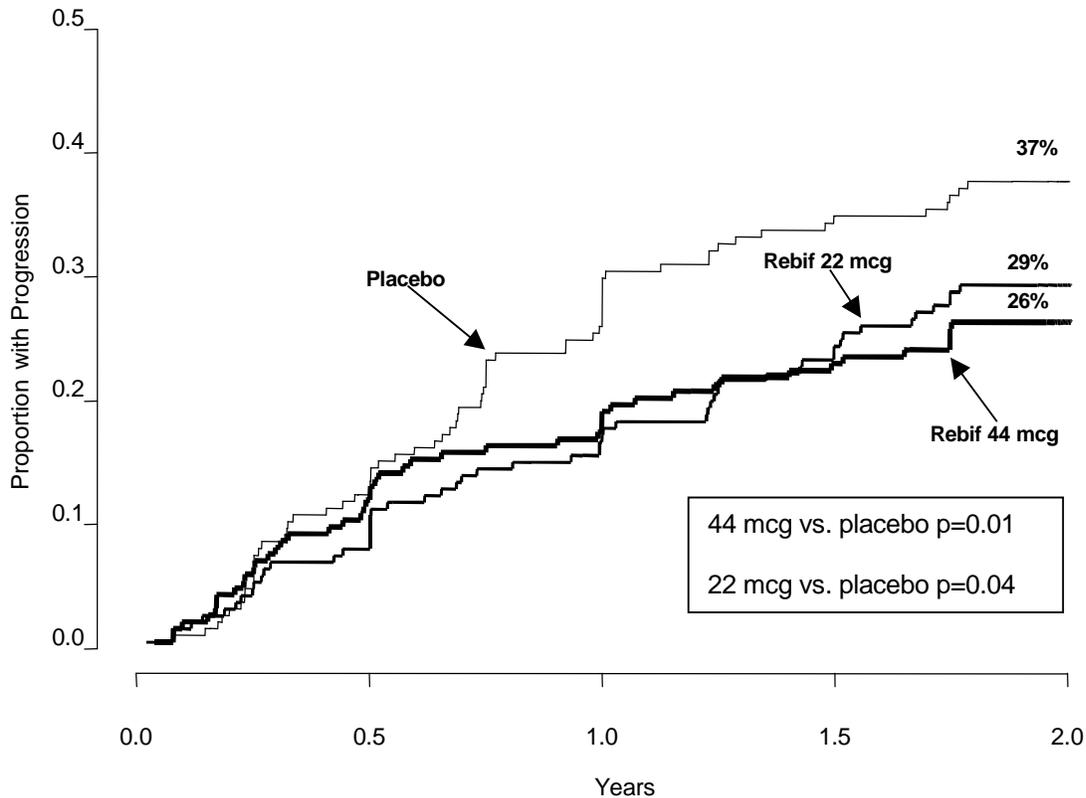
	<b>Placebo</b>	<b>22 mcg tiw</b>	<b>44 mcg tiw</b>
	n = 187	n = 189	n = 184
<b>Exacerbation-related</b>			
Mean number of exacerbations per patient over 2 years <sup>1,2</sup> (Percent reduction)	2.56	1.82** (29%)	1.73*** (32%)
Percent (%) of patients exacerbation-free at 2 years <sup>3</sup>	15%	25%*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

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  
 98 groups, 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

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

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



106

107 The safety and efficacy of treatment with Rebif<sup>®</sup> beyond 2 years have not been established.

108

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

115

116 The primary efficacy endpoint was the proportion of patients who remained exacerbation-free at  
117 24 weeks. The principal secondary endpoint was the mean number per patient per scan of  
118 combined unique active MRI lesions through 24 weeks, defined as any lesion that was T1 active  
119 or T2 active. Neurological examinations were performed every three months by a neurologist

Rebif<sup>®</sup>

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

124

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

129 **Table 2: Clinical and MRI Results from Study 2**

	Rebif <sup>®</sup>	Avonex <sup>®</sup>	Absolute Difference	Risk of relapse on Rebif <sup>®</sup> relative to Avonex <sup>®</sup>
Relapses	N=339	N=338		
Proportion of patients relapse-free at 24 weeks <sup>1</sup>	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 <sup>2</sup> (25 <sup>th</sup> , 75 <sup>th</sup> percentiles)	0.17* (0.00, 0.67)	0.33 (0.00, 1.25)		

130 \* p <0.001, and \*\* p = 0.009, Rebif<sup>®</sup> compared to Avonex<sup>®</sup>

131 (1) Logistic regression model adjusted for treatment and center, intent to treat analysis

132 (2) Nonparametric ANCOVA model adjusted for treatment and center, with baseline combined unique  
 133 lesions as the single covariate.

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

135 Exceptions included injection site disorders (83% of patients on Rebif<sup>®</sup> vs. 28% of patients on  
136 Avonex<sup>®</sup>), hepatic function disorders (18% on Rebif<sup>®</sup> vs. 10% on Avonex<sup>®</sup>), and leukopenia  
137 (6% on Rebif<sup>®</sup> vs. <1% on Avonex<sup>®</sup>), which were observed with greater frequency in the Rebif<sup>®</sup>  
138 group compared to the Avonex<sup>®</sup> group.

## 139 **INDICATIONS AND USAGE**

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

## 144 **CONTRAINDICATIONS**

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

## 147 **WARNINGS**

### 148 **Depression and Suicide**

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

156 **Hepatic Injury**

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

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

171 **Anaphylaxis**

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

176 **Albumin (Human)**

177 This product contains albumin, a derivative of human blood. Based on effective donor screening  
178 and product manufacturing processes, it carries an extremely remote risk for transmission of viral  
179 diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is  
180 considered extremely remote. No cases of transmission of viral diseases or CJD have ever been  
181 identified for albumin.

## 182 **PRECAUTIONS**

### 183 **General**

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

### 190 **Information for Patients**

191 All patients should be instructed to read the Rebif<sup>®</sup> Medication Guide supplied to them. Patients  
192 should be cautioned not to change the dosage or the schedule of administration without medical  
193 consultation.

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

198 Female patients should be cautioned about the abortifacient potential of Rebif<sup>®</sup> (see

199 **PRECAUTIONS:** Pregnancy).

200 Patients should be instructed in the use of aseptic technique when administering Rebif<sup>®</sup>.

201 Appropriate instruction for self-injection or injection by another person should be provided to the

202 patient or their caregiver, including careful review of the Rebif<sup>®</sup> Medication Guide and the

203 Rebif<sup>®</sup> Rebidose<sup>®</sup> autoinjector Instructions for Use that accompanies the product. Users should

204 demonstrate competency in all aspects of the injection prior to independent use. If a patient is to

205 self-administer Rebif<sup>®</sup>, the physical and cognitive ability of that patient to self-administer and

206 properly dispose of pre-filled syringes or the Rebif<sup>®</sup> Rebidose<sup>®</sup> autoinjectors should be assessed.

207 Patients with severe neurological deficits should not self administer injections without assistance

208 from a trained caregiver. The initial injection should be performed under the supervision of an

209 appropriately qualified health care provider. Patients can remove the pre-filled syringes or the

210 Rebif<sup>®</sup> Rebidose<sup>®</sup> autoinjector from the refrigerator at least 30 minutes prior to use so it can

211 warm to room temperature. Patients should be advised of the importance of rotating sites of

212 injection with each dose, to minimize the likelihood of severe injection site reactions or necrosis

213 and whether or not to pinch the skin prior to injection. A puncture-resistant container for

214 disposal of used needles, pre-filled syringes and Rebif<sup>®</sup> Rebidose<sup>®</sup> autoinjectors should be

215 supplied to the patient along with instructions for safe disposal of full containers. Patients

216 should be instructed in the importance of proper disposal of pre-filled syringes and Rebif<sup>®</sup>

217 Rebidose<sup>®</sup> autoinjectors and be cautioned against reuse of these items.

## 218 **Laboratory Tests**

219 In addition to those laboratory tests normally required for monitoring patients with multiple

220 sclerosis, blood cell counts and liver function tests are recommended at regular intervals (1, 3,

221 and 6 months) following introduction of Rebif<sup>®</sup> therapy and then periodically thereafter in the

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

## 226 **Drug Interactions**

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

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

## 233 **Immunization**

234 In a nonrandomized prospective clinical study, 86 multiple sclerosis (MS) patients on Rebif<sup>®</sup>  
235 44 mcg three times per week for at least 6 months and 77 patients not receiving interferon  
236 received influenza vaccination. The proportion of patients achieving a positive antibody  
237 response (defined as a titer > 1:40 measured by a hemagglutination inhibition assay) was similar  
238 in the two groups (93% and 91%, respectively). The exact relationship of antibody titers to  
239 vaccine efficacy was not studied and is not known in patients receiving Rebif<sup>®</sup>. Therefore, while  
240 patients receiving Rebif<sup>®</sup> may receive concomitant vaccination, the overall effectiveness of such  
241 vaccination is unknown.

## 242 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

243 *Carcinogenesis:* No carcinogenicity data for Rebif<sup>®</sup> are available in animals or humans.

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

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

### 253 **Pregnancy Category C**

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

### 265 **Nursing Mothers**

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

268 **Pediatric Use:** The safety and effectiveness of Rebif<sup>®</sup> in pediatric patients have not been  
269 studied.

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

## 275 **ADVERSE REACTIONS**

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

282  
283 The most commonly reported adverse reactions were injection site disorders, influenza-like  
284 symptoms (headache, fatigue, fever, rigors, chest pain, back pain, myalgia), abdominal pain,  
285 depression, elevation of liver enzymes and hematologic abnormalities. The most frequently  
286 reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Rebif<sup>®</sup>,  
287 adjustment in dosage, or the need for concomitant medication to treat an adverse reaction  
288 symptom) were injection site disorders, influenza-like symptoms, depression and elevation of  
289 liver enzymes (see **WARNINGS**).

290

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

296  
 297 The rates of adverse reactions and association with Rebif<sup>®</sup> in patients with relapsing-remitting  
 298 multiple sclerosis are drawn from the placebo-controlled study (n = 560) and the active  
 299 comparator-controlled study (n = 339).

300  
 301 The population encompassed an age range from 18 to 55 years. Nearly three-fourths of the  
 302 patients were female, and more than 90% were Caucasian, largely reflecting the general  
 303 demographics of the population of patients with multiple sclerosis.

304  
 305 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
 306 observed in the clinical trials of Rebif<sup>®</sup> cannot be directly compared to rates in the clinical trials  
 307 of other drugs and may not reflect the rates observed in practice.

308  
 309 Table 3 enumerates adverse events and laboratory abnormalities that occurred at an incidence  
 310 that was at least 2% more in either Rebif<sup>®</sup>-treated group than was observed in the placebo group.

311

312 Table 3. Adverse Reactions and Laboratory Abnormalities in Study 1

Body System Preferred Term	Placebo tiw (n=187)	Rebif <sup>®</sup> 22 mcg tiw (n=189)	Rebif <sup>®</sup> 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%

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

## 315 **Immunogenicity**

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

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

329 Anaphylaxis and other allergic reactions have been observed with the use of Rebif<sup>®</sup> (see

330 **WARNINGS:** Anaphylaxis).

## 331 **DRUG ABUSE AND DEPENDENCE**

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

## 334 **OVERDOSAGE**

335 Safety of doses higher than 44 mcg sc three times per week has not been adequately evaluated.

336 The maximum amount of Rebif<sup>®</sup> that can be safely administered has not been determined.

## 337 **DOSAGE AND ADMINISTRATION**

338 Dosages of Rebif<sup>®</sup> shown to be safe and effective are 22 mcg and 44 mcg injected  
339 subcutaneously three times per week. Rebif<sup>®</sup> should be administered, if possible, at the same  
340 time (preferably in the late afternoon or evening) on the same three days (e.g., Monday,  
341 Wednesday, and Friday) at least 48 hours apart each week (see **CLINICAL STUDIES**).  
342 Generally, patients should be started at 20% of the prescribed dose three times per week and  
343 increased over a 4-week period to the targeted dose, either 22 mcg three times per week (see  
344 Table 4) or 44 mcg three times per week (see Table 5). Patients prescribed a targeted dose of  
345 22 mcg three times per week should use the pre-filled syringes for titration. Following the  
346 administration of each dose, any residual product remaining in the syringe should be discarded in  
347 a safe and proper manner.

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

351  
352 **Table 4: Titration Schedule for a 22 mcg Prescribed Dose\***

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

353 \*Only pre-filled syringes can be used to titrate to 22 mcg Prescribed Dose  
354

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

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

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

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

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357  
358

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

362 Rebif<sup>®</sup> is intended for use under the guidance and supervision of a physician. It is recommended  
363 that physicians or qualified medical personnel train patients in the proper technique for self-  
364 administering subcutaneous (sc) injections using the pre-filled syringe or injection device  
365 approved for use with Rebif<sup>®</sup>. Injection depth of the Rebif<sup>®</sup> Rebidose<sup>®</sup> autoinjector is fixed at  
366 8 mm; the health care provider should determine the injection technique. Patients should be  
367 advised to rotate sites for sc injections (see **PRECAUTIONS:** Information for Patients).  
368 Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms on  
369 treatment days. Rebif<sup>®</sup> should be inspected visually for particulate matter and discoloration prior  
370 to administration.

### 371 **Stability and Storage**

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

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

378 **HOW SUPPLIED**

379 Rebif<sup>®</sup> is supplied as a sterile, preservative-free solution packaged in two different delivery  
380 options:

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

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

The following package presentations are available:

**Pre-Filled Syringes:**

381 **Rebif<sup>®</sup> (interferon beta -1a) Titration Pack, NDC 44087-8822-1**

382 - Six Rebif<sup>®</sup> 8.8 mcg pre-filled syringes and Six Rebif<sup>®</sup> 22 mcg pre-filled syringe

383 **Rebif<sup>®</sup> (interferon beta -1a) 22 mcg Pre-filled syringe**

384 - One Rebif<sup>®</sup> 22 mcg pre-filled syringe, NDC 44087-0022-1

385 - Twelve Rebif<sup>®</sup> 22 mcg pre-filled syringes, NDC 44087-0022-3

386 **Rebif<sup>®</sup> (interferon beta -1a) 44 mcg Pre-filled syringe**

387 - One Rebif<sup>®</sup> 44 mcg pre-filled syringe, NDC 44087-0044-1

388 - Twelve Rebif<sup>®</sup> 44 mcg pre-filled syringes, NDC 44087-0044-3

**Rebif<sup>®</sup> Rebidose<sup>®</sup> Autoinjectors:**

**Rebif<sup>®</sup> (interferon beta-1a) Titration Pack, NDC 44087-0188-1**

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

**Rebif<sup>®</sup> (interferon beta-1a) 22 mcg Rebif<sup>®</sup> Rebidose<sup>®</sup> Autoinjector**

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

**Rebif<sup>®</sup> (interferon beta-1a) 44 mcg Rebif<sup>®</sup> Rebidose<sup>®</sup> Autoinjector**

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

389

390 **Rx only**

391

392 References

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