

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

16 Rebif<sup>®</sup> (interferon beta-1a) is formulated as a sterile solution in a prefilled syringe intended for  
17 subcutaneous (sc) injection. Each 0.5 mL (0.5 cc) of Rebif<sup>®</sup> contains either 22 mcg or 44 mcg of  
18 interferon beta-1a, 2 or 4 mg albumin (human) USP, 27.3 mg mannitol USP, 0.4 mg sodium  
19 acetate and Water for Injection USP. Each 0.2 mL (0.2 cc) of Rebif<sup>®</sup> contains 8.8 mcg of  
20 interferon beta-1a, 0.8 mg albumin (human) USP, 10.9 mg mannitol USP, 0.16 mg sodium  
21 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 48  
56 hours. All three markers remained elevated for up to four days. Administration of Rebif 22®  
57 mcg three times per week (tiw) inhibited mitogen-induced release of pro-inflammatory cytokines  
58 (IFN- $\gamma$ , IL-1, IL-6, TNF- $\alpha$  and TNF- $\beta$ ) 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.<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 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<sup>®</sup> 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
<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>MRI</b>			
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***

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

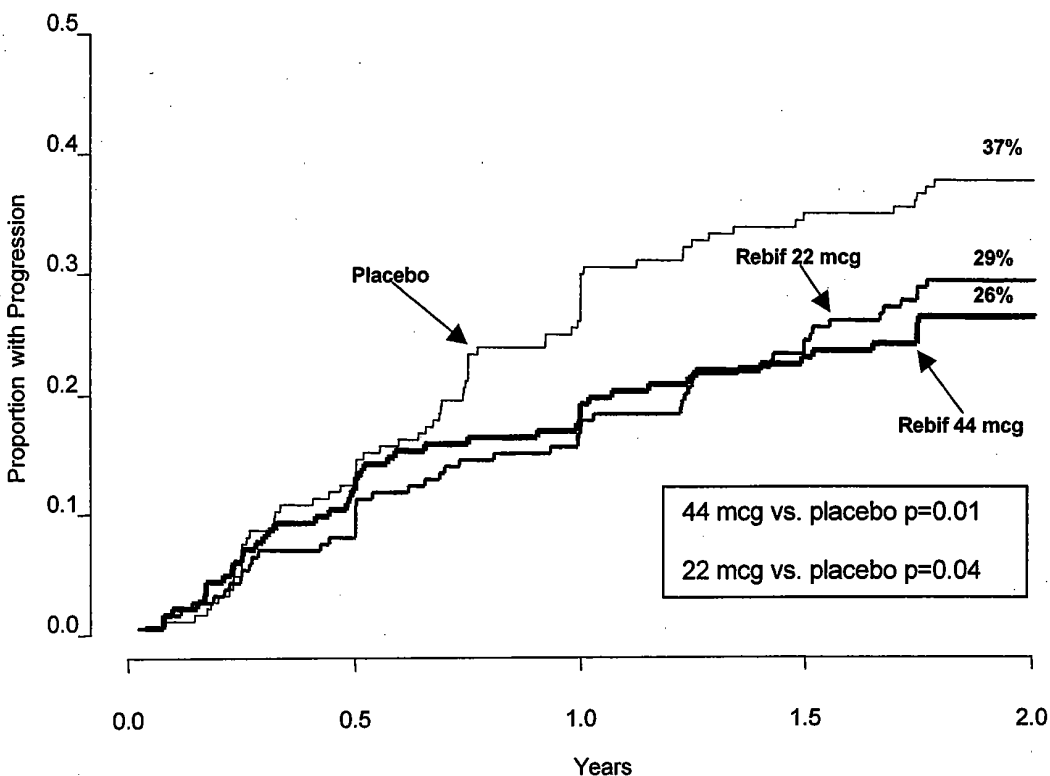
100 (5) ANOVA on ranks adjusted for center. Patients with missing scans were excluded from this analysis

101 The time to onset of progression in disability sustained for three months was significantly longer

102 in patients treated with Rebif<sup>®</sup> than in placebo-treated patients. The Kaplan-Meier estimates of

103 the proportions of patients with sustained disability are depicted in Figure 1.

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



105

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

107

108 Study 2 was a randomized, open-label, evaluator-blinded, active comparator study.<sup>(2)</sup> 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<sup>®</sup> 44 mcg tiw by sc injection (n=339) or Avonex<sup>®</sup> 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

119 blinded to treatment assignment. Patient visits were conducted monthly, and mid-month  
 120 telephone contacts were made to inquire about potential exacerbations. If an exacerbation was  
 121 suspected, the patient was evaluated with a neurological examination. MRI scans were  
 122 performed monthly and analyzed in a treatment-blinded manner.  
 123 Patients treated with Rebif® 44 mcg sc tiw were more likely to remain relapse-free at 24 and 48  
 124 weeks than were patients treated with Avonex® 30 mcg im qw (Table 2). This study does not  
 125 support any conclusion regarding effects on the accumulation of physical disability.

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

	Rebif®	Avonex®	Absolute Difference	Risk of relapse on Rebif® relative to Avonex®
<b>Relapses</b>	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)
<b>MRI (through 24 weeks)</b>	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)		

127 \* p <0.001, and \*\* p = 0.009, Rebif® compared to Avonex®

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

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

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

132 Exceptions included injection site disorders (83% of patients on Rebif<sup>®</sup> vs. 28% of patients on  
133 Avonex<sup>®</sup>), hepatic function disorders (18% on Rebif<sup>®</sup> vs. 10% on Avonex<sup>®</sup>), and leukopenia  
134 (6% on Rebif<sup>®</sup> vs. <1% on Avonex<sup>®</sup>), which were observed with greater frequency in the Rebif<sup>®</sup>  
135 group compared to the Avonex<sup>®</sup> group.

## 136 **INDICATIONS AND USAGE**

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

## 141 **CONTRAINDICATIONS**

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

## 144 **WARNINGS**

### 145 **Depression**

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

152

153 **Hepatic Injury**

154 Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has  
155 been reported rarely in patients taking Rebif<sup>®</sup>. Symptoms of liver dysfunction began from one to  
156 six months following the initiation of Rebif<sup>®</sup>. If jaundice or other symptoms of liver dysfunction  
157 appear, treatment with Rebif<sup>®</sup> should be discontinued immediately due to the potential for rapid  
158 progression to liver failure. Asymptomatic elevation of hepatic transaminases (particularly  
159 SGPT) is common with interferon therapy (see **ADVERSE REACTIONS**). Rebif<sup>®</sup> should be  
160 initiated with caution in patients with active liver disease, alcohol abuse, increased serum SGPT  
161 (> 2.5 times ULN), or a history of significant liver disease. Also, the potential risk of Rebif<sup>®</sup>  
162 used in combination with known hepatotoxic products should be considered prior to Rebif<sup>®</sup>  
163 administration, or when adding new agents to the regimen of patients already on Rebif<sup>®</sup>.  
164 Reduction of Rebif<sup>®</sup> dose should be considered if SGPT rises above 5 times the upper limit of  
165 normal. The dose may be gradually re-escalated when enzyme levels have normalized (see  
166 **PRECAUTIONS: Laboratory Tests and Drug Interactions; and DOSAGE AND**  
167 **ADMINISTRATION**).

168 **Anaphylaxis**

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

173 **Albumin (Human)**

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

179 **PRECAUTIONS**

180 **General**

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

187 **Information for Patients**

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

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

195 Female patients should be cautioned about the abortifacient potential of Rebif® (see

196 **PRECAUTIONS: Pregnancy**).

197 Patients should be instructed in the use of aseptic technique when administering Rebif®.  
198 Appropriate instruction for self-injection or injection by another person should be provided,  
199 including careful review of the Rebif® Medication Guide. If a patient is to self-administer  
200 Rebif®, the physical and cognitive ability of that patient to self-administer and properly dispose  
201 of syringes should be assessed. The initial injection should be performed under the supervision  
202 of an appropriately qualified health care professional. Patients should be advised of the  
203 importance of rotating sites of injection with each dose, to minimize the likelihood of severe  
204 injection site reactions or necrosis. A puncture-resistant container for disposal of used needles  
205 and syringes should be supplied to the patient along with instructions for safe disposal of full  
206 containers. Patients should be instructed in the technique and importance of proper syringe  
207 disposal and be cautioned against reuse of these items.

#### 208 **Laboratory Tests**

209 In addition to those laboratory tests normally required for monitoring patients with multiple  
210 sclerosis, blood cell counts and liver function tests are recommended at regular intervals (1, 3,  
211 and 6 months) following introduction of Rebif® therapy and then periodically thereafter in the  
212 absence of clinical symptoms. Thyroid function tests are recommended every 6 months in  
213 patients with a history of thyroid dysfunction or as clinically indicated. Patients with  
214 myelosuppression may require more intensive monitoring of complete blood cell counts, with  
215 differential and platelet counts.

216 **Drug Interactions**

217 No formal drug interaction studies have been conducted with Rebif<sup>®</sup>. Due to its potential to  
218 cause neutropenia and lymphopenia, proper monitoring of patients is required if Rebif<sup>®</sup> is given  
219 in combination with myelosuppressive agents. Also, the potential for hepatic injury should be  
220 considered when Rebif<sup>®</sup> is used in combination with other products associated with hepatic  
221 injury, or when new agents are added to the regimen of patients already on Rebif<sup>®</sup> (see  
222 **WARNINGS: Hepatic Injury**).

223

224 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

235 **Pregnancy Category C**

236 Rebif<sup>®</sup> treatment has been associated with significant increases in embryolethal or abortifacient  
237 effects in cynomolgus monkeys administered doses approximately 2 times the cumulative

238 weekly human dose (based on either body weight or surface area) either during the period of  
239 organogenesis (gestation day 21-89) or later in pregnancy. There were no fetal malformations or  
240 other evidence of teratogenesis noted in these studies. These effects are consistent with the  
241 abortifacient effects of other type I interferons. There are no adequate and well-controlled  
242 studies of Rebif® in pregnant women. However, in Studies 1 and 2, there were 2 spontaneous  
243 abortions observed and 5 fetuses carried to term among 7 women in the Rebif® groups. If a  
244 woman becomes pregnant or plans to become pregnant while taking Rebif®, she should be  
245 informed about the potential hazards to the fetus, and discontinuation of Rebif® should be  
246 considered.

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

#### 250 **Nursing Mothers**

251 It is not known whether Rebif® is excreted in human milk. Because many drugs are excreted in  
252 human milk, caution should be exercised when Rebif® is administered to a nursing woman.

253 **Pediatric Use:** The safety and effectiveness of Rebif® in pediatric patients have not been  
254 studied.

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

260 **ADVERSE REACTIONS**

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

267

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

275

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

281

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

285

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

289

290 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
291 observed in the clinical trials of Rebif® cannot be directly compared to rates in the clinical trials  
292 of other drugs and may not reflect the rates observed in practice.

293

294 Table 3 enumerates adverse events and laboratory abnormalities that occurred at an incidence  
295 that was at least 2% more in either Rebif®-treated group than was observed in the placebo group.

296

297 **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)
<b>BODY AS A WHOLE</b>			
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%
<b>INJECTION SITE DISORDERS</b>			
Injection Site Reaction	39%	89%	92%
Injection Site Necrosis	0%	1%	3%
<b>CENTRAL &amp; PERIPH NERVOUS SYSTEM DISORDERS</b>			
Hypertonia	5%	7%	6%
Coordination Abnormal	2%	5%	4%
Convulsions	2%	5%	4%
<b>ENDOCRINE DISORDERS</b>			
Thyroid Disorder	3%	4%	6%
<b>GASTROINTESTINAL SYSTEM DISORDERS</b>			
Abdominal Pain	17%	22%	20%
Dry Mouth	1%	1%	5%
<b>LIVER AND BILIARY SYSTEM DISORDERS</b>			

SGPT Increased	4%	20%	27%
SGOT Increased	4%	10%	17%
Hepatic Function Abnormal	2%	4%	9%
Bilirubinaemia	1%	3%	2%
<b>MUSCULO-SKELETAL SYSTEM DISORDERS</b>			
Myalgia	20%	25%	25%
Back Pain	20%	23%	25%
Skeletal Pain	10%	15%	10%
<b>HEMATOLOGIC DISORDERS</b>			
Leukopenia	14%	28%	36%
Lymphadenopathy	8%	11%	12%
Thrombocytopenia	2%	2%	8%
Anemia	3%	3%	5%
<b>PSYCHIATRIC DISORDERS</b>			
Somnolence	1%	4%	5%
<b>SKIN DISORDERS</b>			
Rash Erythematous	3%	7%	5%
Rash Maculo-Papular	2%	5%	4%
<b>URINARY SYSTEM DISORDERS</b>			
Micturition Frequency	4%	2%	7%
Urinary Incontinence	2%	4%	2%
<b>VISION DISORDERS</b>			
Vision Abnormal	7%	7%	13%
Xerophthalmia	0%	3%	1%

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

### 300 **Immunogenicity**

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

307 The data reflect the percentage of patients whose test results were considered positive for  
308 antibodies to Rebif<sup>®</sup> using an antiviral cytopathic effect assay, and are highly dependent on the  
309 sensitivity and specificity of the assay. Additionally, the observed incidence of NAb positivity in

310 an assay may be influenced by several factors including sample handling, timing of sample  
311 collection, concomitant medications and underlying disease. For these reasons, comparison of  
312 the incidence of antibodies to Rebif<sup>®</sup> with the incidence of antibodies to other products may be  
313 misleading.

314 Anaphylaxis and other allergic reactions have been observed with the use of Rebif<sup>®</sup> (see  
315 **WARNINGS: Anaphylaxis**).

### 316 **DRUG ABUSE AND DEPENDENCE**

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

### 319 **OVERDOSAGE**

320 Safety of doses higher than 44 mcg sc tiw have not been adequately evaluated. The maximum  
321 amount of Rebif<sup>®</sup> that can be safely administered has not been determined.

### 322 **DOSAGE AND ADMINISTRATION**

323 Dosages of Rebif<sup>®</sup> shown to be safe and effective are 22 mcg and 44 mcg injected  
324 subcutaneously three times per week. Rebif<sup>®</sup> should be administered, if possible, at the same  
325 time (preferably in the late afternoon or evening) on the same three days (e.g., Monday,  
326 Wednesday, and Friday) at least 48 hours apart each week (see **CLINICAL STUDIES**).

327 Generally, patients should be started at 20% of the prescribed dose tiw and increased over a 4-  
328 week period to the targeted dose, either 22 mcg or 44 mcg tiw (see **Table 4**). Following the  
329 administration of each dose, any residual product remaining in the syringe should be discarded in  
330 a safe and proper manner.

331 A Rebif® Titration Pack containing 6 doses of 8.8 mcg (0.2 mL) and 6 doses of 22 mcg (0.5 mL)  
332 is available for use during the titration period.

333 **Table 4: Schedule for Patient Titration**  
334

	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

335  
336 Leukopenia or elevated liver function tests may necessitate dose reduction or discontinuation of  
337 Rebif® administration until toxicity is resolved (see **WARNINGS: Hepatic Injury,**  
338 **PRECAUTIONS: General and ADVERSE REACTIONS**).

339 Rebif® is intended for use under the guidance and supervision of a physician. It is recommended  
340 that physicians or qualified medical personnel train patients in the proper technique for self-  
341 administering subcutaneous injections using the pre-filled syringe. Patients should be advised to  
342 rotate sites for sc injections (see **PRECAUTIONS: Information for Patients**). Concurrent use  
343 of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days.  
344 Rebif® should be inspected visually for particulate matter and discoloration prior to  
345 administration.

#### 346 **Stability and Storage**

347 Rebif® should be stored refrigerated between 2-8°C (36-46°F). DO NOT FREEZE. If a  
348 refrigerator is not available, Rebif® may be stored at or below 25° C/77° F for up to 30 days and  
349 away from heat and light.

350 Do not use beyond the expiration date printed on packages. Rebif® contains no preservatives.

351 Each syringe is intended for single use. Unused portions should be discarded.

## 352 **HOW SUPPLIED**

353 Rebif® is supplied as a sterile, preservative-free solution packaged in graduated, ready to use

354 0.2 mL or 0.5 mL pre-filled syringes with 29-gauge, 0.5 inch needle for subcutaneous injection.

355 The following package presentations are available.

### 356 **Rebif® (interferon beta -1a) Titration Pack, NDC 44087-8822-1**

357 - Six Rebif® 8.8 mcg pre-filled syringes and Six Rebif® 22 mcg pre-filled syringes

### 358 **Rebif® (interferon beta -1a) 22 mcg Pre-filled syringe**

359 - One Rebif® 22 mcg pre-filled syringe, NDC 44087-0022-1

360 - Twelve Rebif® 22 mcg pre-filled syringes, NDC 44087-0022-3

### 361 **Rebif® (interferon beta -1a) 44 mcg Pre-filled syringe**

362 - One Rebif® 44 mcg pre-filled syringe, NDC 44087-0044-1

363 - Twelve Rebif® 44 mcg pre-filled syringes, NDC 44087-0044-3

364 **RX only.**

365

366 References

367 1. PRISMS Study Group. Randomized double-blind placebo-controlled study of interferon

368  $\beta$ -1a in relapsing/remitting multiple sclerosis. Lancet 1998; 352: 1498-1504.

369 2. Data on file.

370

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

372

373 Co-Marketed by:

374 Serono, Inc.

375 Rockland, MA 02370

376 Pfizer Inc.

377 New York, NY 10017

378

379 Revised: December 2004

380

381 \*Avonex<sup>®</sup> is a registered trademark of Biogen, Inc.

382

383 N6700101C