1   **Rebif® (interferon beta-1a)**

2   DESCRIPTION

3   Rebif® (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® is identical to that of natural fibroblast derived

7   human interferon beta. Natural interferon beta and interferon beta-1a (Rebif®) 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® 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® 8.8 mcg, 22 mcg and 44 mcg

14   contains approximately 2.4 MIU, 6 MIU or 12 MIU, respectively, of antiviral activity using this

15   method.

16   Rebif® (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® contain either 22 mcg or 44 mcg of

18   interferon beta-1a, 2 mg or 4 mg albumin (human) USP, 27.3 mg mannitol USP, 0.4 mg sodium

19   acetate, Water for Injection USP. Each 0.2 ml (0.2 cc) of Rebif® contains 8.8 mcg of interferon

20   beta-1a, 0.8 mg albumin (human) USP, 10.9 mg mannitol USP, 0.16 mg sodium acetate, and

21   Water for Injection USP.

22

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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 ± 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.

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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***
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.

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Figure 1: Proportions of Patients with Sustained Disability Progression
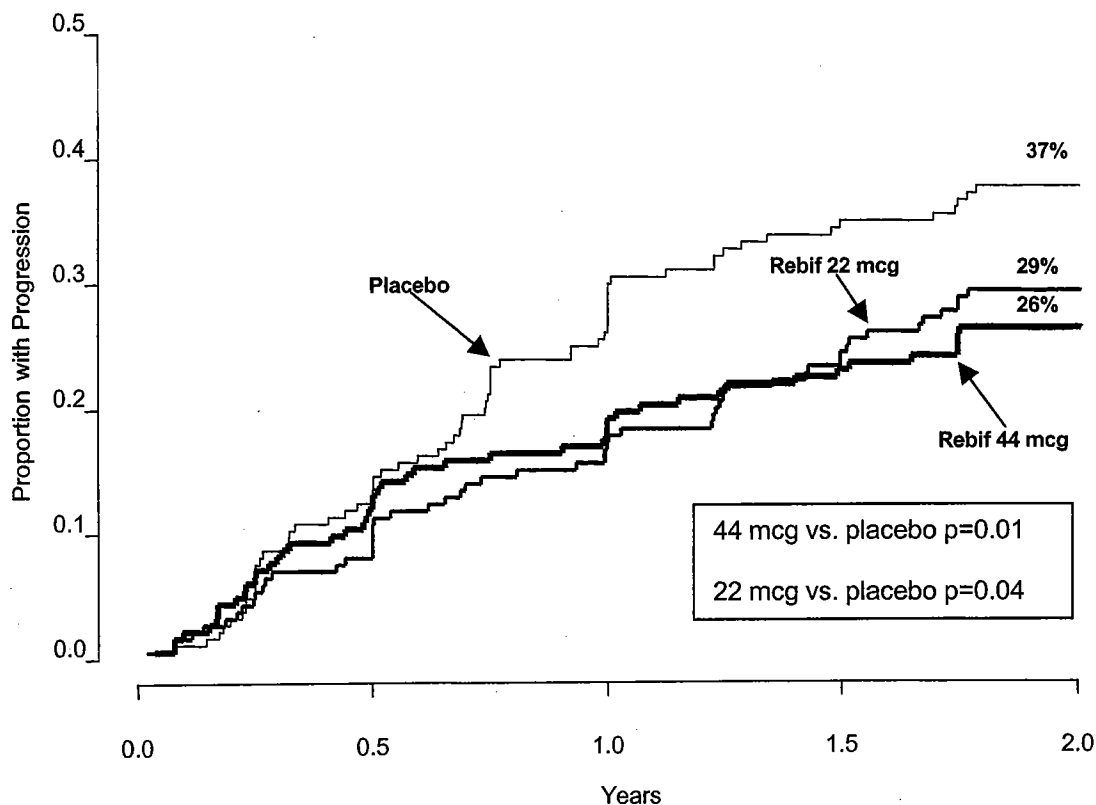
The safety and efficacy of treatment with Rebif® beyond 2 years have not been established.

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

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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®
Relapses Proportion of patients relapse-free at 24 weeks[1]	N=339 75%*	N=338 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) Median of the mean number of combined unique MRI lesions per patient per scan[2](25th, 75th percentiles)	N=325 0.17* (0.00, 0.67)	N=325 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.

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® vs. 28% of patients on

133 Avonex®), hepatic function disorders (18% on Rebif® vs. 10% on Avonex®), and leukopenia

134 (6% on Rebif® vs. <1% on Avonex®), which were observed with greater frequency in the

135 Rebif® group compared to the Avonex® group.

136 **INDICATIONS AND USAGE**

137 Rebif® (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® in chronic progressive multiple sclerosis has not been

140 established.

141 **CONTRAINDICATIONS**

142 Rebif® (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® (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®. 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® 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®. Symptoms of liver dysfunction began from one

156 to six months following the initiation of Rebif®. If jaundice or other symptoms of liver

157 dysfunction appear, treatment with Rebif® should be discontinued immediately due to the

158 potential for rapid progression to liver failure.

159 Asymptomatic elevation of hepatic transaminases (particularly SGPT) is common with interferon

160 therapy (see **ADVERSE REACTIONS**). Rebif® should be initiated with caution in patients

161 with active liver disease, alcohol abuse, increased serum SGPT (> 2.5 times ULN), or a history

162 of significant liver disease. Also, the potential risk of Rebif® used in combination with known

163 hepatotoxic products should be considered prior to Rebif® administration, or when adding new

164 agents to the regimen of patients already on Rebif®. Reduction of Rebif® dose should be

165 considered if SGPT rises above 5 times the upper limit of normal. The dose may be gradually

166 re-escalated when enzyme levels have normalized. (See **PRECAUTIONS:** Laboratory Tests

167 and Drug Interactions; and **DOSAGE AND ADMINISTRATION**)

168 **Anaphylaxis**

169 Anaphylaxis has been reported as a rare complication of Rebif® 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

174

175 **Albumin (Human)**

176 This product contains albumin, a derivative of human blood. Based on effective donor screening

177 and product manufacturing processes, it carries an extremely remote risk for transmission of viral

178 diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is

179 considered extremely remote. No cases of transmission of viral diseases or CJD have ever been

180 identified for albumin.

181 <mark>**PRECAUTIONS**</mark>

182 **General**

183 Caution should be exercised when administering Rebif® to patients with pre-existing seizure

184 disorders. Seizures have been associated with the use of beta interferons. A relationship

185 between occurrence of seizures and the use of Rebif® has not been established. Leukopenia and

186 new or worsening thyroid abnormalities have developed in some patients treated with Rebif®

187 (see **ADVERSE REACTIONS**). Regular monitoring for these conditions is recommended (see

188 **PRECAUTIONS: Laboratory Tests**).

189 **Information for Patients**

190 All patients should be instructed to read the Rebif® Medication Guide supplied to them. Patients

191 should be cautioned not to change the dosage or the schedule of administration without medical

192 consultation.

193 Patients should be informed of the most common and the most severe adverse reactions

194 associated with the use of Rebif® (see **WARNINGS and ADVERSE REACTIONS**). Patients

195 should be advised of the symptoms associated with these conditions, and to report them to their

196 physician.

Rebif®

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

198 **PRECAUTIONS: Pregnancy).**

199 Patients should be instructed in the use of aseptic technique when administering Rebif®.

200 Appropriate instruction for self-injection or injection by another person should be provided,

201 including careful review of the Rebif® Medication Guide. If a patient is to self-administer

202 Rebif®, the physical and cognitive ability of that patient to self-administer and properly dispose

203 of syringes should be assessed. The initial injection should be performed under the supervision

204 of an appropriately qualified health care professional. Patients should be advised of the

205 importance of rotating sites of injection with each dose, to minimize the likelihood of severe

206 injection site reactions or necrosis. A puncture-resistant container for disposal of used needles

207 and syringes should be supplied to the patient along with instructions for safe disposal of full

208 containers. Patients should be instructed in the technique and importance of proper syringe

209 disposal and be cautioned against reuse of these items.

210 **Laboratory Tests**

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

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

213 and 6 months) following introduction of Rebif® therapy and then periodically thereafter in the

214 absence of clinical symptoms. Thyroid function tests are recommended every 6 months in

215 patients with a history of thyroid dysfunction or as clinically indicated. Patients with

216 myelosuppression may require more intensive monitoring of complete blood cell counts, with

217 differential and platelet counts.

Rebif®   11

Drug Interactions

219   No formal drug interaction studies have been conducted with Rebif®. Due to its potential to

220   cause neutropenia and lymphopenia, proper monitoring of patients is required if Rebif® is given

221   in combination with myelosuppressive agents.

222   Also, the potential for hepatic injury should be considered when Rebif® is used in combination

223   with other products associated with hepatic injury, or when new agents are added to the regimen

224   of patients already on Rebif® (see **WARNINGS: Hepatic injury**).

225   **Immunization**

226   In a nonrandomized prospective clinical study, 86 multiple sclerosis (MS) patients on Rebif® 44

227   mcg tiw for at least 6 months and 77 patients not receiving interferon received influenza

228   vaccination. The proportion of patients achieving a positive antibody response (defined as a titer

229   > 1:40 measured by a hemagglutination inhibition assay) was similar in the two groups (93% and

230   91%, respectively). The exact relationship of antibody titers to vaccine efficacy was not studied

231   and is not known in patients receiving Rebif®. Therefore, while patients receiving Rebif® may

232   receive concomitant vaccination, the overall effectiveness of such vaccination is unknown.

233   **Carcinogenesis, Mutagenesis, Impairment of Fertility**

234   *Carcinogenesis:* No carcinogenicity data for Rebif® are available in animals or humans.

235   *Mutagenesis:* Rebif® was not mutagenic when tested in the Ames bacterial test and in an *in vitro*

236   cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation.

237   *Impairment of Fertility:* No studies have been conducted to evaluate the effects of Rebif® on

238   fertility in humans. In studies in normally cycling female cynomolgus monkeys given daily sc

239   injections of Rebif® for six months at doses of up to 9 times the recommended weekly human

240   dose (based on body surface area), no effects were observed on either menstrual cycling or serum

241   estradiol levels. The validity of extrapolating doses used in animal studies to human doses is not

242   103795.5062PI.final 6.7.05 established. In male monkeys, the same doses of Rebif® had no demonstrable adverse effects on

243   sperm count, motility, morphology, or function.

244   **Pregnancy Category C**

245   Rebif® treatment has been associated with significant increases in embryolethal or abortifacient

246   effects in cynomolgus monkeys administered doses approximately 2 times the cumulative

247   weekly human dose (based on either body weight or surface area) either during the period of

248   organogenesis (gestation day 21-89) or later in pregnancy. There were no fetal malformations or

249   other evidence of teratogenesis noted in these studies. These effects are consistent with the

250   abortifacient effects of other type I interferons. There are no adequate and well-controlled

251   studies of Rebif® in pregnant women. However, in Studies 1 and 2, there were 2 spontaneous

252   abortions observed and 5 fetuses carried to term among 7 women in the Rebif® groups. If a

253   woman becomes pregnant or plans to become pregnant while taking Rebif®, she should be

254   informed about the potential hazards to the fetus, and discontinuation of Rebif® should be

255   considered.

256   **Nursing Mothers**

257   It is not known whether Rebif® is excreted in human milk. Because many drugs are excreted in

258   human milk, caution should be exercised when Rebif® is administered to a nursing woman.

259   **Pediatric Use:** The safety and effectiveness of Rebif® in pediatric patients have not been

260   studied.

261   **Geriatric Use:** Clinical studies of Rebif® did not include sufficient numbers of subjects aged 65

262   and over to determine whether they respond differently than younger subjects. In general, dose

263   selection for an elderly patient should be cautious, usually starting at the low end of the dosing

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range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of

265   concomitant disease or other drug therapy.

266   **ADVERSE REACTIONS**

267   The most frequently reported serious adverse reactions with Rebif® were psychiatric disorders

268   including depression and suicidal ideation or attempt (see **WARNINGS**). The incidence of

269   depression of any severity in the Rebif®-treated groups and placebo-treated group was

270   approximately 25%. In post-marketing experience, Rebif® administration has been rarely

271   associated with severe liver dysfunction, including hepatic failure requiring liver transplantation

272   (see **WARNINGS: Hepatic Injury**).

273

274   The most commonly reported adverse reactions were injection site

275   disorders, influenza-like symptoms (headache, fatigue, fever, rigors, chest pain, back pain,

276   myalgia), abdominal pain, depression, elevation of liver enzymes and hematologic abnormalities.

277   The most frequently reported adverse reactions resulting in clinical intervention (e.g.,

278   discontinuation of Rebif®, adjustment in dosage, or the need for concomitant medication to treat

279   an adverse reaction symptom) were injection site disorders, influenza-like symptoms, depression

280   and elevation of liver enzymes (see **WARNINGS**).

281

282   In Study 1, 6 patients randomized to Rebif® 44 mcg tiw (3%), and 2 patients who received

283   Rebif® 22 mcg tiw (1%) developed injection site necrosis during two years of therapy. Rebif®

284   was continued in 7 patients and interrupted briefly in one patient. There was one report of

285   injection site necrosis in Study 2 during 48 weeks of Rebif treatment. All events resolved with

286   conservative management; none required skin debridement or grafting.

287

The rates of adverse reactions and association with Rebif® in patients with relapsing-remitting

289 multiple sclerosis are drawn from the placebo-controlled study (n = 560) and the active

290 comparator-controlled study (n = 339).

291

292 The population encompassed an age range from 18 to 55 years. Nearly three-fourths of the

293 patients were female, and more than 90% were Caucasian, largely reflecting the general

294 demographics of the population of patients with multiple sclerosis.

295

296 Because clinical trials are conducted under widely varying conditions, adverse reaction rates

297 observed in the clinical trials of Rebif® cannot be directly compared to rates in the clinical trials

298 of other drugs and may not reflect the rates observed in practice.

299

300 Table 3 enumerates adverse events and laboratory abnormalities that occurred at an incidence

301 that was at least 2% more in either Rebif®-treated group than was observed in the placebo group.

302

303 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%

304   The adverse reactions were generally similar in Studies 1 and 2, taking into account the disparity

305   in study durations.

306   **Immunogenicity**

307   As with all therapeutic proteins, there is a potential for immunogenicity. In study 1, the presence

308   of neutralizing antibodies (NAb) to Rebif® was determined by collecting and analyzing serum

309   pre-study and at 6 month time intervals during the 2 years of the clinical trial. Serum NAb were

310   detected in 59/189 (31%) and 45/184 (24%) of Rebif®-treated patients at the 22 mcg and 44 mcg

311   tiw doses, respectively, at one or more times during the study. The clinical significance of the

312   presence of NAb to Rebif® is unknown.

313 The data reflect the percentage of patients whose test results were considered positive for

314 antibodies to Rebif® using an antiviral cytopathic effect assay, and are highly dependent on the

315 sensitivity and specificity of the assay. Additionally, the observed incidence of NAb positivity in

316 an assay may be influenced by several factors including sample handling, timing of sample

317 collection, concomitant medications and underlying disease. For these reasons, comparison of

318 the incidence of antibodies to Rebif® with the incidence of antibodies to other products may be

319 misleading.

320 Anaphylaxis and other allergic reactions have been observed with the use of Rebif® (see

321 **WARNINGS: Anaphylaxis**).

322 **DRUG ABUSE AND DEPENDENCE**

323 There is no evidence that abuse or dependence occurs with Rebif® therapy. However, the risk of

324 dependence has not been systematically evaluated.

325 **OVERDOSAGE**

326 Safety of doses higher than 44 mcg sc tiw has not been adequately evaluated. The maximum

327 amount of Rebif® that can be safely administered has not been determined.

328 **DOSAGE AND ADMINISTRATION**

329 Dosages of Rebif® shown to be safe and effective are 22 mcg and 44 mcg injected

330 subcutaneously three times per week. Rebif® should be administered, if possible, at the same

331 time (preferably in the late afternoon or evening) on the same three days (e.g., Monday,

332 Wednesday, and Friday) at least 48 hours apart each week (see **CLINICAL STUDIES**).

333 Generally, patients should be started at 20% of the prescribed dose tiw and increased over a 4-

334 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

336   a safe and proper manner.

337   A Rebif® Titration Pack containing 6 doses of 8.8 mcg (0.2 mL) and 6 doses of 22 mcg (0.5 mL)

338   is available for use during the titration period.

339   **Table 4:   Schedule for Patient Titration**
340
341

	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

342
343   Leukopenia or elevated liver function tests may necessitate dose reduction or discontinuation of

344   Rebif® administration until toxicity is resolved (see **WARNINGS: Hepatic Injury,**

345   **PRECAUTIONS: General and ADVERSE REACTIONS**).

346   Rebif® is intended for use under the guidance and supervision of a physician. It is recommended

347   that physicians or qualified medical personnel train patients in the proper technique for self-

348   administering subcutaneous injections using the pre-filled syringe. Patients should be advised to

349   rotate sites for sc injections (see **PRECAUTIONS: Information for Patients**). Concurrent use

350   of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days.

351   Rebif® should be inspected visually for particulate matter and discoloration prior to

352   administration.

Rebif®   18

Stability and Storage

354   Rebif® should be stored refrigerated between 2-8°C (36-46°F). DO NOT FREEZE. If a

355   refrigerator is not available, Rebif® may be stored at or below 25° C/77° F for up to 30 days and

356   away from heat and light.

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

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

359   # HOW SUPPLIED

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

361   0.2 mL or 0.5 mL pre-filled syringes with 27-gauge, 0.5 inch needle for subcutaneous injection.

362   The following package presentations are available.

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

364   - Six Rebif® 8.8 mcg pre-filled syringes and Six Rebif® 22 mcg pre-filled syringe

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

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

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

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

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

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

371   **RX only.**

373 References

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

375 β-1a in relapsing/remitting multiple sclerosis. Lancet 1998; 352: 1498-1504.

376 2. Data on file.

377

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

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380 Co-Marketed by:
381 Serono, Inc.
382 Rockland, MA 02370
383 Pfizer Inc.
384 New York, NY 10017
385

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390 N6700101D