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Label for LEMTRADA: Approved 11/14/2014

Label for CAMPATH: Approved 9/5/2014

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEMTRADA safely and effectively. See full prescribing information for LEMTRADA.

LEMTRADA™ (alemtuzumab) injection, for intravenous use
Initial U.S. Approval: 2001

WARNING: AUTOIMMUNITY, INFUSION REACTIONS, AND MALIGNANCIES

See full prescribing information for complete boxed warning.

- LEMTRADA causes serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine counts at periodic intervals for 48 months after the last dose. (5.1)
- LEMTRADA causes serious and life-threatening infusion reactions. LEMTRADA must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for two hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2 hour monitoring period. (5.2)
- LEMTRADA may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams. (5.3)
- LEMTRADA is available only through a restricted distribution program. (5.4)

INDICATIONS AND USAGE

- LEMTRADA is a CD52-directed cytolytic monoclonal antibody indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of LEMTRADA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. (1)

DOSAGE AND ADMINISTRATION

- Administer LEMTRADA by intravenous infusion over 4 hours for 2 treatment courses:
 - First course: 12 mg/day on 5 consecutive days. (2.1)
 - Second course: 12 mg/day on 3 consecutive days 12 months after first treatment course. (2.1)

- Premedicate with corticosteroids prior to LEMTRADA infusion for the first 3 days of each treatment course. (2.3)
- Administer antiviral agents for herpetic prophylaxis starting on the first day of LEMTRADA dosing and continuing for a minimum of two months after completion of LEMTRADA dosing or until CD4+ lymphocyte count is more than 200 cells per microliter, whichever occurs later. (2.3)
- Must be diluted prior to administration. (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 12 mg/1.2 mL (10 mg/mL) in a single-use vial. (3)

CONTRAINDICATIONS

Infection with Human Immunodeficiency Virus. (4)

WARNINGS AND PRECAUTIONS

- Thyroid Disorders: Obtain thyroid function tests prior to initiation of treatment and every 3 months until 48 months after the last infusion. (5.7)
- Other Autoimmune Cytopenias: Monitor complete blood counts monthly until 48 months after the last infusion. (5.8)
- Consider delaying initiation of LEMTRADA in patients with active infections until the infection is fully controlled. Do not administer live viral vaccines following a course of LEMTRADA. (5.9)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 10\%$ and $>$ interferon beta-1a): rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-800-745-4447 (option 2) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2014

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1 **FULL PRESCRIBING INFORMATION**

WARNING: AUTOIMMUNITY, INFUSION REACTIONS, AND MALIGNANCIES

- **LEMTRADA causes serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals for 48 months after the last dose of LEMTRADA [see *Warnings and Precautions (5.1)*].**
- **LEMTRADA causes serious and life threatening infusion reactions. LEMTRADA must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for two hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2-hour monitoring period [see *Warnings and Precautions (5.2)*].**
- **LEMTRADA may cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. Perform baseline and yearly skin exams [see *Warnings and Precautions (5.3)*].**
- **Because of the risk of autoimmunity, infusion reactions, and malignancies, LEMTRADA is available only through restricted distribution under a Risk Evaluation Mitigation Strategy (REMS) Program. Call 1-855-676-6326 to enroll in the LEMTRADA REMS program [see *Warnings and Precautions (5.4)*].**

2

3

4 **1 INDICATIONS AND USAGE**

5 LEMTRADA is indicated for the treatment of patients with relapsing forms of multiple
6 sclerosis (MS). Because of its safety profile, the use of LEMTRADA should generally be
7 reserved for patients who have had an inadequate response to two or more drugs
8 indicated for the treatment of MS.

9 **2 DOSAGE AND ADMINISTRATION**

10 **2.1 Dosage Information**

11 The recommended dosage of LEMTRADA is 12 mg/day administered by intravenous
12 infusion for 2 treatment courses:

- 13
- **First Treatment Course: 12 mg/day on 5 consecutive days (60 mg total dose)**

- 14 • Second Treatment Course: 12 mg/day on 3 consecutive days (36 mg total dose)
15 administered 12 months after the first treatment course.

16 **2.2 Vaccinations**

17 Patients should complete any necessary immunizations at least 6 weeks prior to treatment
18 with LEMTRADA [see *Warnings and Precautions (5.9)*].

19 Prior to LEMTRADA treatment determine whether patients have a history of varicella or
20 have been vaccinated for varicella zoster virus (VZV). If not, test the patient for
21 antibodies to VZV and consider vaccination for those who are antibody-negative.
22 Postpone treatment with LEMTRADA until 6 weeks after VZV vaccination.

23 **2.3 Recommended Premedication and Concomitant Medication**

24 Corticosteroids

25 Premedicate patients with high dose corticosteroids (1,000 mg methylprednisolone or
26 equivalent) immediately prior to LEMTRADA infusion and for the first 3 days of each
27 treatment course [see *Warnings and Precautions (5.2)*].

28 Herpes Prophylaxis

29 Administer anti-viral prophylaxis for herpetic viral infections starting on the first day of
30 each treatment course and continue for a minimum of two months following treatment
31 with LEMTRADA or until the CD4+ lymphocyte count is ≥ 200 cells per microliter,
32 whichever occurs later [see *Warnings and Precautions (5.9)*].

33 **2.4 Preparation Instructions**

34 Follow the steps below to prepare the diluted solution of LEMTRADA for intravenous
35 infusion:

- 36 • Inspect LEMTRADA visually for particulate matter and discoloration prior to
37 administration. Do not use if particulate matter is present or the solution is
38 discolored. Do not freeze or shake vials prior to use.
- 39 • Withdraw 1.2 mL of LEMTRADA from the vial into a syringe using aseptic
40 technique and inject into a 100 mL bag of sterile 0.9% Sodium Chloride, USP or
41 5% Dextrose in Water, USP.

- 42 • Gently invert the bag to mix the solution. Ensure the sterility of the prepared
43 solution, because it contains no antimicrobial preservatives. Each vial is for
44 single use only.

45 Prior to administration, protect diluted LEMTRADA solution from light and store for as
46 long as 8 hours either at room temperature 15°C to 25°C (59°F to 77°F) or keep
47 refrigerated at conditions 2°C to 8°C (36°F to 46°F).

48 **2.5 Infusion Instructions**

49 Infuse LEMTRADA over 4 hours starting within 8 hours after dilution. Extend the
50 duration of the infusion if clinically indicated.

51 Administer LEMTRADA in a setting in which equipment and personnel to appropriately
52 manage anaphylaxis or serious infusion reactions are available [*see Warnings and*
53 *Precautions (5.4)*].

54 Do not add or simultaneously infuse other drug substances through the same intravenous
55 line. Do not administer as an intravenous push or bolus.

56 Monitor vital signs before the infusion and periodically during the infusion. Provide
57 appropriate symptomatic treatment for infusion reactions as needed. Consider immediate
58 discontinuation of the intravenous infusion if severe infusion reactions occur.

59 Observe patients for infusion reactions during and for at least 2 hours after each
60 LEMTRADA infusion. Consider longer periods of observation if clinically indicated.
61 Inform patients that they should report symptoms that occur during and after each
62 infusion because they may indicate a need for prompt medical intervention [*see Warnings*
63 *and Precautions (5.2)*].

64 **2.6 Laboratory Testing and Monitoring to Assess Safety**

65 Conduct the following laboratory tests at baseline and at periodic intervals for 48 months
66 following the last treatment course of LEMTRADA in order to monitor for early signs of
67 potentially serious adverse effects:

- 68 • Complete blood count (CBC) with differential (prior to treatment initiation and at
69 monthly intervals thereafter)
- 70 • Serum creatinine levels (prior to treatment initiation and at monthly intervals
71 thereafter)

- 72 • Urinalysis with urine cell counts (prior to treatment initiation and at monthly
73 intervals thereafter)
- 74 • A test of thyroid function, such as thyroid stimulating hormone (TSH) level (prior
75 to treatment initiation and every 3 months thereafter)

76 Conduct baseline and yearly skin exams to monitor for melanoma [see *Warnings and*
77 *Precautions (5.3)*].

78 **3 DOSAGE FORMS AND STRENGTHS**

79 Injection: 12 mg/1.2 mL (10 mg/mL) in a single-use vial. LEMTRADA is a clear and
80 colorless to slightly yellow solution that requires dilution prior to intravenous infusion.

81 **4 CONTRAINDICATIONS**

82 LEMTRADA is contraindicated in patients who are infected with Human
83 Immunodeficiency Virus (HIV) because LEMTRADA causes prolonged reductions of
84 CD4+ lymphocyte counts.

85 **5 WARNINGS AND PRECAUTIONS**

86 **5.1 Autoimmunity**

87 Treatment with LEMTRADA can result in the formation of autoantibodies and increase
88 the risk of serious autoimmune mediated conditions. In clinical studies LEMTRADA-
89 treated patients experienced thyroid disorders (34%), immune thrombocytopenia (2%),
90 and glomerular nephropathies (0.3%) [see *Warnings and Precautions (5.5, 5.6, 5.7)*].

91 Autoimmune hemolytic anemia and autoimmune pancytopenia [see *Warnings and*
92 *Precautions (5.8)*], undifferentiated connective tissue disorders, and acquired hemophilia
93 A (anti-Factor VIII antibodies) each occurred in 0.2% of patients. Rheumatoid arthritis,
94 type I diabetes, vitiligo, and retinal pigment epitheliopathy occurred in 0.1% of patients.

95 During postmarketing use, additional autoimmune events including Guillain-Barré
96 syndrome and chronic inflammatory demyelinating polyradiculoneuropathy have been
97 reported in the treatment of patients with B-cell chronic lymphocytic leukemia (B-CLL),
98 as well as other disorders, generally at higher and more frequent doses than
99 recommended in MS. An oncology patient treated with alemtuzumab had fatal
100 transfusion-associated graft-versus-host disease.

101 Autoantibodies may be transferred from the mother to the fetus during pregnancy. A
102 case of transplacental transfer of anti-thyrotropin receptor antibodies resulting in neonatal
103 Graves' disease occurred after alemtuzumab treatment in the mother [*see Use in Specific*
104 *Populations (8.1)*].

105 LEMTRADA may increase the risk of other autoimmune conditions because of the broad
106 range of autoantibody formation with LEMTRADA.

107 Monitor complete blood counts with differential, serum creatinine levels, and urinalysis
108 with urine cell counts before starting treatment and then at monthly intervals for 48
109 months after the last dose of LEMTRADA to allow for early detection and treatment of
110 autoimmune adverse reactions [*see Dosage and Administration (2.6)*]. After 48 months,
111 testing should be performed based on clinical findings suggestive of autoimmunity.

112 LEMTRADA is available only through a restricted program under a REMS [*see*
113 *Warnings and Precautions (5.4)*].

114 **5.2 Infusion Reactions**

115 LEMTRADA causes cytokine release syndrome resulting in infusion reactions, some of
116 which may be serious and life threatening. In clinical studies, 92% of LEMTRADA-
117 treated patients experienced infusion reactions. In some patients, infusion reactions were
118 reported more than 24 hours after LEMTRADA infusion. Serious reactions occurred in
119 3% of patients and included anaphylaxis in 2 patients (including anaphylactic shock),
120 angioedema, bronchospasm, hypotension, chest pain, bradycardia, tachycardia (including
121 atrial fibrillation), transient neurologic symptoms, hypertension, headache, pyrexia, and
122 rash. Other infusion reactions included nausea, urticaria, pruritus, insomnia, chills,
123 flushing, fatigue, dyspnea, pulmonary infiltrates, dysgeusia, dyspepsia, dizziness, and
124 pain. In clinical studies, 0.6% of patients with infusion reactions received epinephrine or
125 atropine.

126 During postmarketing use, other serious and sometimes fatal infusion reactions included
127 hypoxia, syncope, acute respiratory distress syndrome, respiratory arrest, myocardial
128 infarction, acute cardiac insufficiency, and cardiac arrest have been reported in the
129 treatment of patients with B-CLL, as well as other disorders, generally at higher and more
130 frequent doses than recommended in MS.

131 Premedicate patients with corticosteroids immediately prior to LEMTRADA infusion for
132 the first 3 days of each treatment course. In clinical trials, patients received 1,000 mg of

133 methylprednisolone for the first 3 days of each LEMTRADA treatment course. Consider
134 pretreatment with antihistamines and/or antipyretics prior to LEMTRADA
135 administration. Infusion reactions may occur despite pretreatment.

136 Consider additional monitoring in patients with medical conditions which predispose
137 them to cardiovascular or pulmonary compromise.

138 LEMTRADA can only be administered in certified healthcare settings that have on-site
139 access to equipment and personnel trained to manage infusion reactions (including
140 anaphylaxis and cardiac and respiratory emergencies).

141 LEMTRADA is available only through a restricted program under a REMS [*see*
142 *Warnings and Precautions (5.4)*].

143 **5.3 Malignancies**

144 Thyroid cancer

145 LEMTRADA may increase the risk of thyroid cancer. In controlled clinical studies, 3
146 of 919 (0.3%) LEMTRADA-treated patients developed thyroid cancer, compared to
147 none in the interferon beta-1a-treated group. However, screening for thyroid cancer
148 was performed more frequently in the LEMTRADA-treated group, because of the
149 higher incidence of autoimmune thyroid disorders in those patients. Two additional
150 cases of thyroid cancer in LEMTRADA-treated patients occurred in uncontrolled
151 studies.

152 Patients and healthcare providers should monitor for symptoms of thyroid cancer
153 including a new lump or swelling in the neck, pain in the front of the neck, persistent
154 hoarseness or other voice changes, trouble swallowing or breathing, or a constant
155 cough not due to an upper respiratory tract infection.

156 Melanoma

157 LEMTRADA may increase the risk of melanoma. In uncontrolled studies, 4 of 1486
158 (0.3%) LEMTRADA-treated patients developed melanoma or melanoma *in situ*. One
159 of those patients had evidence of locally advanced disease.

160 Perform baseline and yearly skin examinations to monitor for melanoma in patients
161 receiving LEMTRADA.

162 Lymphoproliferative disorders and lymphoma

163 Cases of lymphoproliferative disorders and lymphoma have occurred in
164 LEMTRADA-treated patients with MS, including a MALT lymphoma, Castleman's
165 Disease, and a fatality following treatment of non-Epstein Barr Virus-associated
166 Burkitt's lymphoma. There are postmarketing reports of Epstein Barr Virus-
167 associated lymphoproliferative disorders in non-MS patients.

168 Because LEMTRADA is an immunomodulatory therapy, caution should also be
169 exercised in initiating LEMTRADA in patients with pre-existing or ongoing
170 malignancies.

171 LEMTRADA is available only through a restricted program under a REMS [*see*
172 *Warnings and Precautions (5.4)*].

173 **5.4 LEMTRADA REMS Program**

174 LEMTRADA is available only through a restricted program under a REMS called the
175 LEMTRADA REMS Program, because of the risks of autoimmunity, infusion reactions,
176 and malignancies [*see Warnings and Precautions (5.1, 5.2, 5.3)*].

177 Notable requirements of the LEMTRADA REMS Program include the following:

- 178 • Prescribers must be certified with the program by enrolling and completing
179 training.
- 180 • Patients must enroll in the program and comply with ongoing monitoring
181 requirements [*see Dosage and Administration (2.6)*].
- 182 • Pharmacies must be certified with the program and must only dispense to certified
183 healthcare facilities that are authorized to receive LEMTRADA.
- 184 • Healthcare facilities must enroll in the program and verify that patients are
185 authorized before infusing LEMTRADA. Healthcare facilities must have on-site
186 access to equipment and personnel trained to manage infusion reactions.

187 Further information, including a list of qualified healthcare facilities, is available at 1-
188 855-676-6326.

189 **5.5 Immune Thrombocytopenia**

190 Immune thrombocytopenia (ITP) occurred in 2% of LEMTRADA-treated patients in
191 clinical studies in MS.

192 In a controlled clinical trial in patients with MS, one LEMTRADA-treated patient
193 developed ITP that went unrecognized prior to the implementation of monthly blood
194 monitoring requirements, and died from intracerebral hemorrhage. Nadir platelet counts
195 $\leq 20,000$ cells per microliter as a result of ITP occurred in 2% of all LEMTRADA-treated
196 patients in clinical studies in MS. Anti-platelet antibodies did not precede ITP onset. ITP
197 has been diagnosed more than 3 years after the last LEMTRADA dose.

198 Symptoms of ITP include easy bruising, petechiae, spontaneous mucocutaneous bleeding
199 (e.g., epistaxis, hemoptysis), and heavier than normal or irregular menstrual bleeding.
200 Hemoptysis may also be indicative of anti-glomerular basement membrane (GBM)
201 disease [see *Warnings and Precautions (5.6)*], and an appropriate differential diagnosis
202 has to be undertaken. Remind the patient to remain vigilant for symptoms they may
203 experience and to seek immediate medical help if they have any concerns.

204 Obtain complete blood counts (CBCs) with differential prior to initiation of treatment and
205 at monthly intervals thereafter until 48 months after the last infusion [see *Dosage and*
206 *Administration (2.6)*]. After this period of time, testing should be performed based on
207 clinical findings suggestive of ITP. If ITP is suspected, a complete blood count should be
208 obtained immediately. If ITP onset is confirmed, promptly initiate appropriate medical
209 intervention.

210 **5.6 Glomerular Nephropathies**

211 Glomerular nephropathies occurred in 0.3% of LEMTRADA-treated patients in MS
212 clinical trials. There were 3 cases of membranous glomerulonephritis and 2 cases of anti-
213 glomerular basement membrane (anti-GBM) disease. There are published and post-
214 marketing cases of MS patients treated with alemtuzumab who developed anti-GBM
215 disease and subsequently developed end stage renal disease requiring renal
216 transplantation. Cases of anti-GBM disease have been diagnosed up to 40 months after
217 the last dose of LEMTRADA. Urgent evaluation and treatment is required because anti-
218 GBM disease can lead to renal failure requiring dialysis or transplantation and can be
219 life-threatening if left untreated.

220 Clinical manifestations of nephropathy may include elevated serum creatinine levels,
221 hematuria, or proteinuria. Alveolar hemorrhage manifested as hemoptysis is a common
222 component of anti-GBM disease but did not occur in clinical trials.

223 Obtain serum creatinine levels and urinalysis with cell counts prior to initiation of
224 treatment and at monthly intervals thereafter until 48 months after the last infusion. After
225 this period of time, testing should be performed based on clinical findings suggestive of
226 nephropathies.

227 If clinically significant changes from baseline in serum creatinine, unexplained
228 hematuria, or proteinuria are observed, perform further evaluation for nephropathies.
229 Early detection and treatment of nephropathies may decrease the risk of poor outcomes.

230 **5.7 Thyroid Disorders**

231 Autoimmune thyroid disorders occurred in 34% of LEMTRADA-treated patients in
232 clinical studies. Newly diagnosed thyroid disorders occurred throughout the uncontrolled
233 clinical study follow-up period, more than 7 years after the first LEMTRADA dose.
234 Autoimmune thyroid disorders included Graves' disease, hyperthyroidism and
235 hypothyroidism. Graves' ophthalmopathy with decreased vision, eye pain, and
236 exophthalmos occurred in 1% of LEMTRADA-treated patients. Two patients required
237 surgical orbital decompression. Serious thyroid events occurred in about 2% of
238 LEMTRADA-treated patients in clinical studies and included cardiac and psychiatric
239 events associated with thyroid disease. Of all LEMTRADA-treated patients, 3%
240 underwent thyroidectomy.

241 Thyroid disease poses special risks in women who are pregnant [*see Use in Specific*
242 *Populations (8.1)*].

243 Obtain thyroid function tests, such as TSH levels, prior to initiation of treatment and
244 every 3 months thereafter until 48 months after the last infusion. Continue to test thyroid
245 function after 48 months if clinically indicated.

246 In patients with ongoing thyroid disorder, LEMTRADA should be administered only if
247 the potential benefit justifies the potential risks.

248 **5.8 Other Autoimmune Cytopenias**

249 Autoimmune cytopenias such as neutropenia (0.1%), hemolytic anemia (0.2%), and
250 pancytopenia (0.2%) occurred in LEMTRADA-treated patients in clinical studies in MS.

251 In cases of autoimmune hemolytic anemia, patients tested positive for direct antiglobulin
252 antibodies, and nadir hemoglobin levels ranged from 2.9-8.6 g/dL. Symptoms of
253 autoimmune hemolytic anemia include weakness, chest pain, jaundice, dark urine, and
254 tachycardia. One LEMTRADA-treated patient with autoimmune pancytopenia died from
255 sepsis.

256 During postmarketing use, additional autoimmune cytopenias including fatal autoimmune
257 hemolytic anemia and aplastic anemia have been reported in the treatment of patients
258 with B-CLL, as well as other disorders, generally at higher and more frequent doses than
259 recommended in MS.

260 Use CBC results to monitor for cytopenias. Prompt medical intervention is indicated if a
261 cytopenia is confirmed.

262 **5.9 Infections**

263 Infections occurred in 71% of LEMTRADA-treated patients compared to 53% of patients
264 treated with interferon beta-1a in controlled clinical trials in MS up to 2 years in duration.
265 Infections that occurred more often in LEMTRADA-treated patients than interferon beta-
266 1a patients included nasopharyngitis, urinary tract infection, upper respiratory tract
267 infection, sinusitis, herpetic infections, influenza, and bronchitis. Serious infections
268 occurred in 3% of patients treated with LEMTRADA as compared to 1% of patients
269 treated with interferon beta-1a. Serious infections in the LEMTRADA group included:
270 appendicitis, gastroenteritis, pneumonia, herpes zoster, and tooth infection.

271 Do not administer live viral vaccines following a course of LEMTRADA. Patients
272 treated with LEMTRADA have altered immunity and may be at increased risk of
273 infection following administration of live viral vaccines.

274 Consider delaying LEMTRADA administration in patients with active infection until the
275 infection is fully controlled.

276 Concomitant use of LEMTRADA with antineoplastic or immunosuppressive therapies
277 could increase the risk of immunosuppression.

278 Herpes Viral Infections

279 In controlled clinical trials, 16% of LEMTRADA-treated patients developed a herpes
280 viral infection compared to 3% of interferon beta-1a patients. These events included
281 oral herpes (8.8%), herpes zoster (4.2%), herpes simplex (1.8%), and genital herpes

282 (1.3%). Serious herpetic infections in LEMTRADA-treated patients included
283 primary varicella (0.1%), herpes zoster (0.2%), and herpes meningitis (0.1%).
284 Administer antiviral agents for herpetic prophylaxis at appropriate suppressive dosing
285 regimens. Administer anti-viral prophylaxis for herpetic viral infections starting on
286 the first day of each treatment course and continue for a minimum of two months
287 following treatment with LEMTRADA or until the CD4+ lymphocyte count is ≥ 200
288 cells per microliter, whichever occurs later [see *Dosage and Administration (2.3)*].

289 Human Papilloma Virus

290 Cervical human papilloma virus (HPV) infection, including cervical dysplasia,
291 occurred in 2% of LEMTRADA-treated patients. Annual HPV screening is
292 recommended for female patients.

293 Tuberculosis

294 Tuberculosis occurred in patients treated with LEMTRADA and interferon beta-1a in
295 controlled clinical trials. Active and latent tuberculosis cases occurred in 0.3% of
296 LEMTRADA-treated patients, most often in endemic regions. Perform tuberculosis
297 screening according to local guidelines prior to initiation of LEMTRADA. For
298 patients testing positive in tuberculosis screening, treat by standard medical practice
299 prior to therapy with LEMTRADA.

300 Fungal Infections

301 Fungal infections, especially oral and vaginal candidiasis, occurred more commonly
302 in LEMTRADA-treated patients (12%) than in patients treated with interferon beta-1a
303 (3%) in controlled clinical trials in MS.

304 Listeria Infections

305 Listeria meningitis has been reported in LEMTRADA-treated patients. Cases of
306 listeria meningitis occurred within 1 month of alemtuzumab dosing. The duration of
307 increased risk for listeria meningitis is unclear. Patients should avoid or adequately
308 heat foods that are potential sources of *Listeria monocytogenes*.

309 Infections in non-MS patients

310 During postmarketing use, serious and sometimes fatal viral, bacterial, protozoan, and
311 fungal infections, including some due to reactivation of latent infections, have been

312 reported in the treatment of patients with B-CLL, as well as other disorders, generally
313 at higher and more frequent doses than recommended in MS.

314 Hepatitis

315 No data are available on the association of LEMTRADA with Hepatitis B virus
316 (HBV) or Hepatitis C virus (HCV) reactivation because patients with evidence of
317 active or chronic infections were excluded from the clinical trials. Consider
318 screening patients at high risk of HBV and/or HCV infection before initiation of
319 LEMTRADA and exercise caution in prescribing LEMTRADA to patients identified
320 as carriers of HBV and/or HCV as these patients may be at risk of irreversible liver
321 damage relative to a potential virus reactivation as a consequence of their pre-existing
322 status.

323 **5.10 Pneumonitis**

324 In clinical studies, 6 of 1217 (0.5%) LEMTRADA-treated patients had pneumonitis of
325 varying severity. Cases of hypersensitivity pneumonitis and pneumonitis with fibrosis
326 occurred in clinical studies. Patients should be advised to report symptoms of
327 pneumonitis, which include shortness of breath, cough, wheezing, chest pain or tightness,
328 and hemoptysis.

329 **5.11 Drug Products with Same Active Ingredient**

330 LEMTRADA contains the same active ingredient (alemtuzumab) found in CAMPATH®.
331 If LEMTRADA is considered for use in a patient who has previously received
332 CAMPATH, exercise increased vigilance for additive and long-lasting effects on the
333 immune system.

334 **6 ADVERSE REACTIONS**

335 The following serious adverse reactions are described below and elsewhere in the
336 labeling:

- 337 • Autoimmunity [*see Boxed Warning and Warnings and Precautions (5.1)*]
- 338 • Infusion reactions [*see Boxed Warning and Warnings and Precautions (5.2)*]
- 339 • Malignancies [*see Warnings and Precautions (5.3)*]
- 340 • Immune Thrombocytopenia [*see Warnings and Precautions (5.5)*]

- 341 • Glomerular Nephropathies [*see Warnings and Precautions (5.6)*]
- 342 • Thyroid Disorder [*see Warnings and Precautions (5.7)*]
- 343 • Other Autoimmune Cytopenias [*see Warnings and Precautions (5.8)*]
- 344 • Infections [*see Warnings and Precautions (5.9)*]
- 345 • Pneumonitis [*see Warnings and Precautions (5.10)*]

346 **6.1 Clinical Trials Experience**

347 Because clinical trials are conducted under widely varying conditions, adverse reaction
348 rates observed in the clinical trials of a drug cannot be directly compared to rates in the
349 clinical trials of another drug and may not reflect the rates observed in practice.

350 In controlled clinical trials (Study 1 and Study 2), a total of 811 patients with relapsing
351 forms of MS received LEMTRADA. A total of 811 patients received 1 course of
352 therapy, and 789 patients received a second course of therapy at 12 months. The overall
353 follow-up in the controlled trials was equivalent to 1622 patient years, with an additional
354 3411 person-years of follow-up in an open label extension study. The population was 18-
355 55 years of age, 65% were female, and 92% were Caucasian.

356 Most Common Adverse Reactions

357 In clinical trials, the most common adverse reactions with LEMTRADA (in at least 10%
358 of patients and more frequently than in interferon beta-1a) were rash, headache, pyrexia,
359 nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract
360 infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal
361 infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain,
362 paresthesia, dizziness, abdominal pain, flushing, and vomiting.

363 [Table 1](#) lists adverse reactions occurring in $\geq 5\%$ of LEMTRADA-treated patients in
364 Study 1 and 2 and at the same or at a higher rate than interferon beta-1a.

Table 1: Adverse Reactions in the Pooled 2-Year Active-Controlled Studies in Patients with Relapsing-Remitting Multiple Sclerosis

	LEMTRADA (N=811) %	interferon beta-1a 44 mcg (N=389) %
Rash	53	6
Headache	52	23
Pyrexia	29	9
Nasopharyngitis	25	19
Nausea	21	9
Urinary tract infection	19	8
Fatigue	18	13
Insomnia	16	15
Upper respiratory tract infection	16	13
Herpes viral infection	16	3
Urticaria	16	2
Pruritus	14	2
Thyroid gland disorders	13	3
Fungal infection	13	4
Arthralgia	12	9
Pain in extremity	12	9
Back pain	12	8
Diarrhea	12	6
Sinusitis	11	8
Oropharyngeal pain	11	5
Paresthesia	10	8
Dizziness	10	5
Abdominal pain	10	5
Flushing	10	4
Vomiting	10	3
Cough	9	4
Chills	9	3
Dysgeusia	8	7
Influenza	8	6
Dermatitis	8	5
Dyspepsia	8	4
Blood in urine	8	3
Dyspnea	8	1
Tachycardia	8	1
Anxiety	7	6
Muscular weakness	7	6
Bronchitis	7	4
Chest discomfort	7	2
Muscle spasms	6	5
Myalgia	6	5
Decrease in CD4 lymphocytes	6	2
Decrease in CD8 lymphocytes	6	2
Asthenia	5	4

Table 1: Adverse Reactions in the Pooled 2-Year Active-Controlled Studies in Patients with Relapsing-Remitting Multiple Sclerosis

	LEMTRADA (N=811) %	interferon beta-1a 44 mcg (N=389) %
Decrease in T-lymphocyte count	5	3
Erythema	5	2
Peripheral edema	5	2
Epistaxis	5	2
Neck Pain	5	2
Abnormal uterine bleeding	5	1

365

366

367 **6.2 Lymphopenia**

368 Nearly all (99.9%) patients treated with LEMTRADA in MS clinical trials experienced
369 lymphopenia. The lowest lymphocyte counts occurred approximately by 1 month after
370 each course of treatment. The mean lymphocyte count at 1 month after LEMTRADA
371 treatment was $0.25 \times 10^9/L$ (range 0.02 - $2.30 \times 10^9/L$) and 0.32 (0.02 - $1.81 \times 10^9/L$) for
372 treatment courses 1 and 2, respectively. Total lymphocyte counts increased to reach the
373 lower limit of normal in approximately 40% of patients by 6 months after each
374 LEMTRADA treatment course and approximately 80% of patients by 12 months after
375 each course [see *Clinical Pharmacology (12.2)*].

376 **6.3 Suicidal Behavior or Ideation**

377 In clinical studies, 0.6% of patients in both the LEMTRADA and interferon beta-1a
378 groups had events of attempted suicide or suicidal ideation. There were no completed
379 suicides in either clinical study treatment group. Suicidal behavior or ideation occurred in
380 patients with or without a history of a psychiatric or thyroid disorder. Advise patients to
381 report immediately any symptoms of depression or suicidal ideation to the prescribing
382 physician.

383 **6.4 Immunogenicity**

384 As with all therapeutic proteins, there is potential for immunogenicity. Using an enzyme-
385 linked immunosorbent assay (ELISA) and a competitive binding assay, anti-alemtuzumab
386 binding antibodies were detected in 62%, 67%, and 29% of LEMTRADA-treated
387 patients, at months 1, 3, 12 (Course 1) as well as 83%, 83%, and 75% of LEMTRADA-
388 treated patients at months 13, 15, and 24 (Course 2). Samples that tested positive for
389 binding antibodies were further evaluated for evidence of *in vitro* inhibition using a flow

390 cytometry assay. Neutralizing antibodies were detected in 87%, 46%, and 5% of positive
391 binding antibody patients at months 1, 3, 12 (Course 1) as well as 94%, 88%, and 42% of
392 positive binding antibody patients at months 13, 15, and 24 (Course 2). Anti-
393 alemtuzumab antibodies were associated with decreased alemtuzumab concentration
394 during Course 2 but not Course 1. There was no evidence from clinical trials that the
395 presence of binding or inhibitory anti-alemtuzumab antibodies had a significant effect on
396 clinical outcomes, total lymphocyte count, or adverse events.

397 The incidence of antibodies is highly dependent on the sensitivity and specificity of the
398 assay. Additionally, the observed incidence of antibody (including inhibitory antibody)
399 positivity in an assay may be influenced by several factors including assay methodology,
400 sample handling, timing of sample collection, concomitant medications, and underlying
401 disease. For these reasons, comparison of the incidence of antibodies to LEMTRADA
402 with the incidence of antibodies to other products may be misleading.

403 **6.5 Postmarketing Experience**

404 The following adverse reactions, not described elsewhere, were identified during post-
405 approval use of alemtuzumab (CAMPATH) for the treatment of B-cell chronic
406 lymphocytic leukemia (B-CLL), as well as for the treatment of other disorders, generally
407 at higher and more frequent doses (e.g., 30 mg) than that recommended in the treatment
408 of MS. Because these reactions are reported voluntarily from a population of uncertain
409 size, it is not always possible to reliably estimate their frequency or establish a causal
410 relationship to drug exposure.

411 Cardiac Disorders

412 Congestive heart failure, cardiomyopathy, and decreased ejection fraction in non-MS
413 patients previously treated with potentially cardiotoxic agents.

414 **8 USE IN SPECIFIC POPULATIONS**

415 **8.1 Pregnancy**

416 Pregnancy Category C

417 There are no adequate and well-controlled studies in pregnant women. LEMTRADA was
418 embryolethal in pregnant huCD52 transgenic mice when administered during
419 organogenesis. Auto-antibodies may develop after administration of LEMTRADA.
420 Placental transfer of anti-thyroid antibodies resulting in neonatal Graves' disease has

421 been reported. LEMTRADA should be used during pregnancy only if the potential
422 benefit justifies the potential risk to the fetus.

423

424 Animal Data

425 When LEMTRADA was administered to pregnant huCD52 transgenic mice during
426 organogenesis (gestation days [GD] 6-10 or GD 11-15) at doses of 3 or 10 mg/kg IV, no
427 teratogenic effects were observed. However, there was an increase in embryoletality
428 (increased post-implantation loss and the number of dams with all fetuses dead or
429 resorbed) in pregnant animals dosed during GD 11-15.

430

431 In a separate study in pregnant huCD52 transgenic mice, administration of LEMTRADA
432 during organogenesis (GD 6-10 or GD 11-15) at doses of 3 or 10 mg/kg/IV, decreases in
433 B lymphocytes and T-lymphocyte populations were observed in the offspring at both
434 doses tested. The effects of LEMTRADA, administered during organogenesis, on
435 postnatal development have not been adequately assessed.

436

437 Clinical Considerations

438 To avoid in utero exposure to LEMTRADA, women of child bearing potential should use
439 effective contraceptive measures when receiving a course of treatment with LEMTRADA
440 and for 4 months following that course of treatment.

441

442 LEMTRADA induces persistent thyroid disorders [*see Warnings and Precautions (5.7)*].
443 Untreated hypothyroidism in pregnant women increases the risk for miscarriage and may
444 have effects on the fetus including mental retardation and dwarfism. In mothers with
445 Graves' disease, maternal thyroid stimulating hormone receptor antibodies can be
446 transferred to a developing fetus and can cause neonatal Graves' disease. In a patient who
447 developed Graves' disease after treatment with alemtuzumab, placental transfer of anti-
448 thyrotropin receptor antibodies resulted in neonatal Graves' Disease with thyroid storm in
449 her infant who was born 1 year after alemtuzumab dosing [*see Warnings and Precautions*
450 *(5.1)*].

451 **8.3 Nursing Mothers**

452 Alemtuzumab was detected in the milk of lactating mice administered 10 mg/kg
453 LEMTRADA on Days 8 through 12 postpartum. Serum levels of alemtuzumab were

454 similar in lactating mice and offspring on Day 13 postpartum, and were associated with
455 evidence of pharmacological activity (decrease in lymphocyte counts) in the offspring.

456 It is not known whether alemtuzumab is excreted in human milk. Because many drugs
457 are excreted in human milk, and because of the potential for serious adverse reactions in
458 nursing infants from LEMTRADA, a decision should be made whether to discontinue
459 nursing or to discontinue the drug, taking into account the importance of the drug to the
460 mother.

461 **8.4 Pediatric Use**

462 Safety and effectiveness in pediatric patients less than 17 years of age have not been
463 established. Use of LEMTRADA is not recommended in pediatric patients due to the
464 risks of autoimmunity, infusion reactions, and because it may increase the risk of
465 malignancies (thyroid, melanoma, lymphoproliferative disorders, and lymphoma) [*see*
466 *Warnings and Precautions (5.1, 5.2, 5.3)*].

467 **8.5 Geriatric Use**

468 Clinical studies of LEMTRADA did not include sufficient numbers of patients aged 65
469 and over to determine whether they respond differently than younger patients.

470 **10 OVERDOSAGE**

471 Two MS patients experienced serious reactions (headache, rash, and either hypotension
472 or sinus tachycardia) after a single accidental infusion up to 60 mg of LEMTRADA.
473 Doses of LEMTRADA greater than those recommended may increase the intensity
474 and/or duration of infusion reactions or its immune effects. There is no known antidote
475 for alemtuzumab overdosage.

476 **11 DESCRIPTION**

477 LEMTRADA (alemtuzumab) is a recombinant humanized IgG1 kappa monoclonal
478 antibody directed against the cell surface glycoprotein, CD52. Alemtuzumab has an
479 approximate molecular weight of 150kD. LEMTRADA is produced in mammalian cell
480 (Chinese hamster ovary) suspension culture in a nutrient medium containing neomycin.
481 Neomycin is not detectable in the final product. LEMTRADA is a sterile, clear and
482 colorless to slightly yellow, solution (pH 7.2±0.2) for infusion.

483 Each 1 mL of solution contains alemtuzumab 10 mg, dibasic sodium phosphate (1.15
484 mg), disodium edetate dihydrate (0.0187 mg), polysorbate 80 (0.1 mg), potassium

485 chloride (0.2 mg), potassium dihydrogen phosphate (0.2 mg), sodium chloride (8 mg),
486 and water for injection.

487 **12 CLINICAL PHARMACOLOGY**

488 **12.1 Mechanism of Action**

489 The precise mechanism by which alemtuzumab exerts its therapeutic effects in multiple
490 sclerosis is unknown but is presumed to involve binding to CD52, a cell surface antigen
491 present on T and B lymphocytes, and on natural killer cells, monocytes, and
492 macrophages. Following cell surface binding to T and B lymphocytes, alemtuzumab
493 results in antibody-dependent cellular cytotoxicity and complement-mediated lysis.

494 **12.2 Pharmacodynamics**

495 Effects of LEMTRADA on the Lymphocyte Population

496 LEMTRADA depletes circulating T and B lymphocytes after each treatment course. In
497 clinical trials, the lowest cell counts occurred 1 month after a course of treatment at the
498 time of the first post-treatment blood count. Lymphocyte counts then increased over
499 time: B cell counts usually recovered within 6 months; T cell counts increased more
500 slowly and usually remained below baseline 12 months after treatment. Approximately
501 60% of patients had total lymphocyte counts below the lower limit of normal 6 months
502 after each treatment course and 20% had counts below the lower limit of normal after 12
503 months.

504 Reconstitution of the lymphocyte population varies for the different lymphocyte
505 subtypes. At Month 1 in clinical trials, the mean CD4+ lymphocyte count was 40 cells
506 per microliter, and, at Month 12, 270 cells per microliter. At 30 months, approximately
507 half of patients had CD4+ lymphocyte counts that remained below the lower limit of
508 normal.

509 Cardiac Electrophysiology

510 In a study of 53 MS patients, alemtuzumab 12 mg per day for 5 days caused no changes
511 in the QTc interval greater than 20ms. An average 22 to 26 beats-per-minute increase in
512 heart rate was observed for at least 2 hours after the first but not subsequent infusions.

513 **12.3 Pharmacokinetics**

514 The pharmacokinetics of LEMTRADA were evaluated in a total of 148 patients with
515 relapsing forms of MS who received 12 mg/day on 5 consecutive days, followed by 12
516 mg/day on 3 consecutive days 12 months following the first treatment course.

517 Absorption

518 Serum concentrations increased with each consecutive dose within a treatment course,
519 with the highest observed concentrations occurring following the last infusion of a
520 treatment course. The mean maximum concentration was 3014 ng/mL on Day 5 of the
521 first treatment course, and 2276 ng/mL on Day 3 of the second treatment course.

522 Distribution

523 LEMTRADA is largely confined to the blood and interstitial space with a central volume
524 of distribution of 14.1 L.

525 Elimination

526 The elimination half-life was approximately 2 weeks and was comparable between
527 courses. The serum concentrations were generally undetectable (< 60 ng/mL) within
528 approximately 30 days following each treatment course.

529 Specific Populations

530 Age, race, or gender had no effect on the pharmacokinetics of LEMTRADA.

531 **13 NONCLINICAL TOXICOLOGY**

532 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

533 Studies to assess the carcinogenic or genotoxic potential of LEMTRADA have not been
534 conducted.

535 When LEMTRADA (3 or 10 mg/kg IV) was administered to huCD52 transgenic male
536 mice on 5 consecutive days prior to cohabitation with untreated wild-type females, no
537 effect on fertility or reproductive performance was observed. However, adverse effects
538 on sperm parameters (including abnormal morphology [detached /no head] and reduced
539 total count and motility) were observed at both doses tested.

540 When LEMTRADA (3 or 10 mg/kg IV) was administered to huCD52 transgenic female
541 mice for 5 consecutive days prior to cohabitation with untreated wild-type males, there

542 was a decrease in the average number of corpora lutea and implantation sites and an
543 increase in post-implantation loss, resulting in fewer viable embryos at the higher dose
544 tested.

545 **14 CLINICAL STUDIES**

546 The efficacy of LEMTRADA was demonstrated in two studies (Study 1 and 2) that
547 evaluated LEMTRADA 12 mg in patients with relapsing-remitting multiple sclerosis
548 (RRMS). LEMTRADA was administered by intravenous infusion once daily over a 5-
549 day course, followed one year later by intravenous infusion once daily over a 3-day
550 course. Both studies included patients who had experienced at least 2 relapses during the
551 2 years prior to trial entry and at least 1 relapse during the year prior to trial entry.
552 Neurological examinations were performed every 12 weeks and at the time of suspected
553 relapse. Magnetic resonance imaging (MRI) evaluations were performed annually.

554 Study 1

555 Study 1 was a 2 year randomized, open-label, rater-blinded, active comparator (interferon
556 beta-1a 44 micrograms administered subcutaneously three times a week) controlled study
557 in patients with RRMS. Patients entering Study 1 had Expanded Disability Status Scale
558 (EDSS) scores of 5 or less and had to have experienced at least one relapse while on
559 interferon beta or glatiramer acetate therapy.

560 Patients were randomized to receive LEMTRADA (n=426) or interferon beta-1a (n=202).
561 At baseline, the mean age was 35 years, the mean disease duration was 4.5 years, and the
562 mean EDSS score was 2.7.

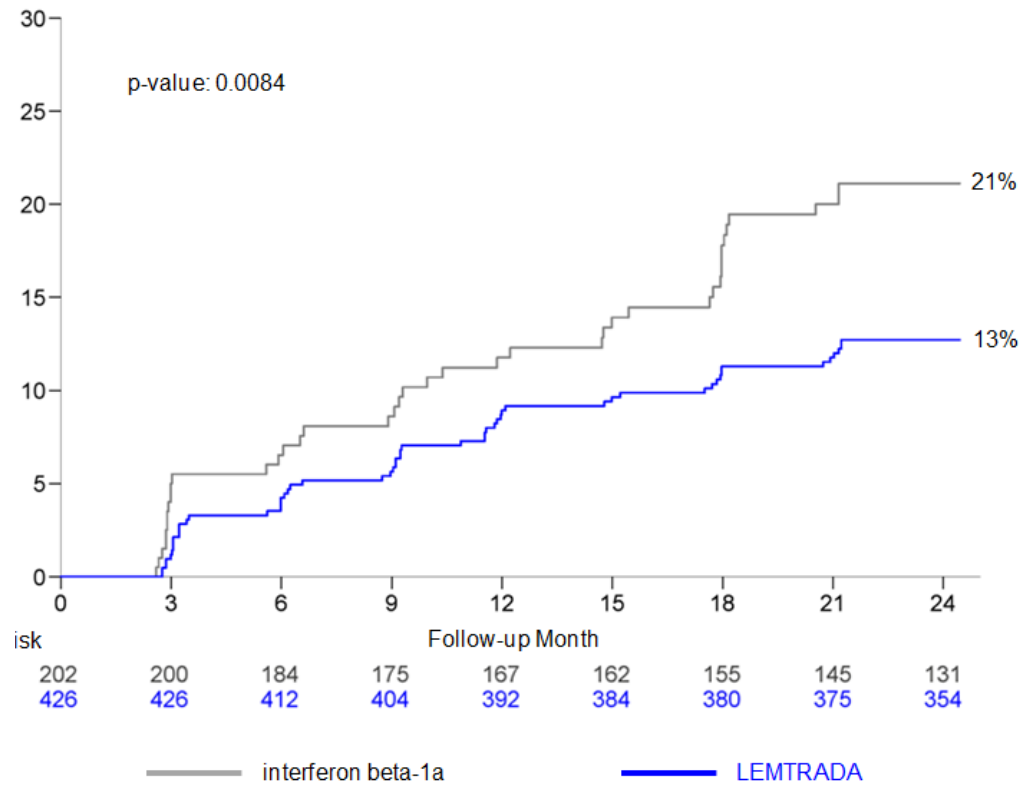
563 The clinical outcome measures were the annualized relapse rate (ARR) over 2 years and
564 the time to confirmed disability progression. Confirmed disability progression was
565 defined as at least a 1 point increase above baseline EDSS (1.5 point increase for patients
566 with baseline EDSS of 0) sustained for 6 months. The MRI outcome measure was the
567 change in T2 lesion volume.

568 The annualized relapse rate was significantly lower in patients treated with LEMTRADA
569 than in patients who received interferon beta-1a. Time to onset of 6-month confirmed
570 disability progression was significantly delayed with LEMTRADA treatment compared
571 to interferon beta-1a. There was no significant difference between the treatment groups
572 for the change in T2 lesion volume. The results of Study 1 are shown in [Table 2](#) and
573 [Figure 1](#).

Table 2: Clinical and MRI Results of Study 1

	LEMTRADA (N=426)	interferon beta-1a 44 mcg (N=202)	p-value
Clinical Outcomes			
Annualized relapse rate Relative reduction	0.26 49%	0.52	<0.0001
Proportion of patients with disability progression at Year 2 Relative risk reduction	13% 42%	21%	0.0084
Percent of patients remaining relapse-free at Year 2	65%	47%	<0.0001
MRI Outcomes			
Percent change in T2 lesion volume from baseline	-1.3	-1.2	0.14

Figure 1: Time to 6-month Confirmed Disability Progression (Study 1)



574 Study 2

575 Study 2 was a 2-year randomized, open-label, rater-blinded, active comparator (interferon
576 beta-1a 44 micrograms administered subcutaneously three times a week) controlled study
577 in patients with RRMS. Patients entering Study 2 had EDSS scores of 3 or less and no
578 prior treatment for multiple sclerosis.

579 Patients were randomized to receive LEMTRADA (n=376) or interferon beta-1a (n=187).
580 At baseline, the mean age was 33 years, the mean disease duration was 2 years, and the
581 mean EDSS score was 2.

582 The clinical outcome measures were the annualized relapse rate (ARR) over 2 years and
583 the time to confirmed disability progression, as defined in Study 1. The MRI outcome
584 measure was the change in T2 lesion volume.

585 The annualized relapse rate was significantly lower in patients treated with LEMTRADA
586 than in patients who received interferon beta-1a. There was no significant difference
587 between the treatment groups for the time to confirmed disability progression and for the
588 primary MRI endpoint (change in T2 lesion volume). The results for Study 2 are shown
589 in Table 3.

Table 3: Clinical and MRI Results of Study 2

	LEMTRADA (N=376)	interferon beta-1a 44 mcg (N=187)	p-value
Clinical Outcomes			
Annualized relapse rate Relative reduction	0.18 55%	0.39	<0.0001
Proportion of patients with disability progression at Year 2 Relative risk reduction	8% 30%	11%	0.22
Percent of patients remaining relapse-free at Year 2	78%	59%	<0.0001
MRI Outcomes			
Percent change in T2 lesion volume from baseline	-9.3	-6.5	0.31

590 **16 HOW SUPPLIED/STORAGE AND HANDLING**

591 **16.1 How Supplied**

592 Each LEMTRADA carton (NDC: 58468-0200-1) contains 1 single-use vial that delivers
593 12 mg/1.2 mL (10 mg/mL). The vial stopper is not made with natural rubber latex.

594 LEMTRADA is a sterile, clear and colorless to slightly yellow solution for infusion,
595 containing no antimicrobial preservatives.

596 **16.2 Storage and Handling**

597 Store LEMTRADA vials at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Store in
598 original carton to protect from light.

599 **17 PATIENT COUNSELING INFORMATION**

600 Advise the patient to read the FDA-approved patient labeling (Medication Guide).

601 Autoimmunity

- 602 • Advise patients to contact their healthcare provider promptly if they experience any
603 symptoms of potential autoimmune disease. Give examples of important symptoms
604 such as bleeding, easy bruising, petechiae, purpura, hematuria, edema, jaundice, or
605 hemoptysis [*see Warnings and Precautions (5.1)*].
- 606 • Advise patients of the importance of monthly blood and urine tests for 48 months
607 following the last course of LEMTRADA to monitor for signs of autoimmunity
608 because early detection and prompt treatment can help prevent serious and
609 potentially fatal outcomes associated with these events. Advise patients that
610 monitoring may need to continue past 48 months if they have signs or symptoms of
611 autoimmunity.
- 612 • Advise patients that LEMTRADA may cause hyperthyroid or hypothyroid disorders.
- 613 • Advise patients to contact their healthcare provider if they experience symptoms
614 reflective of a potential thyroid disorder such as unexplained weight loss or gain, fast
615 heartbeat or palpitations, eye swelling, constipation, or feeling cold.
- 616 • Advise women of childbearing potential of the risks of pregnancy with concomitant
617 thyroid disease. Advise women of childbearing potential to discuss pregnancy
618 planning with their doctor.

619 Infusion Reactions

- 620 • Advise patients that infusion reactions can occur after they leave the infusion center
621 *[see Warnings and Precautions (5.2)]*.
- 622 • Instruct the patient to remain at the infusion center for 2 hours after each
623 LEMTRADA infusion, or longer at the discretion of the physician. Advise patients
624 that symptoms of infusion reactions may occur after they leave the infusion center
625 and to report these symptoms to their doctor.
- 626 • Advise patients to contact their healthcare provider promptly if they experience
627 infusion reactions, which include swelling in the mouth or throat, difficulty
628 breathing, weakness, abnormal heart rate (fast, slow, or irregular), chest pain, and
629 rash.

630 Malignancies

- 631 • Advise patients that LEMTRADA may increase their risk of malignancies including
632 thyroid cancer and melanoma *[see Warnings and Precautions (5.3)]*.
- 633 • Advise patients to report symptoms of thyroid cancer, including a new lump or
634 swelling in the neck, pain in the front of the neck, hoarseness or other voice changes
635 that do not go away, trouble swallowing or breathing, or a constant cough not due to
636 a cold.
- 637 • Advise patients that they should have baseline and yearly skin examinations.

638 LEMTRADA REMS Program

- 639 • LEMTRADA is available only through a restricted program called the LEMTRADA
640 REMS Program *[see Warnings and Precautions (5.4)]*. Inform the patient of the
641 following notable requirements:
- 642 ○ Patients and providers must be enrolled in the program.
- 643 ○ Patients must comply with the ongoing monitoring requirements.
- 644 ○ Patients must report any side effects or symptoms to their doctor.
- 645 • LEMTRADA is available only at certified infusion centers participating in the
646 program. Therefore, provide patients with information on the LEMTRADA REMS
647 Program in order to locate an infusion center.

- 648 • Advise patients to read the LEMTRADA REMS material for patients, *What You*
649 *Need to Know About LEMTRADA Treatment: A Patient Guide* and *What You Need*
650 *to Know About LEMTRADA Treatment and Infusion Reactions: A Patient Guide*.
- 651 • Instruct patients to carry the LEMTRADA REMS Patient Safety Information Card
652 with them in case of an emergency.

653 Infections

- 654 • Advise patients to contact their healthcare provider if they develop symptoms of
655 serious infection such as fever or swollen glands [*see Warnings and Precautions*
656 (5.9)].
- 657 • Advise patients to complete any necessary immunizations at least 6 weeks prior to
658 treatment with LEMTRADA [*see Dosage and Administration (2.2)*]. Advise patients
659 that they should talk to their healthcare provider before taking any vaccine after
660 recent treatment with LEMTRADA [*see Warnings and Precautions (5.9)*].
- 661 • Advise patients to take their prescribed medication for herpes prophylaxis as directed
662 by their healthcare provider [*see Warnings and Precautions (5.9)*].
- 663 • Advise patients that yearly HPV screening is recommended [*see Warnings and*
664 *Precautions (5.9)*].
- 665 • Advise patients to avoid or adequately heat foods that are potential sources of *Listeria*
666 *monocytogenes* if they have had a recent course of LEMTRADA. The duration of
667 increased risk for listeria infection after LEMTRADA administration is not known
668 [*see Warnings and Precautions (5.9)*].

669 Pneumonitis

- 670 • Advise patients that pneumonitis has been reported in patients treated with
671 LEMTRADA [*see Warnings and Precautions (5.10)*]. Advise patients to report
672 symptoms of lung disease such as shortness of breath, cough, wheezing, chest pain or
673 tightness, and hemoptysis.

674 Concomitant Use of Campath

- 675 • Advise patients that alemtuzumab is the same drug as Campath for use in B-CLL.
676 Patients should inform their healthcare provider if they have taken Campath [*see*
677 *Warnings and Precautions (5.11)*].

678 Manufactured and distributed by:
679 Genzyme Corporation
680 500 Kendall Street
681 Cambridge, MA 02142
682
683 US License Number: 1596
684 LEMTRADA is a trademark of Genzyme Corporation.

685 CAMPATH is a registered trademark of Genzyme Corporation.

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MEDICATION GUIDE
LEMTRADA™ (lem-TRA-da)
(alemtuzumab)

Injection for intravenous infusion

Read this Medication Guide before you start receiving LEMTRADA and before you begin each treatment course. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about LEMTRADA?

LEMTRADA can cause serious side effects, including:

- 1. Serious autoimmune problems.** Some people receiving LEMTRADA develop a condition where the immune cells in your body attack other cells or organs in the body (autoimmunity) which can be serious and may cause death. Serious autoimmune problems may include:
 - **immune thrombocytopenic purpura (ITP).** LEMTRADA may cause the number of platelets in your blood to be reduced (ITP). ITP can cause severe bleeding that, if not treated, may cause life-threatening problems. Call your healthcare provider right away if you have any of the following symptoms:
 - easy bruising
 - bleeding from a cut that is hard to stop
 - heavier menstrual periods than normal
 - bleeding from your gums or nose that is new or takes longer than usual to stop
 - small, scattered spots on your skin that are red, pink, or purple
 - **kidney problems.** LEMTRADA may cause a serious kidney problem, called anti-glomerular basement membrane disease. If this happens and you do not get treated, anti-glomerular basement membrane disease can lead to severe kidney damage, kidney failure that needs dialysis, a kidney transplant, or death. Call your healthcare provider right away if you have any of the following symptoms:
 - blood in the urine (red or tea-colored urine)
 - swelling in your legs or feet
 - coughing up blood

Side effects may happen while you receive LEMTRADA and for 4 years after you stop receiving LEMTRADA. Your healthcare provider will order blood and urine tests before you receive, while you are receiving, and every month for 4 years after you receive your last LEMTRADA infusion. You may need to continue these blood and urine tests after 4 years if you have any autoimmune signs or

symptoms. The blood and urine tests will help your healthcare provider watch for signs and symptoms of serious autoimmune problems.

It is important to have your blood and urine tested, even if you are feeling well and do not have any symptoms from LEMTRADA and your multiple sclerosis. This may help your healthcare provider find any problems early and will increase your chances of getting better.

- 2. Serious infusion reactions.** LEMTRADA can cause serious infusion reactions that may cause death. Serious infusion reactions may happen while you receive, or up to 24 hours or longer after you receive LEMTRADA.

You will receive your infusion at a healthcare facility with equipment and staff trained to manage infusion reactions. You will be watched while you receive and for 2 hours after you receive LEMTRADA. **It is important** that you stay at the infusion center for **2** hours after your infusion is finished or longer if your healthcare provider decides you need to stay longer. If a serious infusion reaction happens while you are receiving LEMTRADA, your infusion may be stopped.

Tell your healthcare provider right away if you have any of the following symptoms of a serious infusion reaction during the infusion, and after you have left the healthcare facility:

- swelling in your mouth or throat
- trouble breathing
- weakness
- fast, slow, or irregular heart beat
- chest pain
- rash

To lower your chances of getting a serious infusion reaction, your healthcare provider will give you a medicine called corticosteroids before your first 3 infusions of a treatment course. You may also be given other medicines before or after the infusion to try reduce your chances of these reactions or to treat them after they happen.

- 3. Certain cancers.** Receiving LEMTRADA may increase your chance of getting some kinds of cancers, including thyroid cancer, skin cancer (melanoma), and blood cancers called lymphoproliferative disorders and lymphoma. Call your healthcare provider if you have the following symptoms that may be a sign of thyroid cancer:

- new lump
- swelling in your neck
- pain in the front of your neck
- hoarseness or other voice changes that do not go away
- trouble swallowing or breathing
- cough that is not caused by a cold

You should have your skin checked before you start receiving LEMTRADA and each year while you are receiving treatment to monitor symptoms of skin cancer.

Because of your risk of autoimmunity, infusion reactions and the risk of some kinds of cancers, LEMTRADA is only available through a restricted program called the LEMTRADA Risk Evaluation and Mitigation Strategy (REMS) Program. Call 1-855-676-6326 to enroll in the LEMTRADA REMS Program.

- You and your healthcare provider must be enrolled in the LEMTRADA REMS Program.
- LEMTRADA can only be given at a certified healthcare facility that participates in the LEMTRADA REMS Program. Your healthcare provider can give you information on how to find a certified healthcare facility.
- Read the LEMTRADA REMS “What You Need to Know About LEMTRADA Treatment: A Patient Guide” and “What you Need to Know About LEMTRADA Treatment and Infusion Reactions: A Patient Guide” after you are enrolled in the program.
- Carry your LEMTRADA REMS Patient Safety Information Card with you in case of an emergency.

What is LEMTRADA?

LEMTRADA is a prescription medicine used to treat adults with relapsing forms of multiple sclerosis (MS). Because of its risks, LEMTRADA is generally used in people who have tried 2 or more MS medicines that have not worked well enough. It is not known if LEMTRADA is safe and effective for use in children under 17 years of age.

Who should not receive LEMTRADA?

Do not receive LEMTRADA if you are infected with human immunodeficiency virus (HIV).

What should I tell my healthcare provider before receiving LEMTRADA?

Before receiving LEMTRADA, tell your healthcare provider if you:

- are taking a medicine called Campath[®]. Alemtuzumab the active ingredient in LEMTRADA is the same drug as Campath.
- have bleeding problems
- have thyroid problems
- have kidney problems
- have a recent history of infection
- have HIV
- have received a live vaccine in the past 6 weeks before receiving LEMTRADA or plan to receive any live vaccines. Ask your healthcare provider if you are not sure if your vaccine is a live vaccine.

- are pregnant or plan to become pregnant. LEMTRADA may harm your unborn baby. You should use birth control while receiving LEMTRADA and for 4 months after your course of treatment.
- are breastfeeding or plan to breastfeed. It is not known if LEMTRADA passes into your breast milk. You and your healthcare provider should decide if you should receive LEMTRADA or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

LEMTRADA and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you take medicines that increase your chance of getting infections, including medicines used to treat cancer or to control your immune system.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How will I receive LEMTRADA?

- LEMTRADA is given through a needle placed in your vein (IV infusion).
- It takes about 4 hours to receive a full dose of LEMTRADA each day.
- You will receive LEMTRADA over 2 treatment courses.
- You will receive LEMTRADA for 5 days in a row (consecutive) for the first treatment course and then for 3 days in a row (consecutive) about 1 year later for your second treatment course.

What are the possible side effects of LEMTRADA?

LEMTRADA may cause serious side effects including:

- See **“What is the most important information I should know about LEMTRADA?”**
- **thyroid problems.** Some people who receive LEMTRADA may get thyroid problems including an overactive thyroid (hyperthyroidism) or an underactive thyroid (hypothyroidism). Your healthcare provider will do blood tests to check how your thyroid is working. Call your healthcare provider if you have any of the symptoms of thyroid problems.

Symptoms of **hyperthyroidism** may include:

- excessive sweating
- unexplained weight loss
- eye swelling
- nervousness
- fast heartbeat

Symptoms of **hypothyroidism** may include:

- unexplained weight gain
- feeling cold
- worsening tiredness
- constipation

- **low blood counts (cytopenias).** LEMTRADA may cause a decrease in some types of blood cells. Some people with these low blood counts have increased infections. Symptoms of cytopenias may include:
 - weakness
 - chest pain
 - yellowing of the skin or whites of eyes (jaundice)
 - dark urine
 - fast heartbeat

Your healthcare provider will do blood tests to check for cytopenias. Call your healthcare provider right away if you have symptoms listed above.

- **serious infections.** LEMTRADA may cause you to have serious infections while you receive and after receiving a treatment course. Serious infections may include:
 - **herpes viral infections.** Some people taking LEMTRADA have an increased chance of getting herpes viral infections. Your healthcare provider will prescribe medicines to reduce your chances of getting these infections. Take these medicines exactly as your healthcare provider tells you to.
 - **human papilloma virus (HPV).** Females have an increased chance of getting a cervical HPV infection. If you are a female, you should have an HPV screening each year.
 - **tuberculosis.** Your healthcare provider should check you for tuberculosis before you receive LEMTRADA.
 - **fungal infections.**
 - **listeria.** People who receive LEMTRADA have an increased chance of getting an infection caused by the bacteria, listeria. Avoid foods that may be a source for listeria (for example, deli meat, unpasteurized milk and cheese products, or undercooked meat, seafood or poultry) or make sure that the food you eat which may contain listeria is heated well if you receive treatment with LEMTRADA.

Call your healthcare provider right away if you have symptoms of a serious infection, such as fever or swollen glands. You may need to go to the hospital for treatment if you get a serious infection. It is important to tell the healthcare providers that you have received LEMTRADA.

Talk to your healthcare provider before you get vaccinations after receiving LEMTRADA. Certain vaccinations may increase your chances of getting infections.

- **swelling of lung tissue (pneumonitis).** Some people have had swelling of the lung tissue while receiving LEMTRADA. Call your healthcare provider right away if you have the following symptoms:
 - shortness of breath
 - cough
 - wheezing
 - chest pain or tightness
 - coughing up blood

The most common side effects of LEMTRADA include:

- rash
- headache
- thyroid problems
- fever
- swelling of your nose and throat (nasopharyngitis)
- nausea
- urinary tract infection
- feeling tired
- trouble sleeping
- upper respiratory tract infection
- herpes viral infection
- hives
- itching
- fungal infection
- joint pain
- pain in your arms or legs
- back pain
- diarrhea
- sinus infection
- mouth pain or sore throat
- tingling sensation
- dizziness
- stomach pain
- sudden redness in face, neck, or chest
- vomiting

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of LEMTRADA. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

General information about the safe and effective use of LEMTRADA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LEMTRADA for a condition for which it was not prescribed. Do not give LEMTRADA to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about LEMTRADA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about LEMTRADA that is written for health professionals.

For more information, go to www.LemtradaREMS.com or call Genzyme at 1-855-676-6326.

What are the ingredients in LEMTRADA?

Active ingredient: alemtuzumab

Inactive ingredients: sodium chloride, dibasic sodium phosphate, potassium chloride, potassium dihydrogen phosphate, polysorbate 80, disodium edetate dihydrate, and water for injection.

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

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500 Kendall Street

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