

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125370

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

BENLYSTA® (belimumab)
for injection, for intravenous use only
Initial U.S. Approval: 2011

INDICATIONS AND USAGE

BENLYSTA is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. (1, 14)

Limitations of Use: The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus (1). BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide (1). Use of BENLYSTA is not recommended in these situations.

DOSAGE AND ADMINISTRATION

- Recommended dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Reconstitute, dilute and administer as an intravenous infusion only, over a period of 1 hour. (2.1)
- Consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions (2.2)

DOSAGE FORMS AND STRENGTHS

Single-use vials of belimumab lyophilized powder:

- 120 mg per vial (3)
- 400 mg per vial (3)

CONTRAINDICATIONS

Previous anaphylaxis to belimumab. (4)

WARNINGS AND PRECAUTIONS

- Mortality: There were more deaths reported with BENLYSTA than with placebo during the controlled period of clinical trials. (5.1)
- Serious Infections: Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. Use with caution in patients with chronic infections. Consider interrupting BENLYSTA therapy if patients develop a new infection during BENLYSTA treatment. (5.2)
- Hypersensitivity Reactions, Including Anaphylaxis: Serious reactions have been reported. BENLYSTA should be administered by healthcare providers prepared to manage anaphylaxis. Monitor patients during and for an appropriate period of time after administration of BENLYSTA. (2.2, 5.4)
- Depression: Depression and suicidality have been reported in BENLYSTA studies. Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or other mood changes. (5.6)
- Immunization: Live vaccines should not be given concurrently with BENLYSTA. (5.7)

ADVERSE REACTIONS

Common adverse reactions (≥5%) in clinical trials were: nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Human Genome Sciences, Inc. at 1-877-423-6597 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Registry available. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: March 2011

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 BENLYSTA[®] (belimumab) is indicated for the treatment of adult patients with active,
4 autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

6 *Limitations of Use*

7 The efficacy of BENLYSTA has not been evaluated in patients with severe active lupus nephritis
8 or severe active central nervous system lupus. BENLYSTA has not been studied in combination
9 with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended
10 in these situations.

11 2 DOSAGE AND ADMINISTRATION

13 2.1 Dosage Schedule

14 BENLYSTA is for intravenous infusion **only** and must be reconstituted and diluted prior to
15 administration [*see Dosage and Administration 2.3*]. Do not administer as an intravenous push
16 or bolus.

17
18 The recommended dosage regimen is 10 mg/kg at 2-week intervals for the first 3 doses and at
19 4-week intervals thereafter. Reconstitute, dilute and administer as an intravenous infusion only,
20 over a period of 1 hour. The infusion rate may be slowed or interrupted if the patient develops an
21 infusion reaction. The infusion must be discontinued immediately if the patient experiences a
22 serious hypersensitivity reaction [*see Contraindications (4), Warnings and Precautions (5.4)*].

24 2.2 Premedication Recommendations

25 Prior to dosing with BENLYSTA, consider administering premedication for prophylaxis against
26 infusion reactions and hypersensitivity reactions. [*see Warnings and Precautions (5.4,5.5) and*
27 *Adverse Reactions (6.1)*].

29 2.3 Preparation of Solutions

30 BENLYSTA is provided as a lyophilized powder in a single-use vial for intravenous infusion
31 only and should be reconstituted and diluted by a healthcare professional using aseptic technique
32 as follows:

33 **Reconstitution Instructions**

- 34 1. Remove BENLYSTA from the refrigerator and allow to stand 10 to 15 minutes for the vial to
35 reach room temperature.
- 36 2. Reconstitute the BENLYSTA powder with Sterile Water for Injection, USP, as follows. The
37 reconstituted solution will contain a concentration of 80 mg/mL belimumab.
 - 38 • Reconstitute the 120 mg vial with 1.5 mL Sterile Water for Injection, USP.
 - 39 • Reconstitute the 400 mg vial with 4.8 mL Sterile Water for Injection, USP.
- 40 3. The stream of sterile water should be directed toward the side of the vial to minimize
41 foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature
42 during reconstitution, gently swirling the vial for 60 seconds every 5 minutes until the
43 powder is dissolved. *Do not shake*. Reconstitution is typically complete within 10 to
44 15 minutes after the sterile water has been added, but it may take up to 30 minutes. Protect

- 45 the reconstituted solution from sunlight.
- 46 4. If a mechanical reconstitution device (swirler) is used to reconstitute BENLYSTA, it should
- 47 not exceed 500 rpm and the vial swirled for no longer than 30 minutes.
- 48 5. Once reconstitution is complete, the solution should be opalescent and colorless to pale
- 49 yellow, and without particles. Small air bubbles, however, are expected and acceptable.

50 **Dilution Instructions**

- 51 6. Dextrose intravenous solutions are incompatible with BENLYSTA. BENLYSTA should
- 52 only be diluted in 0.9% Sodium Chloride Injection, USP. Dilute the reconstituted product to
- 53 250 mL in 0.9% Sodium Chloride Injection, USP (normal saline) for intravenous infusion.
- 54 From a 250-mL infusion bag or bottle of normal saline, withdraw and discard a volume equal
- 55 to the volume of the reconstituted solution of BENLYSTA required for the patient's dose.
- 56 Then add the required volume of the reconstituted solution of BENLYSTA into the infusion
- 57 bag or bottle. Gently invert the bag or bottle to mix the solution. Any unused solution in the
- 58 vials must be discarded.
- 59 7. Parenteral drug products should be inspected visually for particulate matter and discoloration
- 60 prior to administration, whenever solution and container permit. Discard the solution if any
- 61 particulate matter or discoloration is observed.
- 62 8. The reconstituted solution of BENLYSTA, if not used immediately, should be stored
- 63 protected from direct sunlight and refrigerated at 2° to 8°C (36° to 46°F). Solutions of
- 64 BENLYSTA diluted in normal saline may be stored at 2° to 8°C (36° to 46°F) or room
- 65 temperature. The total time from reconstitution of BENLYSTA to completion of infusion
- 66 should not exceed 8 hours.
- 67 9. No incompatibilities between BENLYSTA and polyvinylchloride or polyolefin bags have
- 68 been observed.

69

70 **2.4 Administration Instructions**

- 71 1. The diluted solution of BENLYSTA should be administered by intravenous infusion only,
- 72 over a period of 1 hour.
- 73 2. BENLYSTA should be administered by healthcare providers prepared to manage
- 74 anaphylaxis. [see *Warnings and Precautions (5.4)*]
- 75 3. BENLYSTA should not be infused concomitantly in the same intravenous line with other
- 76 agents. No physical or biochemical compatibility studies have been conducted to evaluate the
- 77 coadministration of BENLYSTA with other agents.

78 **3 DOSAGE FORMS AND STRENGTHS**

79 Single-use vials of belimumab lyophilized powder for injection:

- 80 • 120 mg per vial
- 81 • 400 mg per vial

82 **4 CONTRAINDICATIONS**

83 BENLYSTA is contraindicated in patients who have had anaphylaxis with belimumab.

84 **5 WARNINGS AND PRECAUTIONS**

85

86 **5.1 Mortality**

87 There were more deaths reported with BENLYSTA than with placebo during the controlled

88 period of the clinical trials. Out of 2133 patients in 3 clinical trials, a total of 14 deaths occurred

89 during the placebo-controlled, double-blind treatment periods: 3/675 (0.4%), 5/673 (0.7%),
90 0/111 (0%), and 6/674 (0.9%) deaths in the placebo, BENLYSTA 1 mg/kg, BENLYSTA 4
91 mg/kg, and BENLYSTA 10 mg/kg groups, respectively. No single cause of death
92 predominated. Etiologies included infection, cardiovascular disease and suicide.

93

94 **5.2 Serious Infections**

95 Serious and sometimes fatal infections have been reported in patients receiving
96 immunosuppressive agents, including BENLYSTA. Physicians should exercise caution when
97 considering the use of BENLYSTA in patients with chronic infections. Patients receiving any
98 therapy for chronic infection should not begin therapy with BENLYSTA. Consider interrupting
99 BENLYSTA therapy in patients who develop a new infection while undergoing treatment with
100 BENLYSTA and monitor these patients closely.

101

102 In the controlled clinical trials, the overall incidence of infections was 71% in patients treated
103 with BENLYSTA compared with 67% in patients who received placebo. The most frequent
104 infections (>5% of patients receiving BENLYSTA) were upper respiratory tract infection,
105 urinary tract infection, nasopharyngitis, sinusitis, bronchitis, and influenza. Serious infections
106 occurred in 6.0% of patients treated with BENLYSTA and in 5.2% of patients who received
107 placebo. The most frequent serious infections included pneumonia, urinary tract infection,
108 cellulitis, and bronchitis. Infections leading to discontinuation of treatment occurred in 0.7% of
109 patients receiving BENLYSTA and 1.0% of patients receiving placebo. Infections resulting in
110 death occurred in 0.3% (4/1458) of patients treated with BENLYSTA and in 0.1% (1/675) of
111 patients receiving placebo.

112

113 **5.3 Malignancy**

114 The impact of treatment with BENLYSTA on the development of malignancies is not known. In
115 the controlled clinical trials, malignancies (including non-melanoma skin cancers) were reported
116 in 0.4% of patients receiving BENLYSTA and 0.4% of patients receiving placebo. In the
117 controlled clinical trials, malignancies, excluding non-melanoma skin cancers, were observed in
118 0.2% (3/1458) and 0.3% (2/675) of patients receiving BENLYSTA and placebo, respectively. As
119 with other immunomodulating agents, the mechanism of action of BENLYSTA could increase
120 the risk for the development of malignancies.

121

122 **5.4 Hypersensitivity Reactions, Including Anaphylaxis**

123 In the controlled clinical trials, hypersensitivity reactions (occurring on the same day of infusion)
124 were reported in 13% (191/1458) of patients receiving BENLYSTA and 11% (76/675) of
125 patients receiving placebo. Anaphylaxis was observed in 0.6% (9/1458) of patients receiving
126 BENLYSTA and 0.4% (3/675) of patients receiving placebo. Manifestations included
127 hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea. Due to overlap in signs
128 and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion
129 reactions in all cases [see *Warnings and Precautions (5.5)*]. Some patients (13%) received
130 premedication, which may have mitigated or masked a hypersensitivity response; however, there
131 is insufficient evidence to determine whether premedication diminishes the frequency or severity
132 of hypersensitivity reactions.

133

134 BENLYSTA should be administered by healthcare providers prepared to manage anaphylaxis. In
135 the event of a serious reaction, administration of BENLYSTA must be discontinued immediately
136 and appropriate medical therapy administered. Patients should be monitored during and for an
137 appropriate period of time after administration of BENLYSTA. Patients should be informed of
138 the signs and symptoms of a hypersensitivity reaction and instructed to seek immediate medical
139 care should a reaction occur.

140

141 **5.5 Infusion Reactions**

142 In the controlled clinical trials, adverse events associated with the infusion (occurring on the
143 same day of the infusion) were reported in 17% (251/1458) of patients receiving BENLYSTA
144 and 15% (99/675) of patients receiving placebo. Serious infusion reactions (excluding
145 hypersensitivity reactions) were reported in 0.5% of patients receiving BENLYSTA and 0.4% of
146 patients receiving placebo and included bradycardia, myalgia, headache, rash, urticaria, and
147 hypotension. The most common infusion reactions ($\geq 3\%$ of patients receiving BENLYSTA)
148 were headache, nausea, and skin reactions. Due to overlap in signs and symptoms, it was not
149 possible to distinguish between hypersensitivity reactions and infusion reactions in all cases [*see*
150 *Warnings and Precautions (5.4)*]. Some patients (13%) received premedication, which may
151 have mitigated or masked an infusion reaction; however there is insufficient evidence to
152 determine whether premedication diminishes the frequency or severity of infusion reactions [*see*
153 *Adverse Reactions (6.1)*].

154

155 BENLYSTA should be administered by healthcare providers prepared to manage infusion
156 reactions. The infusion rate may be slowed or interrupted if the patient develops an infusion
157 reaction. Healthcare providers should be aware of the risk of hypersensitivity reactions, which
158 may present as infusion reactions, and monitor patients closely.

159

160 **5.6 Depression**

161 In the controlled clinical trials, psychiatric events were reported more frequently with
162 BENLYSTA (16%) than with placebo (12%), related primarily to depression-related events
163 (6.3% BENLYSTA and 4.7% placebo), insomnia (6.0% BENLYSTA and 5.3% placebo), and
164 anxiety (3.9% BENLYSTA and 2.8% placebo). Serious psychiatric events were reported in 0.8%
165 of patients receiving BENLYSTA (0.6% and 1.2% with 1 and 10 mg/kg, respectively) and 0.4%
166 of patients receiving placebo. Serious depression was reported in 0.4% (6/1458) of patients
167 receiving BENLYSTA and 0.1% (1/675) of patients receiving placebo. Two suicides (0.1%)
168 were reported in patients receiving BENLYSTA. The majority of patients who reported serious
169 depression or suicidal behavior had a history of depression or other serious psychiatric disorders
170 and most were receiving psychoactive medications. It is unknown if BENLYSTA treatment is
171 associated with increased risk for these events.

172

173 Patients receiving BENLYSTA should be instructed to contact their healthcare provider if they
174 experience new or worsening depression, suicidal thoughts, or other mood changes.

175

176 **5.7 Immunization**

177 Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as
178 clinical safety has not been established. No data are available on the secondary transmission of
179 infection from persons receiving live vaccines to patients receiving BENLYSTA or the effect of

180 BENLYSTA on new immunizations. Because of its mechanism of action, BENLYSTA may
181 interfere with the response to immunizations.

182

183 **5.8 Concomitant Use with Other Biologic Therapies or Intravenous** 184 **Cyclophosphamide**

185 BENLYSTA has not been studied in combination with other biologic therapies, including B-cell
186 targeted therapies, or intravenous cyclophosphamide. Therefore, use of BENLYSTA is not
187 recommended in combination with biologic therapies or intravenous cyclophosphamide.

188 **6 ADVERSE REACTIONS**

189 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
190 observed in the clinical trials of a drug cannot be directly compared with rates in the clinical
191 trials of another drug and may not reflect the rates observed in practice.

192

193 The following have been observed with BENLYSTA and are discussed in detail in the Warnings
194 and Precautions section:

- 195 • **Mortality** [*see Warnings and Precautions (5.1)*]
- 196 • **Serious Infections** [*see Warnings and Precautions (5.2)*]
- 197 • **Malignancy** [*see Warnings and Precautions (5.3)*]
- 198 • **Hypersensitivity Reactions, Including Anaphylaxis** [*see Warnings and Precautions (5.4)*]
- 199 • **Infusion reactions** [*see Warnings and Precautions (5.5)*]
- 200 • **Depression** [*see Warnings and Precautions (5.6)*]

201

202 **6.1 Clinical Trials Experience**

203 The data described below reflect exposure to BENLYSTA plus standard of care compared with
204 placebo plus standard of care in 2133 patients in 3 controlled studies. Patients received
205 BENLYSTA at doses of 1 mg/kg (N=673), 4 mg/kg (N=111; Trial 1 only), or 10 mg/kg (N=674)
206 or placebo (N=675) intravenously over a 1-hour period on Days 0, 14, 28, and then every
207 28 days. In two of the studies (Trial 1 and Trial 3), treatment was given for 48 weeks, while in
208 the other study (Trial 2) treatment was given for 72 weeks [*see Clinical Studies (14)*]. Because
209 there was no apparent dose-related increase in the majority of adverse events observed with
210 BENLYSTA, the safety data summarized below are presented for the 3 doses pooled, unless
211 otherwise indicated; the adverse reaction table displays the results for the recommended dose of
212 10 mg/kg compared with placebo.

213

214 The population had a mean age of 39 (range 18-75), 94% were female, and 52% were Caucasian.
215 In these trials, 93% of patients treated with BENLYSTA reported an adverse reaction compared
216 with 92% treated with placebo.

217

218 The most common serious adverse reactions were serious infections (6.0% and 5.2% in the
219 groups receiving BENLYSTA and placebo, respectively) [*see Warnings and Precautions (5.2)*].

220

221 The most commonly-reported adverse reactions, occurring in $\geq 5\%$ of patients in clinical trials
222 were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity,
223 depression, migraine, and pharyngitis.

224

225 The proportion of patients who discontinued treatment due to any adverse reaction during the
 226 controlled clinical trials was 6.2% for patients receiving BENLYSTA and 7.1% for patients
 227 receiving placebo. The most common adverse reactions resulting in discontinuation of treatment
 228 ($\geq 1\%$ of patients receiving BENLYSTA or placebo) were infusion reactions (1.6% BENLYSTA
 229 and 0.9% placebo), lupus nephritis (0.7% BENLYSTA and 1.2% placebo), and infections (0.7%
 230 BENLYSTA and 1.0% placebo).

231
 232 Table 1 lists adverse reactions, regardless of causality, occurring in at least 3% of patients with
 233 SLE who received BENLYSTA 10 mg/kg and at an incidence at least 1% greater than that
 234 observed with placebo in the 3 controlled studies.

235 **Table 1 Incidence of Adverse Reactions Occurring in at Least 3% of Patients Treated With BENLYSTA**
 236 **10 mg/kg Plus Standard of Care and at Least 1% More Frequently Than in Patients Receiving Placebo plus**
 237 **Standard of Care in 3 Controlled SLE Studies**

Preferred Term	BENLYSTA 10 mg/kg + Standard of Care (n = 674) %	Placebo + Standard of Care (n = 675) %
Nausea	15	12
Diarrhea	12	9
Pyrexia	10	8
Nasopharyngitis	9	7
Bronchitis	9	5
Insomnia	7	5
Pain in extremity	6	4
Depression	5	4
Migraine	5	4
Pharyngitis	5	3
Cystitis	4	3
Leukopenia	4	2
Gastroenteritis viral	3	1

238
 239
 240 **6.2 Immunogenicity**
 241 In Trials 2 and 3, anti-belimumab antibodies were detected in 4 of 563 (0.7%) patients receiving
 242 BENLYSTA 10 mg/kg and in 27 of 559 (4.8%) patients receiving BENLYSTA 1 mg/kg. The
 243 reported frequency for the group receiving 10 mg/kg may underestimate the actual frequency due
 244 to lower assay sensitivity in the presence of high drug concentrations. Neutralizing antibodies
 245 were detected in 3 patients receiving BENLYSTA 1 mg/kg. Three patients with anti-belimumab
 246 antibodies experienced mild infusion reactions of nausea, erythematous rash, pruritus, eyelid
 247 edema, headache, and dyspnea; none of the reactions was life-threatening. The clinical relevance
 248 of the presence of anti-belimumab antibodies is not known.

249
 250 The data reflect the percentage of patients whose test results were positive for antibodies to
 251 belimumab in specific assays. The observed incidence of antibody positivity in an assay is highly
 252 dependent on several factors, including assay sensitivity and specificity, assay methodology,

253 sample handling, timing of sample collection, concomitant medications, and underlying disease.
254 For these reasons, comparison of the incidence of antibodies to belimumab with the incidence of
255 antibodies to other products may be misleading.

256 **7 DRUG INTERACTIONS**

257 Formal drug interaction studies have not been performed with BENLYSTA. In clinical trials of
258 patients with SLE, BENLYSTA was administered concomitantly with other drugs, including
259 corticosteroids, antimalarials, immunomodulatory and immunosuppressive agents (including
260 azathioprine, methotrexate, and mycophenolate), angiotensin pathway antihypertensives,
261 HMG-CoA reductase inhibitors (statins), and NSAIDs without evidence of a clinically
262 meaningful effect of these concomitant medications on belimumab pharmacokinetics. The effect
263 of belimumab on the pharmacokinetics of other drugs has not been evaluated [*see*
264 *Pharmacokinetics 12.3*].
265

266 **8 USE IN SPECIFIC POPULATIONS**

267 268 **8.1 Pregnancy**

269 Pregnancy Category C. There are no adequate and well-controlled clinical studies using
270 BENLYSTA in pregnant women. Immunoglobulin G (IgG) antibodies, including BENLYSTA,
271 can cross the placenta. Because animal reproduction studies are not always predictive of human
272 response, BENLYSTA should be used during pregnancy only if the potential benefit to the
273 mother justifies the potential risk to the fetus. Women of childbearing potential should use
274 adequate contraception during treatment with BENLYSTA and for at least 4 months after the
275 final treatment.
276

277 Nonclinical reproductive studies have been performed in pregnant cynomolgus monkeys
278 receiving belimumab at doses of 0, 5 and 150 mg/kg by intravenous infusion (the high dose was
279 approximately 9 times the anticipated maximum human exposure) every 2 weeks from gestation
280 day 20 to 150. Belimumab was shown to cross the placenta. Belimumab was not associated with
281 direct or indirect teratogenicity under the conditions tested. Fetal deaths were observed in 14%,
282 24% and 15% of pregnant females in the 0, 5 and 150 mg/kg groups, respectively. Infant deaths
283 occurred with an incidence of 0%, 8% and 5%. The cause of fetal and infant deaths is not known.
284 The relevance of these findings to humans is not known. Other treatment-related findings were
285 limited to the expected reversible reduction of B cells in both dams and infants and reversible
286 reduction of IgM in infant monkeys. B-cell numbers recovered after the cessation of belimumab
287 treatment by about 1 year post-partum in adult monkeys and by 3 months of age in infant
288 monkeys. IgM levels in infants exposed to belimumab in utero recovered by 6 months of age.
289

290 **Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant women exposed to
291 BENLYSTA, a pregnancy registry has been established. Healthcare professionals are encouraged
292 to register patients and pregnant women are encouraged to enroll themselves by calling
293 1-877-681-6296.
294

295 **8.3 Nursing Mothers**

296 It is not known whether BENLYSTA is excreted in human milk or absorbed systemically after
297 ingestion. However, belimumab was excreted into the milk of cynomolgus monkeys. Because

298 maternal antibodies are excreted in human breast milk, a decision should be made whether to
299 discontinue breastfeeding or to discontinue the drug, taking into account the importance of
300 breastfeeding to the infant and the importance of the drug to the mother.

301

302 **8.4 Pediatric Use**

303 Safety and effectiveness of BENLYSTA have not been established in children.

304

305 **8.5 Geriatric Use**

306 Clinical studies of BENLYSTA did not include sufficient numbers of subjects aged 65 or over to
307 determine whether they respond differently from younger subjects. Use with caution in elderly
308 patients.

309

310 **8.6 Race**

311 In Trial 2 and Trial 3, response rates for the primary endpoint were lower for black subjects in
312 the BENLYSTA group relative to black subjects in the placebo group [*see Clinical Studies (14)*].
313 Use with caution in black/African-American patients.

314 **10 OVERDOSAGE**

315 There is no clinical experience with overdosage of BENLYSTA. Two doses of up to 20 mg/kg
316 have been given by intravenous infusion to humans with no increase in incidence or severity of
317 adverse reactions compared with doses of 1, 4, or 10 mg/kg.

318 **11 DESCRIPTION**

319 BENLYSTA (belimumab) is a human IgG1 λ monoclonal antibody specific for soluble human B
320 lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab
321 has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA
322 technology in a mammalian cell expression system.

323

324 BENLYSTA is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for
325 intravenous infusion. Upon reconstitution with Sterile Water for Injection, USP, [*see Dosage
326 and Administration (2.3)*] each single-use vial delivers 80 mg/mL belimumab in 0.16 mg/mL
327 citric acid, 0.4 mg/mL polysorbate 80, 2.7 mg/mL sodium citrate, and 80 mg/mL sucrose, with a
328 pH of 6.5.

329 **12 CLINICAL PHARMACOLOGY**

330

331 **12.1 Mechanism of Action**

332 BENLYSTA is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell
333 survival factor, to its receptors on B cells. BENLYSTA does not bind B cells directly, but by
334 binding BLyS, BENLYSTA inhibits the survival of B cells, including autoreactive B cells, and
335 reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

336

337 **12.2 Pharmacodynamics**

338 In Trial 1 and Trial 2 in which B cells were measured, treatment with BENLYSTA significantly
339 reduced circulating CD19+, CD20+, naïve, and activated B cells, plasmacytoid cells, and the
340 SLE B-cell subset at Week 52. Reductions in naïve and the SLE B-cell subset were observed as
341 early as Week 8 and were sustained to Week 52. Memory cells increased initially and slowly

342 declined toward baseline levels by Week 52. The clinical relevance of these effects on B cells
343 has not been established.

344
345 Treatment with BENLYSTA led to reductions in IgG and anti-dsDNA, and increases in
346 complement (C3 and C4). These changes were observed as early as Week 8 and were sustained
347 through Week 52. The clinical relevance of normalizing these biomarkers has not been
348 definitively established.

349 350 **12.3 Pharmacokinetics**

351 The pharmacokinetic parameters displayed in Table 2 are based on population parameter
352 estimates which are specific to the 563 patients who received belimumab 10 mg/kg in Trials 2
353 and 3 [see *Clinical Studies (14)*].

354 **Table 2. Population Pharmacokinetic Parameters in Patients with SLE after Intravenous Infusion of**
355 **BENLYSTA 10 mg/kg¹**

Pharmacokinetic Parameter	Population Estimates (n = 563)
Peak concentration (C _{max} , µg/mL)	313
Area under the curve (AUC _{0-∞} , day•µg/mL)	3,083
Distribution half-life (t _{1/2} , days)	1.75
Terminal half-life (t _{1/2} , days)	19.4
Systemic clearance (CL, mL/day)	215
Volume of distribution (V _{ss} , L)	5.29

356 ¹ Intravenous infusions were administered at 2-week intervals for the first 3 doses and at
357 4-week intervals thereafter.

358
359 **Drug Interactions:** No formal drug interaction studies have been conducted with belimumab.
360 Concomitant use of mycophenolate, azathioprine, methotrexate, antimalarials, NSAIDs, aspirin,
361 and HMG-CoA reductase inhibitors did not significantly influence belimumab pharmacokinetics.
362 Coadministration of steroids and angiotensin-converting enzyme (ACE) inhibitors resulted in an
363 increase of systemic clearance of belimumab that was not clinically significant because the
364 magnitude was well within the range of normal variability of clearance. The effect of belimumab
365 on the pharmacokinetics of other drugs has not been evaluated.

366 367 **Special Populations:**

368 The following information is based on the population pharmacokinetic analysis.

369
370 **Age:** Age did not significantly influence belimumab pharmacokinetics in the study population,
371 where the majority of subjects (70%) were between 18 and 45 years of age. No pharmacokinetic
372 data are available in pediatric patients. Limited pharmacokinetic data are available for elderly
373 patients as only 1.4% of the subjects included in the pharmacokinetic analysis were 65 years of
374 age or older [see *Use in Specific Populations (8.5)*].

375
376 **Gender:** Gender did not significantly influence belimumab pharmacokinetics in the largely
377 (94%) female study population.

378

379 *Race:* Race did not significantly influence belimumab pharmacokinetics. The racial distribution
380 was 53% white/Caucasian, 16% Asian, 16% Alaska native/American Indian, and 14%
381 black/African American.

382
383 *Renal Impairment:* No formal studies were conducted to examine the effects of renal
384 impairment on the pharmacokinetics of belimumab. Belimumab has been studied in a limited
385 number of patients with SLE and renal impairment (261 subjects with moderate renal
386 impairment, creatinine clearance ≥ 30 and < 60 mL/min; 14 subjects with severe renal
387 impairment, creatinine clearance ≥ 15 and < 30 mL/min). Although increases in creatinine
388 clearance and proteinuria (> 2 g/day) increased belimumab clearance, these effects were within
389 the expected range of variability. Therefore, dosage adjustment in patients with renal impairment
390 is not recommended.

391
392 *Hepatic Impairment:* No formal studies were conducted to examine the effects of hepatic
393 impairment on the pharmacokinetics of belimumab. Belimumab has not been studied in patients
394 with severe hepatic impairment. Baseline ALT and AST levels did not significantly influence
395 belimumab pharmacokinetics.

396

397 **13 NONCLINICAL TOXICOLOGY**

398

399 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

400 Long-term animal studies have not been performed to evaluate the carcinogenic potential of
401 belimumab. The mutagenic potential of belimumab was not evaluated.

402

403 Effects on male and female fertility have not been directly evaluated in animal studies.

404 **14 CLINICAL STUDIES**

405 The safety and effectiveness of BENLYSTA were evaluated in three randomized, double-blind,
406 placebo-controlled studies involving 2133 patients with SLE according to the American College
407 of Rheumatology criteria (Trial 1, 2, and 3). Patients with severe active lupus nephritis and
408 severe active CNS lupus were excluded. Patients were on a stable standard of care SLE treatment
409 regimen comprising any of the following (alone or in combination): corticosteroids,
410 antimalarials, NSAIDs, and immunosuppressives. Use of other biologics and intravenous
411 cyclophosphamide were not permitted.

412

413 ***Trial 1: BENLYSTA 1 mg/kg, 4 mg/kg, 10 mg/kg***

414 Trial 1 enrolled 449 patients and evaluated doses of 1, 4, and 10 mg/kg BENLYSTA plus
415 standard of care compared with placebo plus standard of care over 52 weeks in patients with
416 SLE. Patients had to have a SELENA-SLEDAI score of ≥ 4 at baseline and a history of
417 autoantibodies (anti-nuclear antibody (ANA) and/or anti-double-stranded DNA (anti-dsDNA),
418 but 28% of the population was autoantibody negative at baseline. The co-primary endpoints
419 were percent change in SELENA-SLEDAI score at Week 24 and time to first flare over 52
420 weeks. No significant differences between any of the BENLYSTA groups and the placebo
421 group were observed. Exploratory analysis of this study identified a subgroup of patients (72%),
422 who were autoantibody positive, in whom BENLYSTA appeared to offer benefit. The results of

423 this study informed the design of Trials 2 and 3 and led to the selection of a target population and
424 indication that is limited to autoantibody-positive SLE patients.

425

426 ***Trials 2 and 3: BENLYSTA 1 mg/kg and 10 mg/kg***

427 Trials 2 and 3 were randomized, double-blind, placebo-controlled trials in patients with SLE that
428 were similar in design except duration - Trial 2 was 76 weeks duration and Trial 3 was 52 weeks
429 duration. Eligible patients had active SLE disease, defined as a SELENA-SLEDAI score ≥ 6 , and
430 positive autoantibody test results at screening. Patients were excluded from the study if they had
431 ever received treatment with a B-cell targeted agent or if they were currently receiving other
432 biologic agents. Intravenous cyclophosphamide was not permitted within the previous 6 months
433 or during study. Trial 2 was conducted primarily in North America and Europe. Trial 3 was
434 conducted in South America, Eastern Europe, Asia, and Australia.

435

436 Baseline concomitant medications included corticosteroids (Trial 2: 76%, Trial 3: 96%),
437 immunosuppressives (Trial 2: 56%, Trial 3: 42%; including azathioprine, methotrexate and
438 mycophenolate), and antimalarials (Trial 2: 63%, Trial 3: 67%). Most patients (>70%) were
439 receiving 2 or more classes of SLE medications.

440

441 In Trial 2 and Trial 3, more than 50% of patients had 3 or more active organ systems at baseline.
442 The most common active organ systems at baseline based on SELENA SLEDAI were
443 mucocutaneous (82% in both studies); immunology (Trial 2: 74%, Trial 3: 85%); and
444 musculoskeletal (Trial 2: 73%, Trial 3: 59%). Less than 16% of patients had some degree of
445 renal activity and less than 7% of patients had activity in the vascular, cardio-respiratory, or CNS
446 systems.

447

448 At screening, patients were stratified by disease severity based on their SELENA-SLEDAI score
449 (≤ 9 vs ≥ 10), proteinuria level (< 2 g/24 hr vs ≥ 2 g/24 hr), and race (African or Indigenous-
450 American descent vs. other), and then randomly assigned to receive BENLYSTA 1 mg/kg,
451 BENLYSTA 10 mg/kg, or placebo in addition to standard of care. The patients were
452 administered study medication intravenously over a 1-hour period on Days 0, 14, 28, and then
453 every 28 days for 48 weeks in Trial 3 and for 72 weeks in Trial 2.

454

455 The primary efficacy endpoint was a composite endpoint (SLE Responder Index or SRI) that
456 defined response as meeting each of the following criteria at Week 52 compared with baseline:

- 457
- 458 • ≥ 4 -point reduction in the SELENA-SLEDAI score, and
 - 459 • no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new
460 BILAG B organ domain scores, and
 - 461 • no worsening (< 0.30 -point increase) in Physician's Global Assessment (PGA) score.

462

463 The SRI uses the SELENA-SLEDAI score as an objective measure of reduction in global disease
464 activity; the BILAG index to ensure no significant worsening in any specific organ system; and
465 the PGA to ensure that improvements in disease activity are not accompanied by worsening of
466 the patient's condition overall.

467

468 In both Trials 2 and 3, the proportion of SLE patients achieving an SRI response, as defined for
the primary endpoint, was significantly higher in the BENLYSTA 10 mg/kg group than in the

469 placebo group in both studies. The effect on the SRI was not consistently significantly different
 470 for the BENLYSTA 1mg/kg group relative to placebo in both trials. The 1 mg/kg dose is not
 471 recommended. The trends in comparisons between the treatment groups for the rates of response
 472 for the individual components of the endpoint were generally consistent with that of the SRI
 473 (Table 3). At Week 76 in Trial 2, the SRI response rate with BENLYSTA 10 mg/kg was not
 474 significantly different from that of placebo (39% and 32%, respectively).
 475
 476

Table 3. Clinical Response Rate in Patients with SLE After 52 Weeks of Treatment

Response ¹	Trial 2			Trial 3		
	Placebo + Standard of Care (n = 275)	BENLYSTA 1 mg/kg + Standard of Care ² (n = 271)	BENLYSTA 10 mg/kg + Standard of Care (n = 273)	Placebo + Standard of Care (n = 287)	BENLYSTA 1 mg/kg + Standard of Care ² (n = 288)	BENLYSTA 10 mg/kg + Standard of Care (n = 290)
SLE Responder Index	34%	41%	43%	44%	51%	58%
		(p = 0.104)	(p = 0.021)		(p = 0.013)	(p < 0.001)
Odds Ratio (95% CI) vs. placebo		1.3 (0.9, 1.9)	1.5 (1.1, 2.2)		1.6 (1.1, 2.2)	1.8 (1.3, 2.6)
Components of SLE Responder Index						
Percent of patients with reduction in SELENA-SLEDAI ≥4	36%	43%	47%	46%	53%	58%
Percent of patients with no worsening by BILAG index	65%	75%	69%	73%	79%	81%
Percent of patients with no worsening by PGA	63%	73%	69%	69%	79%	80%

477 ¹Patients dropping out of the study early or experiencing certain increases in background medication were
 478 considered as failures in these analyses. In both studies, a higher proportion of placebo patients were considered as
 479 failures for this reason as compared to the BENLYSTA groups.

480 ²The 1 mg/kg dose is not recommended.

481
 482 The reduction in disease activity seen in the SRI was related primarily to improvement in the
 483 most commonly involved organ systems namely, mucocutaneous, musculoskeletal, and
 484 immunology.

485
 486 *Effect in Black/African-American Patients*

487 Exploratory sub-group analyses of SRI response rate in patients of black race were performed.
 488 In Trial 2 and Trial 3 combined, the SRI response rate in black patients (N=148) in the
 489 BENLYSTA groups was less than that in the placebo group (22/50 or 44% for placebo, 15/48 or
 490 31% for BENLYSTA 1 mg/kg, and 18/50 or 36% for BENLYSTA 10 mg/kg). In Trial 1, black
 491 patients (N=106) in the BENLYSTA groups did not appear to have a different response than the

492 rest of the study population. Although no definitive conclusions can be drawn from these
493 subgroup analyses, caution should be used when considering BENLYSTA treatment in
494 black/African-American SLE patients.

495
496 *Effect on Concomitant Steroid Treatment:*

497 In Trial 2 and Trial 3, 46% and 69% of patients, respectively, were receiving prednisone at doses
498 > 7.5 mg/day at baseline. The proportion of patients able to reduce their average prednisone
499 dose by at least 25% to ≤7.5 mg/day during Weeks 40 through 52 was not consistently
500 significantly different for BENLYSTA relative to placebo in both trials. In Trial 2, 17% of
501 patients receiving BENLYSTA 10 mg/kg and 19% of patients receiving BENLYSTA 1 mg/kg
502 achieved this level of steroid reduction compared with 13% of patients receiving placebo. In
503 Trial 3, 19%, 21%, and 12% of patients receiving BENLYSTA 10 mg/kg, BENLYSTA 1 mg/kg,
504 and placebo, respectively, achieved this level of steroid reduction.

505
506 *Effect on Severe SLE Flares:*

507 The probability of experiencing a severe SLE flare, as defined by a modification of the SELENA
508 Trial flare criteria which excluded severe flares triggered only by an increase of the SELENA-
509 SLEDAI score to >12, was calculated for both Trials 2 and 3. The proportion of patients having
510 at least 1 severe flare over 52 weeks was not consistently significantly different for BENLYSTA
511 relative to placebo in both trials. In Trial 2, 18% of patients receiving BENLYSTA 10 mg/kg
512 and 16% of patients receiving BENLYSTA 1 mg/kg had a severe flare compared with 24% of
513 patients receiving placebo. In Trial 3, 14%, 18%, and 23% of patients receiving BENLYSTA 10
514 mg/kg, BENLYSTA 1 mg/kg and placebo, respectively, had a severe flare.

515 **16 HOW SUPPLIED/STORAGE AND HANDLING**

516 BENLYSTA is a sterile, preservative-free lyophilized powder for reconstitution, dilution, and
517 intravenous infusion provided in single-use glass vials with a latex-free rubber stopper and a
518 flip-off seal. Each 5-mL vial contains 120 mg of belimumab. Each 20-mL vial contains 400 mg
519 of belimumab.

520
521 BENLYSTA is supplied as follows:

120 mg belimumab in a 5-mL single-use vial	NDC 49401-101-01
400 mg belimumab in a 20-mL single-use vial	NDC 49401-102-01

522
523 Store vials of BENLYSTA refrigerated between 2° to 8°C (36° to 46°F). Vials should be
524 protected from light and stored in the original carton until use. *Do not freeze.* Avoid exposure to
525 heat. Do not use beyond the expiration date.

526 **17 PATIENT COUNSELING INFORMATION**

527 *See Medication Guide.*

528
529 **17.1 Advice for the Patient**

530 Patients should be given the Medication Guide for BENLYSTA and provided an opportunity to
531 read it prior to each treatment session. It is important that the patient's overall health be assessed
532 at each infusion visit and any questions resulting from the patient's reading of the Medication
533 Guide be discussed.

534

535 **Mortality:** Patients should be advised that more patients receiving BENLYSTA in the main
536 clinical trials died than did patients receiving placebo treatment [*see Warnings and Precautions*
537 *(5.1)*].
538

539 **Serious Infections:** Patients should be advised that BENLYSTA may decrease their ability to
540 fight infections. Patients should be asked if they have a history of chronic infections and if they
541 are currently on any therapy for an infection [*see Warnings and Precautions (5.2)*]. Patients
542 should be instructed to tell their healthcare provider if they develop signs or symptoms of an
543 infection.
544

545 **Hypersensitivity/Anaphylactic and Infusion Reactions:** Educate patients on the signs and
546 symptoms of anaphylaxis, including wheezing, difficulty breathing, peri-oral or lingual edema,
547 and rash. Patients should be instructed to immediately tell their healthcare provider if they
548 experience symptoms of an allergic reaction during or after the administration of BENLYSTA
549 [*see Warnings and Precautions (5.4, 5.5)*].
550

551 **Depression:** Patients should be instructed to contact their healthcare provider if they experience
552 new or worsening depression, suicidal thoughts or other mood changes.
553 [*see Warnings and Precautions (5.6)*].
554

555 **Immunizations:** Patients should be informed that they should not receive live vaccines while
556 taking BENLYSTA. Response to vaccinations could be impaired by BENLYSTA [*see Warnings*
557 *and Precautions (5.7)*].
558

559 **Pregnancy and Nursing Mothers:** Patients should be informed that BENLYSTA has not been
560 studied in pregnant women or nursing mothers so the effects of BENLYSTA on pregnant women
561 or nursing infants are not known. Patients should be instructed to tell their healthcare provider if
562 they are pregnant, become pregnant, or are thinking about becoming pregnant [*see Use in*
563 *Specific Populations (8.1)*]. Patients should be instructed to tell their healthcare provider if they
564 plan to breastfeed their infant [*see Use in Specific Populations (8.3)*].
565

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567 GlaxoSmithKline.

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571 Rockville, Maryland 20850
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575 Human Genome Sciences, Inc.
576 Rockville, MD 20850
577



GlaxoSmithKline
Research Triangle Park, NC 27709

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MEDICATION GUIDE

BENLYSTA[®] (ben-LIST-ah) **(belimumab)**

Injection for intravenous use

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

10 What is the most important information I should know about BENLYSTA?

BENLYSTA can cause serious side effects. Some of these side effects may cause death. It is not known if BENLYSTA causes these serious side effects. Tell your healthcare provider right away if you have any of the symptoms listed below while receiving BENLYSTA.

14 1. Infections. Symptoms of an infection can include:

- 15 • fever
- 16 • chills
- 17 • pain or burning with urination
- 18 • urinating often
- 19 • bloody diarrhea
- 20 • coughing up mucus

21 2. Heart Problems. Symptoms of heart problems can include:

- 22 • chest discomfort or pain
- 23 • shortness of breath
- 24 • cold sweats
- 25 • nausea
- 26 • dizziness
- 27 • discomfort in other areas of the upper body

28 3. Mental health problems and suicide. Symptoms of mental health problems can include:

- 29 • thoughts of suicide or dying
- 30 • attempt to commit suicide
- 31 • trouble sleeping (insomnia)
- 32 • new or worse anxiety
- 33 • new or worse depression
- 34 • acting on dangerous impulses
- 35 • other unusual changes in your behavior or mood
- 36 • thoughts of hurting yourself or others

37 **What is BENLYSTA?**

38 BENLYSTA is a prescription medicine used to treat adults with active systemic lupus
39 erythematosus (SLE or lupus) who are receiving other lupus medicines.

40 BENLYSTA contains *belimumab* which is in a group of medicines called *monoclonal*
41 *antibodies*. Lupus is a disease of the immune system (the body system that fights infection).
42 People with active lupus often have high levels of a certain protein in their blood. BENLYSTA
43 binds to and limits the activity of the protein. When given together with other medicines for
44 lupus, BENLYSTA decreases lupus disease activity more than other lupus medicines alone.

- 45
- It is not known if BENLYSTA is safe and effective in people with severe active lupus
46 nephritis or severe active central nervous system lupus.
 - It is not known if BENLYSTA is safe and effective in children.
- 47

48 **Who should not receive BENLYSTA?**

49 **Do not receive BENLYSTA if you:**

- 50
- are allergic to belimumab or any of the ingredients in BENLYSTA. See the end of this
51 Medication Guide for a complete list of ingredients in BENLYSTA.

52 **What should I tell my healthcare provider before receiving BENLYSTA?**

53 Before you receive BENLYSTA, tell your healthcare provider if you:

- 54
- think you have an infection or have infections that keep coming back. You should not
55 receive BENLYSTA if you have an infection unless your healthcare provider tells you to.
56 **See “What is the most important information I should know about BENLYSTA.”**
 - have or have had mental health problems such as depression or thoughts of suicide
 - have recently received a vaccination or if you think you may need a vaccination. If you
58 are receiving BENLYSTA, you should not receive live vaccines.
 - are receiving other biologic medicines, monoclonal antibodies or IV infusions of
60 cyclophosphamide (Cytosan[®])
 - have or have had any type of cancer
 - have any other medical conditions
 - are pregnant or plan to become pregnant. It is not known if BENLYSTA will harm your
64 unborn baby. Tell your healthcare provider if you become pregnant during your treatment
65 with BENLYSTA.
 - If you become pregnant while receiving BENLYSTA, talk to your healthcare provider
67 about enrolling in the BENLYSTA Pregnancy Registry. You can enroll in this
68 registry by calling 1-877-681-6296. The purpose of this registry is to monitor the
69 health of you and your baby.
- 70

71 • are breastfeeding or plan to breastfeed. It is not known if BENLYSTA passes into your
72 breast milk. You and your healthcare provider should decide if you will receive
73 BENLYSTA or breastfeed. You should not do both.

74 **Tell your healthcare provider about all the medicines you take**, including prescription and
75 non-prescription medicines, vitamins, and herbal supplements.

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

78 **How will I receive BENLYSTA?**

- 79 • You will be given BENLYSTA by a healthcare provider through a needle placed in a
80 vein (IV infusion). It takes about 1 hour to give you the full dose of BENLYSTA.
- 81 • Your healthcare provider will tell you how often you should receive BENLYSTA.
- 82 • Your healthcare provider may give you medicines before you receive BENLYSTA to
83 help reduce your chance of having a reaction. A healthcare provider will watch you
84 closely while you are receiving BENLYSTA and after your infusion for signs of a
85 reaction.

86 **What are the possible side effects of BENLYSTA?**

87 **BENLYSTA can cause serious side effects.**

- 88 • See “**What is the most important information I should know about BENLYSTA?**”

89 **1. Cancer.** BENLYSTA may reduce the activity of your immune system. Medicines that affect
90 the immune system may increase your risk of certain cancers.

91 **2. Allergic (hypersensitivity) and infusion reactions.** Serious allergic or infusion reactions
92 can happen on the day of or the day after receiving BENLYSTA. Symptoms of an allergic or
93 infusion reaction may include:

- 94 • itching
- 95 • swelling of the face, lips, mouth, tongue, or throat
- 96 • trouble breathing
- 97 • anxiousness
- 98 • low blood pressure
- 99 • dizziness or fainting
- 100 • headache
- 101 • nausea
- 102 • skin rash, redness, or swelling

103 Your healthcare provider will watch you closely while you are receiving BENLYSTA and
104 after your infusion for signs of a reaction.

105 **The most common side effects of BENLYSTA include:**

- 106 • nausea
- 107 • diarrhea
- 108 • fever
- 109 • stuffy or runny nose
- 110 • sore throat
- 111 • cough (bronchitis)
- 112 • trouble sleeping
- 113 • leg or arm pain
- 114 • headache (migraine)
- 115 • urinary tract infection
- 116 • decreased white blood cell count (leukopenia)
- 117 • vomiting
- 118 • stomach pain

119
120 Tell your healthcare provider if you have any side effect that bothers you or that does not go
121 away.

122 These are not all the possible side effects of BENLYSTA. For more information, ask your
123 healthcare provider.

124 Call your doctor for medical advice about side effects. You may report side effects to FDA at
125 1-800-FDA-1088.

126 **General information about the safe and effective use of BENLYSTA**

127 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
128 Do not use BENLYSTA for a condition for which it was not prescribed.

129 This Medication Guide summarizes the most important information about BENLYSTA. For
130 more information about BENLYSTA, talk with your healthcare provider.

131 You can ask your healthcare provider or pharmacist for information about BENLYSTA that is
132 written for healthcare professionals.

133 For more information about BENLYSTA, go to www.BENLYSTA.com or call 1-877-423-6597.

134 **What are the ingredients in BENLYSTA?**

135 **Active ingredient:** belimumab.

136 **Inactive ingredients:** citric acid, polysorbate 80, sodium citrate, sucrose.

137 RX Only

138

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140 GlaxoSmithKline.

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146 Human Genome Sciences, Inc.

147 Rockville, MD 20850



GlaxoSmithKline

Research Triangle Park, NC 27709

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

149 Issued: March 2011

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Benlysta[®]
(belimumab)
For Injection

120 mg/vial

For Intravenous Infusion after dilution only
Single-use vial; Discard unused portion

NDC 49401-101-01

See prescribing information for reconstitution, dilution, and dosage information.

REFRIGERATE: Store at 2° to 8°C (36° to 46° F). Protect from light by storing in original package until use.

Do Not Freeze

Human Genome Sciences

Rockville, MD 20850 USA

US License No. 0000

Rx only

80039 Rev. 001



LOT 000000
EXP XXXXXXX

Benlysta[®]
(belimumab)
For Injection

400 mg/vial

For Intravenous Infusion after dilution only
Single-use vial; Discard unused portion

NDC 49401-102-01

See prescribing information for reconstitution, dilution, and dosage information.

REFRIGERATE: Store at 2° to 8°C (36° to 46° F). Protect from light by storing in original package until use.

Do Not Freeze

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Rockville, MD 20850 USA

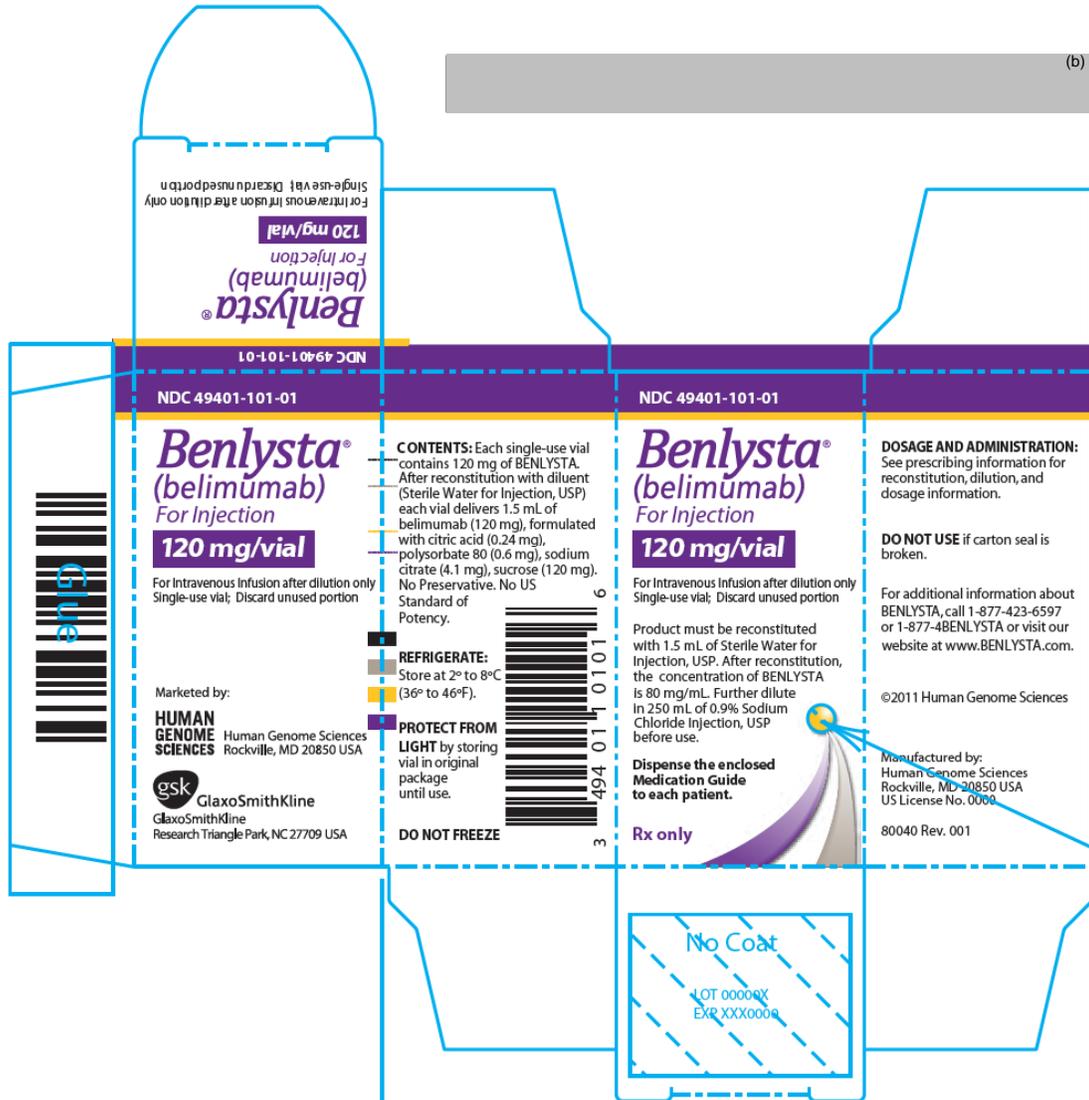
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Rx only

80035 Rev. 001



LOT 000000
EXP XXXXXXX



Single-use vial. Discard unused portion.
 For Intravenous Infusion after dilution only.
120 mg/vial
 For Injection
Benlysta®
 (belimumab)

NDC 49401-101-01

Benlysta®
 (belimumab)
 For Injection
120 mg/vial

For Intravenous Infusion after dilution only
 Single-use vial; Discard unused portion



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 Rockville, MD 20850 USA

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 Research Triangle Park, NC 27709 USA

CONTENTS: Each single-use vial contains 120 mg of BENLYSTA. After reconstitution with diluent (Sterile Water for Injection, USP) each vial delivers 1.5 mL of belimumab (120 mg), formulated with citric acid (0.24 mg), polysorbate 80 (0.6 mg), sodium citrate (4.1 mg), sucrose (120 mg). No Preservative. No US Standard of Potency.

REFRIGERATE:
 Store at 2° to 8°C
 (36° to 46°F).

PROTECT FROM LIGHT by storing vial in original package until use.

DO NOT FREEZE



NDC 49401-101-01

Benlysta®
 (belimumab)
 For Injection
120 mg/vial

For Intravenous Infusion after dilution only
 Single-use vial; Discard unused portion

Product must be reconstituted with 1.5 mL of Sterile Water for Injection, USP. After reconstitution, the concentration of BENLYSTA is 80 mg/mL. Further dilute in 250 mL of 0.9% Sodium Chloride Injection, USP before use.

Dispense the enclosed Medication Guide to each patient.

Rx only

DOSAGE AND ADMINISTRATION: See prescribing information for reconstitution, dilution, and dosage information.

DO NOT USE if carton seal is broken.

For additional information about BENLYSTA, call 1-877-423-6597 or 1-877-4BENLYSTA or visit our website at www.BENLYSTA.com.

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 Rockville, MD 20850 USA
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80040 Rev. 001

No Coat
 LOT 00000X
 EXP XXX0000

Single-use vial; Discard unused portion
For intravenous infusion after dilution only

400 mg/vial
For Injection
Benlysta®
(belimumab)

NDC 49401-102-01

Benlysta®
(belimumab)
For Injection
400 mg/vial

For Intravenous Infusion after dilution only
Single-use vial; Discard unused portion

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Rockville, MD 20850 USA

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Research Triangle Park, NC 27709 USA

CONTENTS: Each single-use vial contains 400 mg of BENLYSTA. After reconstitution with diluent (Sterile Water for Injection, USP) each vial delivers 5 mL of belimumab (400 mg), formulated with citric acid (0.80 mg), polysorbate 80 (2.0 mg), sodium citrate (13.5 mg), sucrose (400 mg). No Preservative. No US Standard of Potency.

REFRIGERATE:
Store at 2° to 8°C (36° to 46°F).

PROTECT FROM LIGHT by storing vial in original package until use.

DO NOT FREEZE

Benlysta®
(belimumab)
For Injection
400 mg/vial

For Intravenous Infusion after dilution only
Single-use vial; Discard unused portion

Product must be reconstituted with 4.8 mL of Sterile Water for Injection, USP. After reconstitution, the concentration of BENLYSTA is 80 mg/mL. Further dilute in 250 mL of 0.9% Sodium Chloride Injection, USP before use.

Dispense the enclosed Medication Guide to each patient.

Rx only

DOSAGE AND ADMINISTRATION:
See prescribing information for reconstitution, dilution, and dosage information.

DO NOT USE if carton seal is broken.

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LOT 00000X
EXP XXX000

