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

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.4) 3/2012

----------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 and fatal 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 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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. BENLYSTA has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of BENLYSTA is not recommended in these situations.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Schedule

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

The 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. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a serious hypersensitivity reaction *[see Contraindications (4), Warnings and Precautions (5.4)]*.

2.2 Premedication Recommendations

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

2.3 Preparation of Solutions

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

Reconstitution Instructions

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

the reconstituted solution from sunlight.

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

Dilution Instructions

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

2.4 Administration Instructions

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

3 DOSAGE FORMS AND STRENGTHS

Single-use vials of belimumab lyophilized powder for injection:

- 120 mg per vial
- 400 mg per vial

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Mortality

There were more deaths reported with BENLYSTA than with placebo during the controlled period of the clinical trials. Out of 2133 patients in 3 clinical trials, a total of 14 deaths occurred

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

5.2 Serious Infections

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

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

5.3 Malignancy

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

5.4 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis and death, have been reported in association with BENLYSTA. Delay in the onset of acute hypersensitivity reactions has been observed. Limited data suggest that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. In the controlled clinical trials, hypersensitivity reactions (occurring on the same day of infusion) were reported in 13% (191/1458) of patients receiving BENLYSTA and 11% (76/675) of patients receiving placebo. Anaphylaxis was observed in 0.6% (9/1458) of patients receiving BENLYSTA and 0.4% (3/675) of patients receiving placebo. Manifestations included hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea. Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases *[see Warnings and Precautions (5.5)]*. Some patients (13%) received premedication, which may have mitigated or

masked a hypersensitivity response; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions.

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

5.5 Infusion Reactions

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

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

5.6 Depression

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

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

5.7 Immunization

Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving BENLYSTA or the effect of BENLYSTA on new immunizations. Because of its mechanism of action, BENLYSTA may interfere with the response to immunizations.

5.8 Concomitant Use with Other Biologic Therapies or Intravenous Cyclophosphamide

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

6 ADVERSE REACTIONS

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

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

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

6.1 Clinical Trials Experience

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

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

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

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

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

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

Table 1. Incidence of Adverse Reactions Occurring in at Least 3% of Patients Treated With BENLYSTA 10 mg/kg Plus Standard of Care and at Least 1% More Frequently Than in Patients Receiving Placebo plus 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

6.2 Immunogenicity

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

The data reflect the percentage of patients whose test results were positive for antibodies to belimumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to belimumab with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of BENLYSTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Fatal anaphylaxis *[see Warnings and Precautions (5.4)]*.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

8.3 Nursing Mothers

It is not known whether BENLYSTA is excreted in human milk or absorbed systemically after ingestion. However, belimumab was excreted into the milk of cynomolgus monkeys. Because maternal antibodies are excreted in human breast milk, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of breastfeeding to the infant and the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Race

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

10 OVERDOSAGE

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

11 DESCRIPTION

BENLYSTA (belimumab) is a human IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

In Trial 1 and Trial 2 in which B cells were measured, treatment with BENLYSTA significantly reduced circulating CD19+, CD20+, naïve, and activated B cells, plasmacytoid cells, and the SLE B-cell subset at Week 52. Reductions in naïve and the SLE B-cell subset were observed as early as Week 8 and were sustained to Week 52. Memory cells increased initially and slowly declined toward baseline levels by Week 52. The clinical relevance of these effects on B cells has not been established.

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

12.3 Pharmacokinetics

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

Table 2. Population Pharmacokinetic Parameters in Patients with SLE after Intravenous Infusion of BENLYSTA 10 mg/kg[1]

Pharmacokinetic Parameter	Population Estimates (n = 563)
Peak concentration (C_{max}, μg/mL)	313
Area under the curve ($AUC_{0-\infty}$, day●μg/mL)	3,083
Distribution half-life ($t_{½}$, days)	1.75
Terminal half-life ($t_{½}$, days)	19.4
Systemic clearance (CL, mL/day)	215
Volume of distribution (Vss, L)	5.29

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

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

Special Populations:

The following information is based on the population pharmacokinetic analysis.

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

14 CLINICAL STUDIES

The safety and effectiveness of BENLYSTA were evaluated in three randomized, double-blind, placebo-controlled studies involving 2133 patients with SLE according to the American College of Rheumatology criteria (Trial 1, 2, and 3). Patients with severe active lupus nephritis and severe active CNS lupus were excluded. Patients were on a stable standard of care SLE treatment regimen comprising any of the following (alone or in combination): corticosteroids,

antimalarials, NSAIDs, and immunosuppressives. Use of other biologics and intravenous cyclophosphamide were not permitted.

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

Trial 1 enrolled 449 patients and evaluated doses of 1, 4, and 10 mg/kg BENLYSTA plus standard of care compared with placebo plus standard of care over 52 weeks in patients with SLE. Patients had to have a SELENA-SLEDAI score of ≥4 at baseline and a history of autoantibodies (anti-nuclear antibody (ANA) and/or anti-double-stranded DNA (anti-dsDNA), but 28% of the population was autoantibody negative at baseline. The co-primary endpoints were percent change in SELENA-SLEDAI score at Week 24 and time to first flare over 52 weeks. No significant differences between any of the BENLYSTA groups and the placebo group were observed. Exploratory analysis of this study identified a subgroup of patients (72%), who were autoantibody positive, in whom BENLYSTA appeared to offer benefit. The results of this study informed the design of Trials 2 and 3 and led to the selection of a target population and indication that is limited to autoantibody-positive SLE patients.

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

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

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

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

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

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

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

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

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

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% (p = 0.104)	43% (p = 0.021)	44%	51% (p = 0.013)	58% (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%

[1]Patients dropping out of the study early or experiencing certain increases in background medication were considered as failures in these analyses. In both studies, a higher proportion of placebo patients were considered as failures for this reason as compared to the BENLYSTA groups.
[2]The 1 mg/kg dose is not recommended.

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

Effect in Black/African-American Patients:
Exploratory sub-group analyses of SRI response rate in patients of black race were performed. In Trial 2 and Trial 3 combined, the SRI response rate in black patients (N=148) in the BENLYSTA groups was less than that in the placebo group (22/50 or 44% for placebo, 15/48 or 31% for BENLYSTA 1 mg/kg, and 18/50 or 36% for BENLYSTA 10 mg/kg). In Trial 1, black patients (N=106) in the BENLYSTA groups did not appear to have a different response than the rest of the study population. Although no definitive conclusions can be drawn from these subgroup analyses, caution should be used when considering BENLYSTA treatment in black/African-American SLE patients.

Effect on Concomitant Steroid Treatment:
In Trial 2 and Trial 3, 46% and 69% of patients, respectively, were receiving prednisone at doses > 7.5 mg/day at baseline. The proportion of patients able to reduce their average prednisone dose

by at least 25% to ≤7.5 mg/day during Weeks 40 through 52 was not consistently significantly different for BENLYSTA relative to placebo in both trials. In Trial 2, 17% of patients receiving BENLYSTA 10 mg/kg and 19% of patients receiving BENLYSTA 1 mg/kg achieved this level of steroid reduction compared with 13% of patients receiving placebo. In Trial 3, 19%, 21%, and 12% of patients receiving BENLYSTA 10 mg/kg, BENLYSTA 1 mg/kg, and placebo, respectively, achieved this level of steroid reduction.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Advice for the Patient

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

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

Serious Infections: Patients should be advised that BENLYSTA may decrease their ability to fight infections. Patients should be asked if they have a history of chronic infections and if they are currently on any therapy for an infection *[see Warnings and Precautions (5.2)]*. Patients

should be instructed to tell their healthcare provider if they develop signs or symptoms of an infection.

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

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

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

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

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Rockville, Maryland 20850
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Human Genome Sciences, Inc.
Rockville, MD 20850

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GlaxoSmithKline
Research Triangle Park, NC 27709

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.

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.

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

   - fever
   - chills
   - pain or burning with urination
   - urinating often
   - bloody diarrhea
   - coughing up mucus

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

   - chest discomfort or pain
   - shortness of breath
   - cold sweats
   - nausea
   - dizziness
   - discomfort in other areas of the upper body

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

   - thoughts of suicide or dying
   - attempt to commit suicide
   - trouble sleeping (insomnia)
   - new or worse anxiety
   - new or worse depression
   - acting on dangerous impulses
   - other unusual changes in your behavior or mood
   - thoughts of hurting yourself or others

What is BENLYSTA?

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

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

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

- It is not known if BENLYSTA is safe and effective in children.

Who should not receive BENLYSTA?

Do not receive BENLYSTA if you:

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

What should I tell my healthcare provider before receiving BENLYSTA?

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

- think you have an infection or have infections that keep coming back. You should not receive BENLYSTA if you have an infection unless your healthcare provider tells you to. **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 are receiving BENLYSTA, you should not receive live vaccines.
- are allergic to other medicines
- are receiving other biologic medicines, monoclonal antibodies or IV infusions of cyclophosphamide (Cytoxan®)
- 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 unborn baby. Tell your healthcare provider if you become pregnant during your treatment with BENLYSTA.

- If you become pregnant while receiving BENLYSTA, talk to your healthcare provider about enrolling in the BENLYSTA Pregnancy Registry. You can enroll in this registry by calling 1-877-681-6296. The purpose of this registry is to monitor the health of you and your baby.
- are breastfeeding or plan to breastfeed. It is not known if BENLYSTA passes into your breast milk. You and your healthcare provider should decide if you will receive BENLYSTA or breastfeed. You should not do both.

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

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

How will I receive BENLYSTA?

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

What are the possible side effects of BENLYSTA?

BENLYSTA can cause serious side effects.

- **See "What is the most important information I should know about BENLYSTA?"**

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

- **Allergic (hypersensitivity) and infusion reactions.** Serious allergic or infusion reactions can happen on the day of or the day after receiving BENLYSTA and may cause death. Tell your healthcare provider right away if you have any of the following symptoms of an allergic or infusion reaction:

  - itching
  - swelling of the face, lips, mouth, tongue, or throat
  - trouble breathing

- anxiousness
- low blood pressure
- dizziness or fainting
- headache
- nausea
- skin rash, redness, or swelling

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

The most common side effects of BENLYSTA include:

- nausea
- diarrhea
- fever
- stuffy or runny nose
- sore throat
- cough (bronchitis)
- trouble sleeping
- leg or arm pain
- headache (migraine)
- urinary tract infection
- decreased white blood cell count (leukopenia)
- vomiting
- stomach pain

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 BENLYSTA. For more information, ask your healthcare provider.

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

General information about the safe and effective use of BENLYSTA

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

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

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

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

What are the ingredients in BENLYSTA?

Active ingredient: belimumab.
Inactive ingredients: citric acid, polysorbate 80, sodium citrate, sucrose.

RX Only

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

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