

Brand Name: Benlysta

Generic Name: belimumab

Manufacturer³: Human Genome Sciences, Inc.

Drug Class^{1,2,3,4,5}: Musculoskeletal Agent, Disease-Modifying Antirheumatic Drug; Monoclonal Antibody, Immunological Agent

Uses:

Labeled Uses^{1,2,3,4,5}: Treatment of active, autoantibody-positive (antinuclear antibody [ANA] and/or anti-double-stranded DNA [anti-ds-DNA], systemic lupus erythematosus (SLE) in combination with standard therapy in adult patients.

Unlabeled Uses: None

Mechanism of Action^{1,2,3,4,5}: Belimumab is an IgG1 λ monoclonal antibody. B lymphocyte stimulator (BLyS), a soluble B-cell survival factor, binds to B-cell receptors to allow B-cell survival. Belimumab works to inhibit BLyS, thus preventing BLyS from binding to B-cell receptors. Therefore, survival of B-cells, including auto reactive B-cells, is inhibited and B-cell differentiation into immunoglobulin-producing plasma cells is reduced as well as B-cell mediated immunity activity and the autoimmune response.

Pharmacokinetics^{1,2,3,4,5}:

Pharmacokinetic Parameter	
Peak Concentration (C_{max})	313 $\mu\text{g/ml}$
Area Under the Curve	3,083 $\text{day}\cdot\mu\text{g/ml}$
Distribution Half-Life	1.75 days
Terminal Half-Life	19.4 days
Systemic Clearance	215 mL/day
Volume of Distribution	5.29 L

Onset: Effects observed as early as 8 weeks after onset.

Elimination⁶: Renal clearance is not expected to be a major component of belimumab's overall clearance.

Efficacy:

Furie R, Stohl W, Ginzler EM, Becker M, Mishra N, Chatham W, Merrill JT, Weinstein A, McCune WJ, Zhong J, Cai W, Freimuth W. Biologic Activity and Safety of Belimumab, A Neutralizing Anti-B-Lymphocyte Stimulator (BLyS) Monoclonal Antibody: A Phase I Trial in Patients with Systemic Lupus Erythematosus. Arthritis Res Ther. 2008;10(5): R109.

Study Design: Multicenter, double-blind, placebo-controlled, dose-escalation study

Description of Study: 70 patients with mild/moderate systemic lupus erythematosus (SLE) were randomized to receive placebo (n=13) or belimumab 1 mg/kg, 4 mg/kg, 10 mg/kg and 20 mg/kg (n=57) as a single infusion or two infusions 21 days apart. Study duration was 15 weeks. Primary outcomes included the SELENA-SLEDAI, Flare Index, and the Physician's Global Disease

Assessment (PGA). The incidence of adverse events was similar in the placebo and belimumab groups. The percentage reduction in CD20⁺ B cells was greater in patients treated with belimumab than in those treated with placebo. Overall, there was a trend toward reduced SELENA-SLEDAI scores in both belimumab and placebo groups and there were no significant differences between belimumab and placebo treatment groups in SELENA-SLEDAI scores or flare rates.

Limitations: This study was limited by a small number of patients and a short treatment duration. Several of the study authors are employees of Human Genome Sciences, the manufacturer of belimumab, and Human Genome Sciences also provided funding for the study. The study patients were largely female and did not include children or many elderly patients.

Conclusion: This study demonstrated that belimumab was biologically active and safely administered to patients with SLE. There was not a significant improvement in SELENA-SLEDAI scores, PGA or SLE Flare Index in patients treated with belimumab, but that would be expected due to the short duration of the study. More studies are needed to determine the long term efficacy of belimumab as well as the specific patient populations which may benefit from belimumab.

Wallace DJ, Stohl W, Furie RA, Lisse JR, McKay JD, Merrill JT, Petri MA, Ginzler EM, Chatham WW, McCune WJ, Fernandez V, Chevrier MR, Zhong ZJ, Freimuth WW. A Phase II, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Belimumab in Patients with Active Systemic Lupus Erythematosus. *Arthritis Rheum.* 2009;61: 1168-78.

Study Design: Multicenter, double-blind, placebo-controlled, parallel group study

Description of Study: 449 patients with a SELENA-SLEDAI score of ≥ 4 were randomized to receive belimumab 1 mg/kg, 4 mg/kg or 10 mg/kg (n=336) or placebo (n=113). Patients received selected treatment by intravenous infusion over 2 hours on days 0, 14 and 28, and then every 28 days for 52 weeks along with standard of care for SLE. The co-primary efficacy endpoints included the percent change in the SELENA-SLEDAI score from baseline to week 24 and the time to first mild/moderate or severe flare as defined by the SFI during 52 weeks. Primary endpoint analysis was analyzed using an intent-to-treat population. There were no significant differences between any of the belimumab treatment groups and the placebo group with regard to the percent change in the SELENA-SLEDAI scores from baseline to weeks 24 or 52. Mean percent changes in SELENA-SLEDAI scores were -19.5% for the combined belimumab groups versus -17.2% for the placebo group at week 24 and -27.2% for the combined belimumab groups versus -20.6% for the placebo group at week 52, which were not significantly different. There was no significant difference in time to first SFI-defined flare over 52 weeks between the combined belimumab groups and the placebo group (67 versus 83 days, respectively).

Limitations: The study may have been confounded by allowing unlimited changes to prednisone and immunosuppressive medications throughout the trial. There are also limitations with the scales used to assess response to treatment because using the same scales to show improvement and worsening could be problematic. The study was funded by the manufacturer of belimumab.

Conclusion: This study, while not showing any significant difference between treatment and placebo groups, did show a much higher response to belimumab in patients who were serologically active at baseline. There was also evidence to show that belimumab may have

more of a sustained response as treatment duration continues. This trial provided insight into further study design for belimumab. Belimumab was well-tolerated throughout the trial and more research is needed to determine response in certain subsets of patients, such as those who are serologically positive for SLE.

Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, Li EKM, Thomas M, Kim HY, Leon MG, Tanasescu C, Nasonov E, Lan JL, Pineda L, Zhong ZJ, Freimuth W, Petri MA. Efficacy and Safety of Belimumab in Patients with Active Systemic Lupus Erythematosus: A Randomised, Placebo-Controlled, Phase 3 Trial. *Lancet*. 2011;377: 721-31.

Study Design: Multicenter, double-blind, placebo-controlled, parallel group study

Description of Study: 867 patients who were seropositive with scores of ≥ 6 on the SELENA-SLEDAI were randomized to receive belimumab 1 mg/kg (n=289), 10 mg/kg (n=290) or placebo (n=287) by intravenous infusion on days 0, 14, and 28, and then every 28 days until 48 weeks. Patients were on a stable standard of care treatment regimen for SLE. The primary efficacy endpoint was the response rate at week 52. Analysis was based on the intent-to-treat population. After 52 weeks of treatment, the SLE responder index response rate for patients receiving belimumab 1 mg/kg was 51% (p=0.0129), 58% (p=0.0006) for patients receiving 10 mg/kg and 44% for patients receiving placebo. 53% (p=0.0181) and 58% (p=0.0024) of patients receiving belimumab 1 mg/kg and 10 mg/kg, compared to 46% of patients receiving placebo, achieved a reduction in SELENA-SLEDAI ≥ 4 . 79% (p=0.1064) and 81% (p=0.0181) of patients receiving belimumab 1 mg/kg and 10 mg/kg had no worsening by BILAG index as opposed to 73% of patients receiving placebo. 79% (p=0.0078) of patients receiving belimumab 1 mg/kg and 80% (p=0.0048) of patients receiving belimumab 10 mg/kg had no worsening of PGA score compared to 69% of patients receiving placebo. Rates of adverse events were similar in the groups given belimumab 1 mg/kg, 10 mg/kg and placebo.

Limitations: The study was conceived, designed, implemented and supervised by Human Genome Sciences, the manufacturer of belimumab. The study population was >90% women and the study did not include patients < 18 years of age. Limited numbers of patients > 65 years were studied.

Conclusion: The 10 mg/kg dose of belimumab does appear to significantly reduce the SLE responder index score compared to patients receiving placebo after 52 weeks of treatment, but the 1 mg/kg dose was not significantly more beneficial than placebo and is not recommended for treatment in patients with SLE. However, the drug does not appear to be beneficial in certain subsets, such as in African American patients. An additional phase III trial for belimumab did not show any significant difference between belimumab and placebo treatment groups after 76 weeks. More research needs to be done to determine the role of belimumab in other populations, such as children and the elderly. Belimumab has not been studied in patients with CNS lupus or active lupus nephritis so the results from this study cannot be applied to patients with those conditions. From this study, it appears that belimumab has promise as a new agent for SLE, but more research is ultimately needed.

Contraindications^{1,2,3,4,5}:

Belimumab-Related Hypersensitivity: Belimumab is contraindicated in patients with a history of hypersensitivity to belimumab or any component of the formulation due to potential for anaphylaxis.

Precautions^{1,2,3,4,5}:

African-American Patients: In a clinical trial, an exploratory subgroup analysis suggested that African-American patients did not respond to belimumab. In another trial, African-American patients did not seem to respond any differently from other study populations. Belimumab should be used cautiously in African-American patients.

Breast-Feeding: Belimumab has been identified in the breast milk of cynomolgus monkeys; however, it is unknown if belimumab is excreted in human milk or absorbed systemically after ingestion. Maternal antibodies are excreted in human milk. A decision should be made as to whether breast feeding should be discontinued or if belimumab should be discontinued during lactation. According to the Thomson Lactation Rating, infant risk cannot be ruled out.

Cardiac Disease: It is unclear if patients with cardiac disease are at an increased risk with belimumab therapy. However, cautious use of belimumab in patients with cardiac disease may be warranted. In clinical trials, there was a small increase in death with belimumab than with placebo. Patients with cardiac disease may also experience hypersensitivity or an infusion reaction that may be poorly tolerated with belimumab.

Depression: There was an increase in psychiatric events seen in patients who received belimumab during clinical trials. Most patients who reported serious depression during the trials also reported a history of depression or other psychiatric disorders, and most were not receiving psychoactive medication. Patients who experience depression, suicidal ideation or mood changes while receiving belimumab should contact their healthcare provider. Belimumab should be used cautiously in patients with pre-existing depression.

Fertility Impairment: Effects on male and female fertility have not been directly evaluated.

Immunosuppression: Serious and potentially fatal infections have been reported in patients receiving immunosuppressives, including belimumab. Patients with immunosuppression may be more susceptible to acquiring infection.

Infection: Use caution when considering initiation of belimumab in patients with a chronic infection. Consider an interruption in therapy if patients develop a new infection while receiving belimumab.

Infusion Reactions: Infusion-related reactions have been associated with belimumab, including angioedema and anaphylaxis, which warrant discontinuation of the infusion. Infusion rate may be slowed or temporarily interrupted for minor reactions. Most reactions occur within 24 hours of the infusion and include headache, nausea, rash and skin reactions. Less common reactions may include hypotension, dyspnea, bradycardia, and myalgia.

Mortality: More deaths have been reported with belimumab than with placebo in controlled, clinical trials. No single cause of death predominated; however, etiologies included cardiovascular disease, infection and suicide.

Pregnancy: Belimumab is classified as FDA pregnancy risk category C and belimumab should only be used during pregnancy if the potential benefit to the mother outweighs the potential risk to the fetus. There are no adequate and well-controlled studies of belimumab in pregnant

women; however, immunoglobulin G antibodies, including belimumab, do cross the placenta. Women of childbearing potential should use adequate contraception while receiving belimumab and for at least four months after the final treatment with belimumab. A pregnancy registry has been established for pregnant women who receive belimumab in order to monitor maternal-fetal outcomes. Healthcare professionals are encouraged to enroll patients by calling 1-877-681-6296 and pregnant women may register themselves.

Requires An Experienced Clinician: Due to the possibility of anaphylaxis and infusion reactions, an experienced clinician is required to monitor belimumab administration. All patients should be monitoring during and after belimumab administration for an adequate duration. Pre-medication should be considered in patients receiving belimumab. If a patient experiences a serious hypersensitivity reaction, belimumab should be discontinued immediately and the patient should be treated accordingly. Patients and caregivers should be advised of the signs and symptoms of hypersensitivity and should be made aware that hypersensitivity reactions may present as infusion reactions. If a patient does develop symptoms, medical attention should be sought.

Malignancy: Leukemia has been reported in patients receiving belimumab. Patients who receive belimumab may be at an increased risk for malignancy due to the mechanism of action of belimumab. Belimumab should be used cautiously in patients with pre-existing cancer or a history of cancer. The exact impact of belimumab on malignancy is currently unknown.

Suicidal Ideation: Belimumab should be used cautiously in patients with pre-existing suicidal ideation or other psychiatric disorder. Most patients who reported suicidal ideation during clinical trials had a history of depression or other psychiatric disorders, most of who were not receiving psychoactive medications. Patients who experience depression, suicidal ideation or mood changes while receiving belimumab should contact their healthcare provider.

Systemic Lupus Erythromatus Appropriate Use: Belimumab has not been studied in patients with severe active lupus nephritis or CNS lupus and use in these patient populations is not recommended.

Adverse Effects^{2,3,4,5}:

Occurring in > 10% of patients

Gastrointestinal:

Nausea (15%)

Diarrhea (12%)

Immunologic Effects

Complication of Infusion (17%)

Immune Hypersensitivity Reaction (13%)

Occurring in ≤3% to 10%

Central Nervous System:

Pyrexia (10%)

Insomnia (7%)

Migraine (5%)

Depression (5%)

Anxiety (4%)

Gastrointestinal:

Viral Gastroenteritis (3%)

Genitourinary:

Cystitis (4%)

Hematologic:

Leukopenia (4%)

Neuromuscular & Skeletal:

Pain in extremity (6%)

Respiratory:

Bronchitis (9%)

Nasopharyngitis (9%)

Pharyngitis (5%)

< 3%, postmarketing, and/or case reports: Angioedema, antibody formation, bradycardia, cellulitis, dyspnea, eyelid edema, headache, hypersensitivity reactions, hypotension, influenza, myalgia, pneumonia, pruritis, upper respiratory infection, rash, sinusitis, urinary tract infection, urticaria, cellulitis, pneumonia, upper respiratory tract infection, death

Drug Interactions^{1,2,3,4,5}:

Abatacept

Abatacept may enhance the adverse/toxic effect of belimumab and the combination should be avoided.

Abciximab

Abciximab may enhance the potential for allergic or hypersensitivity reactions and may also cause thrombocytopenia or diminished therapeutic effects. Monitor therapy if Abciximab is to be administered with belimumab.

Alefacept

Alefacept may enhance the adverse/toxic effect of belimumab and the combination should be avoided.

BCG

Belimumab may diminish the therapeutic effect of BCG and the combination should be avoided.

Belatacept

Belatacept may enhance the adverse/toxic effect of belimumab and the combination should be avoided.

Coccidioidin Skin Test

Belimumab may diminish the diagnostic effect of the Coccidioidin Skin Test and therapy should be monitored.

Cyclophosphamide

Belimumab has not been formally studied in combination with other biologic therapies and is not recommended in combination with intravenous cyclophosphamide.

Denileukin Diftitox

Denileukin Diftitox may enhance the adverse/toxic effect of belimumab and the combination should be avoided.

Denosumab

Denosumab, in combination with belimumab, may increase the risk for infections. Therapy should be monitored.

Echinacea

Echinacea may diminish the therapeutic effect of belimumab and a therapy modification should be considered.

Etanercept

Etanercept may enhance the adverse/toxic effect of belimumab and the combination

should be avoided.

Leflunomide

Belimumab, in combination with Leflunomide, may increase the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. In patients receiving belimumab, consider not using a loading dose of Leflunomide. Patients receiving both belimumab and Leflunomide should be monitored for bone marrow suppression at least once a month and a therapy modification should be considered.

Monoclonal Antibodies

Monoclonal antibodies may enhance the adverse/toxic effect of belimumab and the combination should be avoided.

Natalizumab

Belimumab, in combination with Natalizumab, may increase the risk for concurrent infection and the combination should be avoided.

Pimecrolimus

Pimecrolimus may enhance the adverse/toxic effect of belimumab and the combination should be avoided.

Roflumilast

Roflumilast may enhance the immunosuppressive effect of belimumab and a therapy modification should be considered.

Sipuleucel-T

Belimumab may diminish the therapeutic effect of Sipuleucel-T and therapy should be monitored when both drugs are used in combination.

Tacrolimus (Topical)

Tacrolimus may enhance the adverse/toxic effect of belimumab and the combination should be avoided.

Trastuzumab

Trastuzumab may enhance the neutropenic effect of belimumab and therapy should be monitored when both drugs are used in combination.

Ofatumumab

Belimumab has not been formally studied in combination with other biologic therapies, including B-cell targeted therapies, and is therefore not recommended to be used in combination with ofatumumab.

Rituximab

Belimumab has not been formally studied in combination with other biologic therapies, including B-cell targeted therapies, and is therefore not recommended to be used in combination with rituximab.

Vaccines (Inactivated)

Belimumab may diminish the therapeutic effect of inactivated vaccines and a therapy modification should be considered. If both belimumab and an inactivated vaccine are both to be administered, therapy should be monitored.

Vaccines (Live)

Clinical safety of vaccine administration with belimumab has not been established. It is not recommended for patients receiving belimumab to be administered live vaccines concurrently or 30 days prior to therapy initiation and for at least three months after belimumab is administered. Vaccinial infections may develop if co-administered. The mechanism of action of belimumab may interfere with immunization response.

Dosing/Administration^{1,2,3,4,5}:

Adult Dosing

Initial Dose: 10 mg/kg IV over 1 hour every 2 weeks for the first 3 doses

Maintenance Dose: 10 mg/kg IV over 1 hour every 4 weeks

Pediatrics

Belimumab has not been studied in patients less than 18 years of age. Safety and efficacy has not been studied in this patient population.

Elderly

Initial Dose: 10 mg/kg IV over 1 hour every 2 weeks for the first 3 doses

Maintenance Dose: 10 mg/kg IV over 1 hour every 4 weeks

Use cautiously in patients greater than 65 years of age as safety and efficacy has not been adequately studied in that patient population to determine variations in response.

Renal Impairment

Specific guidelines for dosing in patients with creatinine clearance less than or equal to 15 mL/minute are not available as dosing has not been studied in patients with creatinine clearance less than or equal to 15 mL/minute. It appears that no dosage adjustments are necessary.

Hepatic Impairment

Specific guidelines for dosing in patients with hepatic impairment are not available as dosing in hepatic impairment has not been studied. It appears that no dosage adjustments are necessary.

Administration^{2,3,4,5}: IV

Administer the diluted belimumab solution intravenously over 1 hour through a dedicated I.V. line. Do not give as I.V. push or bolus. Consider pre-medicating patients prior to infusion to attenuate infusion reactions. The infusion may be slowed or temporarily interrupted for minor infusion reactions. Belimumab should be administered by healthcare professionals to manage anaphylaxis. In the event of severe hypersensitivity reactions, such as angioedema or anaphylaxis, the infusion should be discontinued immediately. Belimumab should not be infused concomitantly with other agents in the same intravenous line as compatibility studies have not been conducted.

Storage^{2,3,4,5}:

Vials may be 5 mL, containing 120 mg of belimumab, or 20 mL, containing 400 mg of belimumab. Avoid sunlight and store vials in the original carton until use. Do not freeze. Avoid heat. Prior to reconstitution, store vials between 2° and 8°C (36° to 46°F).

Reconstitution^{2,3,4,5}:

Belimumab is available as a lyophilized powder in a single dose vial for intravenous infusion and should be reconstituted and diluted by a healthcare professional using aseptic technique. Prior to reconstitution, allow unused vial to stand for 10-15 minutes in order to reach room temperature. Reconstitute 120 mg vial with 1.5 mL of Sterile Water For Injection, USP and 400 mg vial with 4.8 mL Sterile Water For Injection, USP. Aim the stream of sterile water toward the side of the vial to minimize foaming. Gently swirl, but do not shake, the vial for 60 seconds every 5 minutes until all powder is dissolved, typically 10-15 minutes total but potentially up to 30 minutes. Mechanical reconstitution devices (swirlers) should not exceed 500 rpm and should not be used for longer than 30 minutes. Once the reconstitution is complete, the solution should be opalescent and colorless to pale yellow, without particles. Further dilute reconstituted solution in 250 mL of 0.9% Sodium Chloride, USP by first removing and discarding the volume equivalent to the volume of the reconstituted solution to be added to prepare the appropriate dose. Add the appropriate volume of the reconstituted solution and invert to mix solution. The reconstituted solution will contain a concentration of belimumab 80 mg/mL. Protect from sunlight. The solution may be stored at room temperature or it may be refrigerated. Storage time, including

infusion to the patient, must be completed within 8 hours of reconstitution. No incompatibilities between belimumab and polyvinylchloride or polyolefin bags have been observed.

IV Compatibility^{1,2,3,4,5}

Belimumab is compatible for dilution with Sodium Chloride 0.9%, but is not compatible with D5W, D5LR, D5 ¼ NS, D5 ½ NS or D5NS.

Conclusion: Belimumab is a modestly effective agent for patients with active, seropositive Systemic Lupus Erythematosus (SLE) receiving standard treatment. There may be limitations with belimumab use in certain patient populations, such as in African American patients. More studies need to be conducted in order to assess efficacy and safety of belimumab in children, elderly patients, males, patients with renal impairment and patients with hepatic impairment. Belimumab appears to be relatively safe, but does require an experienced clinician for administration due to potential for serious infusion reactions. Drug interactions with belimumab have not been extensively studied and therefore more research is also needed in that area. Studies to determine the usage of belimumab in other autoimmune disorders, such as rheumatoid arthritis, should also be conducted. Due to the mechanism of action of belimumab, long-term monitoring is necessary to determine the incidence of malignancy, infection and other potentially serious consequences of therapy. Belimumab is the first new FDA approved agent for SLE in over 50 years. Due to minimal drug interactions and modest efficacy in certain patient subsets, it does show promise as an additional agent for SLE if other options have not shown efficacy.

Recommended References:

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3. Benlysta [package insert]. Rockville, MD: Human Genome Sciences, Inc.; 2011.
4. Belimumab. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed November 1, 2011.
5. Belimumab Injection. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: <http://online.factsandcomparisons.com> Accessed: November 1, 2011.
6. Furie R, Stohl W, Ginzler EM, Becker M, Mishra N, Chatham W, Merrill JT, Weinstein A, McCune WJ, Zhong J, Cai W, Freimuth W. Biologic Activity and Safety of Belimumab, A Neutralizing Anti-B-Lymphocyte Stimulator (BLyS) Monoclonal Antibody: A Phase I Trial in Patients with Systemic Lupus Erythematosus. *Arthritis Res Ther.* 2008;10(5): R109.
7. Wallace DJ, Stohl W, Furie RA, Lisse JR, McKay JD, Merrill JT, Petri MA, Ginzler EM, Chatham WW, McCune WJ, Fernandez V, Chevrier MR, Zhong ZJ, Freimuth WW. A Phase II, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Belimumab in Patients with Active Systemic Lupus Erythematosus. *Arthritis Rheum.* 2009;61: 1168-78.
8. Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, Li EKM, Thomas M, Kim HY, Leon MG, Tanasescu C, Nasonov E, Lan JL, Pineda L, Zhong ZJ, Freimuth W, Petri MA. Efficacy and Safety of Belimumab in Patients with Active Systemic Lupus Erythematosus: A Randomised, Placebo-Controlled, Phase 3 Trial. *Lancet.* 2011;377: 721-31.

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