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New Drug Evaluation: Belimumab Injection, Intravenous and Subcutaneous

Date of Review: May 2018
Generic Name: belimumab
PDL Class: Biologics for Autoimmune Conditions

End Date of Literature Search: 10/20/2017
Brand Name (Manufacturer): Benlysta® (GlaxoSmithKline)
Dossier Received: No

Research Questions:

1. What is the safety and effectiveness of belimumab in reducing symptoms and improving functional outcomes in patients with systemic lupus erythematosus (SLE)?
2. What are the comparative harms of belimumab in patients with SLE?
3. Are there certain sub-populations in which belimumab may be beneficial or cause more harm?

Conclusions:

- The composite SLE responder index (SRI) was developed by investigators after Phase 2 trials of belimumab failed to show a meaningful reduction in disease activity as assessed by the Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score.[1] Consequently, the researchers developed the composite SRI in an effort to avoid relying on one single index to assess response to belimumab in Phase III trials. The composite SRI tool includes the SELENA-SLEDAI score to address global disease improvement, the British Isles Lupus Assessment Group (BILAG) score to assess organ specific disease worsening or improvement, and the Physician Global Assessment (PGA) tool for items that were not addressed by the other two indices.[1] The SRI was not validated prior to use in the belimumab Phase 3 trials, although it was used as the tool to assess primary efficacy of belimumab in these trials. The use of composite outcomes in the belimumab trials is problematic. The 3 assessments may have overstated the response to therapy, relied on subjective assessments and were inadequately reported. These issues may have led to an overstatement of how well belimumab alleviated symptoms of SLE in clinical trials.
- The efficacy of belimumab for intravenous (IV) administration was evaluated in 2 fair quality, Phase III, randomized controlled studies, BLISS-52 (n=865) and BLISS-76 (n=819), in adult patients with SLE.[2,3] The primary outcome measure was the composite SRI which only required 4 point improvement on a 100 point scale (SELENA-SLEDAI) and no worsening in the BILAG or PGA scores. Of note, the American College of Rheumatology (ACR) has defined minimum improvement on the SELENA-SLEDAI score as a 6 point increase and a 4 point change in this scale was used to assess response in the BLISS trials. In the BLISS-52 trial, the proportion of responders as assessed by the composite SRI, was significantly higher for intravenous belimumab groups than for placebo (44% responders) at 52 weeks (1 mg/kg; 51% responders; Odds Ratio (OR) 1.55; 95% CI 1.1 to 2.2; p = 0.013; ARR = 7%; NNT = 15) and (10 mg/kg; 58% responders, OR 1.8; 95% CI 1.3 to 2.6; p = 0.0006; ARR = 14%; NNT = 8).[2] In the BLISS-76 trial, there was a statistical difference in the percentage of participants achieving SLE response rate at 52 weeks in the belimumab 10 mg/kg group versus placebo (43.2% vs. 33.5%, OR 1.5; 95% CI 1.1 to 2.2; p=0.02; ARR = 9.7%; NNT = 11).[3] No significant difference between belimumab 1 mg/kg and placebo was observed at 52 weeks in the BLISS-76 trial. In the BLISS-76

trial, significance in SLE responder rates was not observed at 76 weeks for either belimumab group when compared to placebo. Six years after the publication the of the IV belimumab studies, the efficacy of subcutaneous (SC) belimumab was evaluated at doses of 200 mg once a week over 52 weeks compared to placebo in 816 subjects.[4] After 52 weeks, 61.4% of patients in the SC belimumab group had clinical improvement based on the SRI compared with 48.4% of participants in the placebo group (OR 1.68; 95% CI 1.25–2.25; p= 0.0006; ARR = 13%, NNT = 8).[4]

- The most common adverse reactions that occurred in greater than 5% of subjects who received belimumab intravenously during Phase II and III clinical trials were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine and pharyngitis.[5] Discontinuation of belimumab therapy due to any adverse reaction was similar in the belimumab (6.2%) and placebo-treatment (7.1%) arms.[5] The most common reasons for discontinuation were infusion reactions, lupus nephritis and infections.[5] In the trials of belimumab SC, local injection site reactions were the most frequently reported adverse effects.[5]
- Patients with severe active lupus nephritis and central nervous system lupus were excluded from all belimumab trials. Belimumab in combination with other biologics or intravenous cyclophosphamide has not been studied in clinical trials. Therefore, the use of belimumab is not recommended in these situations.[5] There is insufficient evidence to assess the impact of belimumab therapy on reducing organ damage or mortality in SLE patients.

Recommendations:

- Designate belimumab as a non-preferred agent with prior authorization (PA) criteria on the on the Practitioner-Managed Prescription Drug Plan (PMPDP).

Background:

SLE is a complex autoimmune connective-tissue disorder that affects the skin, joints, kidneys, heart, lungs, nervous system, and blood vessels. The disease has a wide range of clinical symptoms characterized by unpredictable remissions and relapses. SLE predominately affects women aged 15 and 45 years with a female to male ratio of 9:1.[6] African Americans, Asian Americans, and Hispanics have about a 3 to 4 times higher frequency of lupus than white non-Hispanics and often have more severe disease.[7] Generalized symptoms include fever, fatigue, rash, oral ulceration, hair loss and arthralgia. The hallmarks of SLE include abnormal B lymphocyte function, chronic inflammation, and development of autoantibodies. The ACR developed classification criteria in 1982 to assist in diagnosis of SLE which was updated in 1997.[8] The Systemic Lupus International Collaborating Clinics (SLICC) group revised the ACR criteria in 2012 to improve clinical relevance and incorporate new knowledge regarding SLE.[9] Patients are classified as having SLE if: 1) they satisfy 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least one clinical criterion and one immunologic criterion or 2) if they have biopsy-proven nephritis compatible with SLE in the presence of ANA or anti-dsDNA antibodies.[9] Clinical and immunologic criteria from the SLICC classification are presented in **Table 1**.

Table 1. SLE classification criteria from the Systemic Lupus International Collaborating Clinics (SLICC) [9]

A. Clinical Criteria	B. Immunologic Criteria
Cutaneous Lupus (Acute or Chronic)	ANA level above laboratory reference range
Oral Ulcers	Anti-double stranded (ds)DNA antibody level above laboratory reference range
Alopecia	Anti-Sm antibody to Sm nuclear antigen
Synovitis involving 2 or more joints	Antiphospholipid antibody
Serositis (pleuritis or pericarditis)	Low complement (C3, C4, CH50)
Neurologic symptoms	Direct Coombs test in the absence of hemolytic anemia
Hemolytic anemia	
Leukopenia (<4,000/mm^3 at least once)	
Thrombocytopenia (<100,000/mm3at least once)	

Renal involvement with proteinuria or red blood cell casts	

In the U.S., about 35% of adults with SLE have clinical evidence of nephritis at the time of diagnosis, with an estimated total of 50–60% developing nephritis during the first 10 years of disease.[10] The prevalence of nephritis is significantly higher in African Americans and Hispanics than in whites, and is higher in men than in women.[10] Renal damage is more likely to develop in nonwhite groups. Overall survival in patients with SLE is approximately 95% at 5 years after diagnosis and 92% at 10 years after diagnosis.[11] The presence of lupus nephritis (LN) significantly reduces survival to approximately 88% at 10 years, with even lower survival in African Americans.[11] An ACR task force panel developed guidelines for screening, treatment and management of lupus nephritis in 2012.[12]

Clinical trials have used 3 validated scales to measure disease activity in SLE. The British Isles Lupus Assessment Group (BILAG) developed a disease activity index in 1984 which was updated in 2004.[13] There are 101 items within this index distributed over 9 organ systems (mucocutaneous, neurology, musculoskeletal, cardiorespiratory, vasculitis, renal, abdominal, ophthalmic, and hematology). Disease activity occurring over the past month is compared to the month before in each organ system. The BILAG index is evaluated on an ordinal scale ranging from 0 (symptoms not present), 1 (symptoms improving), 2 (same symptoms), 3 (worse symptoms) or 4 (new symptoms).[13] After recording the scores for each assessment into a computer program, the disease activity is categorized into 5 different levels from A through E which scores patients on the need for need for medication therapy. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of 20 mg daily or higher. Grade B represents moderate disease activity requiring a lower dose of systemic corticosteroids, topical corticosteroids, topical immunosuppressive drugs, antimalarials, or non-steroidal anti-inflammatory drugs (NSAIDs). Grade C indicates mild stable disease, while grade D implies no disease activity but the system had previously been affected and symptoms resolved. Grade E indicates no current or previous disease activity.[14] The maximum score on the BILAG index is 81. The Food and Drug Administration (FDA) has designated the BILAG index as its favored scale to measure SLE response in clinical trials.[15] A major clinical response is defined by the FDA guidance as a patient with BILAG C scores or better after 6 months of therapy with no BILAG A or B scores between 6 and 12 months.[15] Partial clinical response is defined as BILAG C score or better at 6 months with no new BILAG A or B scores and maintenance of response without flare for 4 months.[15]

The SLE Disease Activity Index (SLEDAI) was developed in 1985 through consensus of 15 lupus experts in Toronto and was updated in 2002.[16] It has 24 items for assessment of 9 systems: 16 items involve clinical assessment and 8 items are based on laboratory results such as blood complement levels, increased anti-DNA antibody levels, low platelets or low white blood cell count. Symptoms are recorded if they have been present over the past 10 days regardless of severity or whether the symptom has improved or deteriorated. Unlike the BILAG index, organ involvement is weighted by system: central nervous involvement is multiplied by 8 while joint pain and kidney disease are multiplied by 4. Scoring is based on whether manifestations are present or not present (in a range of 1 to 8) for each of the items. All the individual item scores are added to provide a global score, with a possible maximum score of 105.[16] According to ACR, a clinically meaningful difference in the SLEDAI has been reported to be improvement by 6 points or worsening by 8 points.[17] The SLEDAI was modified in The Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial to the SELENA-SLEDAI system.[18] This modification added clarification to some of the definitions of disease activity, but did not change the basic scoring system.

The Physician Global Assessment (PGA) is a 10-centimeter visual analog scale (VAS) using a 4 point scale for assessment of disease activity over the previous 2 weeks.[19] No flare scores 0 points, mild flare scores 1.0 point, moderate flares score between 2.0 and 2.5 points and severe flares score a 3 on the 0–3 analog scale. An increase of at least 0.3 points (> 10% on the 3 point-VAS) from baseline is considered clinically significant worsening of disease.[19] **Table 2** compares the 3 different assessments used to confirm response to drug therapy in SLE clinical trials.

Table 2. Overview of Different SLE Disease Activity Indices[20]

	PGA	BILAG-2004	SELENA-SLEDAI
Number of Items	1	101	24
Number of Organ Systems	All	9	9
Total Score Range	0-3	0-81	0-105
Review Period	Current	30 days	10 days
Objective/Subjective	Subjective	Both	Objective
Weighted Variables	No	No	Yes
Organ Severity Assessment	No	Yes	Yes
Previous Versions	-	BILAG (1988)	SLEDAI (1992) and SLEDAI-2K (2000)
Advantages	Sensitive to patients overall condition	Organ specific severity score	Easy to apply in general practice
Disadvantages	Physician dependent; semi-quantitative	Time consuming; requires training	Only provides global severity score

Abbreviations: BILAG: British Isles Lupus Assessment Group; PGA: Physician Global Assessment; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index;

The composite Systemic Lupus Erythematosus Responder Index (SRI) was developed based on an exploratory analysis of belimumab in a dose-ranging, phase 2 trial.[21] In this trial, belimumab failed to show a meaningful reduction in disease activity as assessed by the SELENA-SLEDAI score or prevent flares relative to placebo at 24 weeks.[1] Consequently, the researchers developed the composite SRI in an effort to avoid relying on one single index to assess response to SLE therapy in Phase 3 trials. According to the investigators, the intent was to capture clinically meaningful change in response to therapy and insure there would not be significant worsening in overall disease activity.[21] Using the SRI, a responder is defined as having the following response to therapy : 1) at least a 4-point reduction in SELENA-SLEDAI score; 2) no worsening in the BILAG score; and 3) no deterioration from baseline in the PGA score by 0.3 or more points.[21] According to the investigators, in the composite SRI tool the SELENA-SLEDAI score addresses global disease improvement, the BILAG assessment covers organ specific disease worsening, and PGA is used as a safety net for items that were not addressed by the other two indices.[21] The SRI was not validated before it was used in the Phase 3 safety and efficacy belimumab trials. The use of composite outcomes in the belimumab trials is problematic. The 3 assessments overstate the response to therapy, consist of subjective assessments and were inadequately reported. These problems may have led to an overstatement of how well belimumab reduced SLE disease activity in clinical trials.

The goal of SLE treatment is to control the inflammatory reaction and organ damage while minimizing the adverse effects of the treatments. Treatments range from anti-malarial drugs (e.g., hydroxychloroquine), systemic corticosteroids and immunosuppressive agents (e.g., azathioprine, cyclophosphamide). Intravenous administration of belimumab, a monoclonal antibody with activity against B-lymphocytes, was approved by the FDA to manage adult SLE patients with active, autoantibody-positive disease in conjunction with standard of care in 2011. A subcutaneous formulation belimumab was FDA approved in adults for the same indication in 2017. Belimumab has not been studied as a solo agent in treating SLE, nor has it been studied in combination with other biologic agents such as rituximab or cyclophosphamide. Efficacy of belimumab has not been evaluated in patients with severe active lupus nephritis or severe active CNS lupus.

Fee for Service Utilization

As of January 2017 there were no fee for service (FFS) claims for belimumab SC at any Oregon pharmacies. There was one single CCO claim in October 2017. There were no medical claims in 2017 for the IV formulation of belimumab.

Clinical Guidelines: National Institute for Health and Care Excellence (NICE)

NICE published guidance regarding the use of belimumab as an IV infusion for treating active autoantibody-positive SLE in June 2016.[22] For assessment of symptom improvement, NICE adopted similar metrics that were used in the BLISS trials (SELENA-SLEDAI improvement by 4 points or more) instead of the ACR recommendations of improvement in SELENA-SLEDAI greater than 6 points or more. Belimumab is recommended as an option as add-on treatment for active autoantibody-positive SLE in adults only if all of the following apply:

- There is evidence for serological disease activity (defined as positive anti-double stranded DNA and low complement) and a SELENA-SLEDAI score of greater than or equal to 10 despite standard treatment.[22]
- Treatment with belimumab is continued beyond 24 weeks only if the SELENA-SLEDAI score has improved by 4 points or more.[22]

As a condition of these recommendations, the committee recommended re-evaluation in 3 years and that efficacy assessments include:

- clinical response measured by BILAG Index and SLEDAI scoring[22]
- organ damage accrual using the SLICC Damage Index and BILAG Index[22]
- use of corticosteroids[22]

NEW DRUG EVALUATION: Belimumab

See **Appendix 1** for **Highlights of Prescribing Information** of belimumab from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The first biologic agent FDA approved for management of SLE is belimumab, a human monoclonal antibody which binds to the soluble form of B-lymphocyte stimulator (BLyS) and inhibits its biologic activity. BLyS is overexpressed in patients with SLE and its concentrations correlate with disease activity and antibody titers.[23] The binding of BLyS with belimumab results in reduced numbers of circulating B-lymphocytes and a reduction in antibody titers in SLE patients.[23]

The safety and efficacy of belimumab for IV administration was evaluated in 2 Phase 3, randomized controlled studies, BLISS-52 (n=865) and BLISS-76 (n=819), in adult patients with SLE. All patients received standard of care treatment with corticosteroids, antimalarials, NSAIDs, and immunosuppressive agents (azathioprine, methotrexate, and mycophenolate) in combination with either belimumab or placebo. Both studies were multi-center, placebo-controlled, double-blinded trials. The studies excluded patients who had received prior B-cell targeted therapy or IV cyclophosphamide, as well as those with active lupus involving the kidneys or central nervous system. Both studies were conducted in a similar fashion, but on different geographic populations with some baseline demographic differences. BLISS-52 was conducted in Eastern Europe, Latin America and Asia-Pacific regions over 52 weeks. BLISS-76 was conducted in North America, Western Europe and Latin America over 76 weeks. The 2 studies randomly assigned a total of 1,684 patients with auto antibody-positive, active disease (defined as a SELENA-SLEDAI score ≥6) to receive IV belimumab 1 mg/kg or 10 mg/kg plus standard therapy or placebo plus standard therapy in a 1:1:1 ratio. The primary outcome was the proportion of patients who responded to therapy as assessed by the composite SRI at week 52. In both trials, at week 52 more patients treated with belimumab 10 mg/kg met the SRI criteria for improvement in disease activity when compared to placebo-treated patients. In BLISS-52 the response rates were 57.6% (belimumab 10 mg/kg) versus 43.6% (placebo) [OR 1.8; 95% CI 1.3 to 2.6; p=0.0006] and in BLISS-76 the response rates were 43.2% for belimumab 10mg/kg and 33.5% for placebo [OR 1.5; 95% CI 1.1 to 2.2; p=0.02].[24,25] There was no significant difference detected in disease response between belimumab 1 mg/kg and placebo in the BLISS-76 trial at week 52. However, a difference was detected in BLISS-52 between belimumab 1 mg/kg and placebo at week 52 (51.4% vs. 43.6% respectively; OR 1.6; 95% CI 1.1 to 2.2; p= 0.013).[2] At week 76 in the BLISS-76 trial, the differences between doses of belimumab 1mg/kg or 10mg/kg compared to the placebo arm were not statistically significant.[25] Reasons for this finding are unclear although compared to

BLISS-52, the patients in BLISS-76 were older, had a longer duration of SLE, and a higher proportion of patients were white and using prednisone greater than 7.5mg per day at baseline. One suggestion is that patients with longer, more established disease, such as those found in the BLISS-76 trial, may be less responsive to belimumab over time.[25] Based on these trial results, the FDA approved belimumab dosing as 10mg/kg via IV infusion at 2 week intervals for the first 3 doses followed by every 4 weeks thereafter.[5]

The efficacy of SC belimumab was evaluated at doses of 200 mg once a week which yielded target plasma concentrations similar to administration of belimumab 10mg/kg IV every 4 weeks.[4] This clinical trial was conducted over 52 weeks at 177 sites in North, Central and South America, Europe, Australia and Asia. Seventy percent of the sites were based outside of the U.S. A total of 816 patients were randomized 2:1 to SC belimumab (n = 544) or placebo (n=272) in adults with active SLE continuing standard therapy. The inclusion criteria for this study required a SELENA–SLEDAI score of 8 or higher at screening, whereas the IV BLISS-52 and BLISS-76 studies required a SELENA–SLEDAI score of 6 or higher. This requirement for a higher SELENA–SLEDAI was driven by data from the IV studies that highlighted that patients needed a higher level of disease activity at baseline in order to have the opportunity to achieve the 4-point reduction on the 100 point SELENA–SLEDAI scale needed to meet the SRI end point.[4] Patients with severe kidney disease or CNS lupus were excluded. The primary endpoint was the composite SRI response rate at week 52, which was a weak definition of response as previously described. More patients who received SC belimumab 200 mg once a week were SRI responders at week 52 than those who received placebo ([61.4% versus 48.4% respectively; OR 1.68; 95% CI 1.25–2.25]; p=0.0006; NNT = 8).[4] A secondary endpoint was the number of patients with reduction in corticosteroid dosage. No statistical difference could be found in the number of patients able to reduce their corticosteroid dosage by more than 25% (to less than 7.5mg per day) during weeks 40 through 52 with belimumab compared to placebo (18.2% versus 11.9% respectively; OR 1.65; 95% CI 0.95–2.84; p = 0.0732).[4]

Limitations

Efficacy of belimumab has not been studied in patients with severe active lupus nephritis or severe active CNS lupus. Belimumab has not been studied as monotherapy in treatment of SLE, nor has it been studied in combination with other biologics or IV cyclophosphamide. Therefore, the use of belimumab is not recommended in these situations.[5] Some fluctuations in background standard of care therapy was allowed during the belimumab IV infusion trials which may have created some imbalance between groups. Prednisone could be increased during the first 24 weeks and immunosuppressive therapy could be increased during the first 16 weeks of study. After that, doses needed to be close to baseline doses. However prednisone taper was encouraged if possible, possibly resulting in a known imbalance with more belimumab-treated patients achieving a steroid sparing endpoint.[26] Use of immunosuppressive drugs was not similar across geographical regions in BLISS-52. Use of antimalarial drugs was less in eastern Europe (54%) compared to Latin America (69%) and Asia-Pacific regions (69%).[26] High dose prednisone (>7.4 mg/day) was greater in Latin America (73%) compared to Asia-Pacific regions (60%).[26] The range of corticosteroid use permitted at baseline varied widely from 0 to 40 mg per day. Use of rescue medications for infusion-related reactions was not mentioned or defined. Patients were removed from the trial and considered non-responders if they started a prohibited medication (e.g., angiotensin converting enzyme-inhibitor, angiotensin receptor blocker, or statin). Starting a prohibited medication occurred more frequently in the placebo arm compared to treatment arm during BLISS-52 (17% placebo vs. 9% 1mg/kg vs. 10% 10 mg/kg) and BLISS-76 (11% placebo vs. 7% 1mg/kg vs. 6% 10mg/kg).[26] Imputing these withdrawn patients as efficacy failures could bias the treatment effect in the primary efficacy endpoint in favor of belimumab.[26] Finally, the composite primary endpoint of SRI not previously used in clinical trials is problematic. The 3 assessments overstated the response to therapy, consisted of subjective assessments and were inadequately reported. These issues may have led to an overstatement of how well belimumab alleviated symptoms of SLE in clinical trials.

Clinical Safety:

The most common adverse reactions that occurred in greater than 5% of subjects who received IV belimumab during Phase 2 and 3 clinical trials were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine and pharyngitis.[5] Discontinuation of belimumab therapy due to any adverse reaction was 6.2% versus 7.1% in the belimumab and placebo arms respectively.[5] The most common reasons for discontinuation were infusion

reactions, lupus nephritis and infections. The most common infusion reactions (> 3%) noted in patients receiving belimumab included headache, nausea and skin reactions.[5] Adverse events occurring on the same day of the infusion were reported in 17% (251/1458) and 15% (99/675) of patients receiving belimumab and placebo, respectively.[5] Serious infusion reactions (except hypersensitivity reactions) were reported in 0.5% vs. 0.4% in the belimumab and placebo arms, respectively.[5] Serious reactions included bradycardia, myalgia, headache, rash, urticaria and hypotension.

In the SC belimumab trial, 449 patients in the belimumab group (80.8%) and 236 patients in the placebo group (84.3%) experienced at least 1 adverse effect.[4] The most frequent adverse events were infections and infestations (55.4% belimumab vs 56.8% placebo); gastrointestinal disorders (22.5% belimumab vs 24.3% placebo); musculoskeletal and connective tissue disorders (22.3% belimumab vs 23.6% placebo); nervous system disorders (20.0% belimumab vs 18.9% placebo) and skin and subcutaneous disorders (14.4% belimumab vs 21.4% placebo).[4] Serious adverse events were reported for 10.8% of belimumab patients and 15.7% of placebo patients.[4] Serious adverse events included infections and infestations, renal and urinary disorders, and nervous system disorders. Treatment-related adverse effects were reported for 31.1% of the belimumab patients and 26.1% of the placebo patients.[4] Local injection site reactions occurred in 34 patients in the belimumab group (6.1%) and 7 patients in the placebo group (2.5%).[4] All local injection site reactions were mild or moderate in severity, and no serious or severe injection site reactions were reported. The incidence of hypersensitivity reactions was similar between treatment groups. Three deaths were reported in the belimumab group (0.5%) and 2 were reported in the placebo group (0.7%).[4] Fifteen patients in the belimumab group (2.7%) and 10 patients in the placebo group (3.6%) experienced depression; none of these episodes were serious.[4]

Look-alike / Sound-alike Error Risk Potential:
Generic name (belimumab): basilixumab, bevacizumab, belatacept
Brand name (Benlysta): Evista, Benylin, Bentyl, Bendamustine

Table 3. Pharmacology and Pharmacokinetic Properties after IV infusion of belimumab 10mg/kg

Parameter	
Mechanism of Action	Binds to soluble human BLyS which results in decreased numbers of B-lymphocytes
Distribution	Volume of Distribution: 5.29 liters
Clearance	215 ml/day
Half-Life	19.4 hours

Abbreviations: BLyS = B-lymphocyte stimulator; ml = milliliters

Comparative Clinical Efficacy:

1) Symptom and disease activity control
2) Prevention of complications
3) Mortality
4) Quality of Life
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Improvement in SRI at week 52

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Navarra et al[24] (BLISS-52) Phase 3 RCT, DB, PC, PG, MC in Latin America (50%), Asia-Pacific (38%) and eastern Europe (13%)	1. Belimumab 1 mg/kg IV 2. Belimumab 10 mg/kg IV 3. Placebo IV Drug or placebo administered on Days 0, 14 and 28 and then every 28 days for 48 weeks in combination with SOC therapy. There were also restrictions to standard care, including that the prednisone dose return to within 25% or 5 mg greater than the baseline dose at 24 weeks and for the remainder of the study, and that the addition of a new immunosuppressive or biological drug at any time or a new antimalarial after 4 months was prohibited.	Demographics: -Mean age: 35.5 y -Female: 95% -White: 27% -Asian: 42% -Mean SELENA-SLEDAI score ≥10: 48-55% -Disease duration: 5 y -Prednisone >7.5 mg/d: 46% Key Inclusion Criteria: -Age ≥18 y -Active SLE (≥6 on SELENA-SLEDAI) -Positive ANA titer (≥1:80) -Stable regimen of prednisone (0-40mg/day) or NSAID, antimalarial or immunosuppressive drug for ≥30 days Key Exclusion Criteria: -Active lupus nephritis or CNS lupus -Pregnancy -Prior treatment with B-lymphocyte targeted drug -IV cyclophosphamide within 6 months -IVIG or prednisone > 100 mg/day within 3 months	ITT: 1.288 2.290 3.287 PP: 1.240 2.241 3.226 Attrition: 1. 48 (16.6%) 2. 49 (16.8%) 3. 61 (21.3%)	Primary Endpoint: Proportion of patients with improvement in composite SRI at week 52: 1. 148 (51%) OR 1.55; 95% CI 1.10 to 2.19; p=0.0129 vs 3 2. 167 (58%) OR 1.83; 95% CI 1.30 to 2.59; p=0.0006 vs 3 3. 125 (44%) Secondary Endpoints: ≥4-point reduction in SELENA-SLEDAI score at week 52: 1. 153 (53%) OR 1.51; 95% CI 1.07 to 2.14; p=0.0189 vs 3 2. 169 (58%) OR 1.71; 95% CI, 1.21 to 2.41; p=0.0024 vs 3 3. 132 (46%) No worsening BILAG at week 52: 1. 226 (78%) OR 1.38; 95% CI 0.93 to 2.04; p=0.1064 vs 3 2. 236 (81%) OR 1.62; 95% CI, 1.09 to 2.42; p=0.0181 vs 3 3. 210 (73%) No worsening in PGA at week 52: 1. 227 (79%) OR 1.68; 95% CI 1.15 to 2.47; p=0.0078 vs 3 2. 231 (80%) OR 1.74; 95% CI 1.18 to 2.55; p=0.0048 vs 3	7%/15 14%/8 7%/15 12%/9 NS 8%/13 10%/10 11%/9	AE: 1.264 (92%) 2.266 (92%) 3.263 (92%) SAE: 1.47 (16%) 2.41 (14%) 3.36 (13%) Discontinuation due to SAE: 1.16 (6%) 2.15 (5%) 3.19 (7%) Deaths: 1.2 (< 1%) 2.4 (1%) 3.3 (1%) Infection: 1.197 (68%) 2.194 (67%) 3.183(64%) Infusion Reactions: 1.47 (16%) 2.48 (17%) 3.49 (17%)	NA NA NA NA NA NA	**Trial Quality: Fair** **Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Central IVRS assigned 1:1:1 ratio, stratified according to SELENA-SLEDAI score (6-9 vs ≥10), extent of proteinuria, and ethnic origin. Baseline characteristics similar across groups. Performance Bias: UNCLEAR: Blinding strategy not discussed. Standard of care regimen may have had some regional variability – prednisone doses were tapered based on provider clinical judgement. Use of high dose prednisone (>7.5mg/day) was higher in Latin America. Detection Bias: LOW: Patients, investigators, study coordinators, and sponsors masked to treatment assignment. Pharmacists that prepared study drug were not blinded to trial assignments. Attrition Bias: UNCLEAR. Higher attrition rate in placebo arm vs drug arms (21% vs 17%). Patients that withdrew or required med changes not per protocol were considered treatment failures in the analysis. Reporting Bias: UNCLEAR. Study protocol available. Funded by GlaxoSmithKline. GSK also assisted in drafting the article and interpreting data. **Applicability**: Patient: Narrow inclusion criteria (serologically active SLE, no severe disease, 1/3 on low dose prednisone) limits generalization to sicker patients: 50% of patients had SELENA-SLEDAI scores ≥ 10. Most of the patients were Asian, limiting applicability to other races, in particular, people of African descent. Intervention: Belimumab 1 mg/kg compared to 10mg/kg and placebo at all sites. Use of immunosuppressive drugs was not similar across regions. Use of antimalarial drugs was less in eastern Europe (54%) vs Latin America (69%) and Asia-Pacific (69%). High dose prednisone (>7.4 mg/day) was greater in Latin America (73 %) vs Asia-Pacific (60%). Comparator: Placebo appropriate to determine efficacy on background SOC. Outcomes: The choice of a reduction from the baseline score ≥ 4 points on the SELENA-SLEDAI was chosen as clinically relevant, whereas a minimum of 6 points had been defined as such by an ACR expert panel.

				3. 199 (69%)				Setting: 90 centers in 13 countries: Latin America (50%), Asia-Pacific (38%), and eastern Europe (13%).
2. Furie et al[25] (BLISS-76) Phase 3 RCT, DB, PC, PG, MC Conducted at 136 centers located in 19 countries in North America (53%) and Europe (36%) and Latin America (11%)	1. Belimumab 1 mg/kg IV 2. Belimumab 10 mg/kg IV 3. Placebo IV Administered on days 0,14 and 28 and then every 28 days for 76 weeks	Demographics: -Mean age: 40 y -Female: 94% -White: 65% -Mean SELENA-SLEDAI score ≥10: 50% -Disease duration: 7.5y -Prednisone dose > 7.5 mg/day: 69% Key Inclusion Criteria: -Age ≥18 y -SLE w/ SELENA-SLEDAI score ≥6 -Positive ANA -Stable regimen of prednisone (0-40mg/day) or NSAID, antimalarial or immunosuppressive drug for ≥30 days prior to study -Stable regimen of ACE-I, ARB, or statin 3≥30 days Key Exclusion Criteria: -Active lupus nephritis or CNS lupus -Pregnancy -Prior treatment with B-lymphocyte targeted drug (rituximab) -Prior treatment with IV cyclophosphamide -Prior treatment with IVIG or prednisone > 100 mg/day -New start of ACE-I, ARB or statin within 60 days	ITT: 1. 271 2. 273 3. 275 PP: 1. 199 2. 191 3. 186 Attrition: 1. 72 (26%) 2. 82 (30%) 3. 89 (32%)	Primary Endpoint: SRI Response Rate at week 52: 1. 110 (40.6%) OR 1.34; 95% CI 0.94 to 1.91; p=0.1041 2. 118 (43.2%) OR 1.52; 95% CI 1.07 to 2.15; p=0.0207 3. 92 (33.5%) Secondary Endpoints: ≥4-point reduction in SELENA-SLEDAI score at week 52: 1. 116 (42.8%) OR 1.36 (95% CI 0.96 to 1.93; p=0.869) 2. 127 (46.5%) OR 1.63 (95% CI 1.15 to 2.32; p=0.0062) 3. 97 (35.3%) No worsening in BILAG at week 52: 1. 203 (74.9%) OR 1.63 (95% CI 1.12 to 2.37; p=0.0108) 2. 189 (69.2%) OR 1.20 (95% CI 0.92 to 1.90; p=0.3193) 3. 180 (65.5%) No worsening in PGA at week 52 compared to placebo 1. 197 (72.7%) OR 1.6 (95% CI 1.11 to 2.30; p=0.0120) 2. 190 (69.6%) OR 1.32 (95% CI 0.92 to 1.90; p=0.1258) 3. 173 (62.9%) SRI response rate at week 76: 1. 106 (39.1%) OR 1.34 (95% CI 0.94 to 1.91; p=0.1050) 2. 105 (38.5%) OR 1.31 (95% CI 0.92 to 1.87; p=0.1323) 3. 89 (32.4%)	NS 10%/10 NS 11%/9 NS 9%/11 NS 10%/10 NS NS	AE: 1. 202 (74.5%) 2. 202 (74%) 3. 190 (69.1%) SAE: 1.51 (18.8%) 2.54 (19.8%) 3.52 (18.9%) Discontinuation due to SAE: 1.18 (6.6%) 2.23 (8.4%) 3.23 (8.4%) Deaths: 1.2 (< 1%) 2.1 (< 1%) 3.0 Infection: 1.202 (74.5%) 2.202 (74%) 3.190(69.1%) Infusion Reactions: 1.42 (15.5%) 2.37 (13.6%) 3.27 (9.8%)	NA NA NA NA NA	**Trial Quality: Fair** **Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Random assignment 1:1:1 via IVRS. Stratified by according to SELENA-SLEDAI score (6-9 vs ≥10), proteinuria (< 2 gm vs ≥2gm/24hrs), and ethnic origin. Baseline characteristics similar across groups. Performance Bias: UNCLEAR: methods of blinding not described. Standard of care regimen may have had some regional variability. Detection Bias: LOW: Patients, investigators, study coordinators, and sponsors masked to treatment assignment. Pharmacists that prepared study drug were not blinded to trial assignments. Attrition Bias: HIGH. High attrition rate (> 26% for all 3 arms). Patients who withdrew or had changes in concomitant medications restricted by protocol were considered treatment failures and last observation was carried forward for imputation. Reporting Bias: UNCLEAR. Study protocol available. Funded by GlaxoSmithKline. **Applicability**: Patient: Narrow inclusion criteria Intervention: Belimumab 1 mg/kg not approved by FDA. Efficacy established with 10 mg/kg. Comparator: Placebo appropriate to establish efficacy Outcomes: The choice of a reduction from the baseline score ≥ 4 points on the SELENA-SLEDAI was chosen as clinically relevant, whereas a minimum of 6 points had been defined as such by an ACR expert panel. Setting: Primarily in North America (53%), Europe (36%) and Latin America (11%)

3.Stohl et al[4] (BLISS-SC) RCT, DB, PC, MC. Conducted in 177 sites in 30 countries in Central and South America 20%), Eastern Europe (21%), Asia (22%); Australia/ Western Europe/ Israel (7%), United States (30%).	1.Belimumab 200 mg SC once weekly 2.Placebo once weekly In addition to SOC over 52 weeks	Demographics: -Mean age: 39 years -Female 94% -Hispanic or Latino: 29% -Mean SELENA-SLEDAI score ≥10: 60% -Mean PGA: 1.5 -Disease duration: 4 years Key Inclusion Criteria: -Age ≥18 y -SLE (SELENA-SLEDAI score ≥8 -Stable SLE medication regimen 30 days prior to study enrollment Key Exclusion Criteria: -Active lupus nephritis or CNS lupus	ITT: 1.556 2.280 PP: 1. 463 2. 214 Attrition: 1. 93 (16.7%) 2. 66 (23.6%)	Primary Endpoint: SRI response rate at week 52 1. 61.4% 2. 48.4% OR 1.68 (95% CI 1.25 to 2.25; p=0.0006) Secondary Endpoint: Number of patients with reduction in corticosteroid dosage at weeks 40-52: 1. 18.2% 2. 11.9% OR 1.65 (95% CI 0.95 to 2.84; p=0.07)	13%/8 NS	AE: 1. 449 (80.8%) 2. 236 (84.3%) SAE: 1. 60 (10.8%) 2. 44 (15.7%) Discontinuation due to SAE: 1. 40 (7.2%) 2. 25 (8.9%)	NA NA NA	**Trial Quality: Poor** Risk of Bias (low/high/unclear): Selection Bias: UNCLEAR. Randomized 2:1, not clear how randomization was completed. Subjects stratified according to SELENA-SLEDAI score, complement level, and race. Performance Bias: UNCLEAR. Not clear how investigators were blinded and if protocol was standardized. Detection Bias: UNCLEAR. Blinding of outcome assessors was by the GSK physicians. Attrition Bias: HIGH. Higher attrition rate in placebo arm vs drug arms (23.6% vs 16.7%) Reporting Bias: UNCLEAR. Study protocol available. Funded by GlaxoSmithKline Applicability: Patient: Patients had more severe disease as assessed by SELENA-SLEDAI score ≥ 8 than BLISS trials (≥ 6). Intervention: 200 mg once per week selected to achieve AUC similar to 10 mg/kg IV every 4 weeks Comparator: Placebo Outcomes: Composite SRI index with limitation as noted above Setting: 177 sites in 30 countries including: Central and South America (20%), Eastern Europe (21%), and Asia (22%). Western Europe, Australia and Israel (7%). 30% of the sites were in the United States.

Abbreviations: ACE-I = angiotensin converting enzyme inhibitors; ACR = American College of Rheumatology; AE =Adverse Event; ANA = antinuclear antibody; ARB = angiotensin receptor blocker; ARR = absolute risk reduction; BILAG = British Isles Lupus Assessment Group; CI = confidence interval; Double Blind = DB; ITT = intention to treat; IV = intravenous; IVIG = intravenous immunoglobulin IVRS = interactive voice response system; MC = Multi-Center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OR = Odds Ratio; PG = Parallel Group; PC = Placebo controlled; PGA = Physician's Global Assessment; PP = per protocol; RCT = Randomized Controlled Trial; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SAE = Serious Adverse Event; SC = subcutaneous; SLE = Systemic Lupus Erythematosus; SOC = standard of care; SRI = Systemic Lupus Erythematosus Responder Index

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Appendix 1: Prescribing Information Highlights

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
BENLYSTA (belimumab) injection, for subcutaneous use

Initial U.S. Approval: 2011

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

Dosage and Administration, Subcutaneous Dosing Instructions (2, 2.2)	07/2017
Warnings and Precautions (5)	07/2017

---------- 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)

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. (1)

----------DOSAGE AND ADMINISTRATION----------

Intravenous Administration
- 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 over a period of 1 hour. (2.1)
- Consider administering premedication for prophylaxis against infusion reactions and hypersensitivity reactions. (2.1)

Subcutaneous Administration
- 200 mg once weekly. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------

Intravenous Infusion
For Injection: 120 mg or 400 mg lyophilized powder in single-dose vials for reconstitution and dilution prior to intravenous infusion. (3)
Subcutaneous Injection
Injection: 200 mg/mL single-dose prefilled autoinjector or single-dose prefilled syringe. (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 severe or chronic infections. Consider interrupting therapy with BENLYSTA if patients develop a new infection during treatment with BENLYSTA. (5.2)
- Progressive Multifocal Leukoencephalopathy (PML): Patients presenting with new-onset or deteriorating neurological signs and symptoms should be evaluated for PML by an appropriate specialist. If PML is confirmed, consider discontinuation of immunosuppressant therapy, including BENLYSTA. (5.2)
- Hypersensitivity Reactions, including Anaphylaxis: Serious and fatal reactions have been reported. BENLYSTA for intravenous use should be administered by healthcare providers prepared to manage anaphylaxis. Monitor patients during and for an appropriate period of time after intravenous administration of BENLYSTA. (2.1, 5.3)
- Depression: Depression and suicidality have been reported in trials with BENLYSTA. Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes. (5.5)
- Immunization: Live vaccines should not be given concurrently with BENLYSTA. (5.7)

---------- ADVERSE REACTIONS ----------

- Common adverse reactions (≥5%): nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, and injection site reactions (subcutaneous administration). (6.1, 6.2)

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2017

Belimumab (Benlysta®)

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

- 6 months

Requires PA:

- Benlysta® (Belimumab)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the patient have severe active lupus nephritis or severe active central nervous system lupus?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient currently on other biologic therapy or intravenous cyclophosphamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.	**No:** Go to # 6

Approval Criteria		
6. Is the drug being prescribed by or in consultation with a rheumatologist or a provider with experience treating SLE?	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have active autoantibody-positive SLE and is a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index	**Yes:** Go to # 8. Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the patient currently receiving standard of care treatment for Systemic Lupus Erythematosus (SLE) e.g., hydroxychloroquine, systemic corticosteroids, non-steroidal anti-inflammatory drugs, azathioprine, mycophenolate, or methotrexate?	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied as monotherapy in patients with SLE.

Renewal Criteria		
1. Is the patient currently on other biologic therapy or intravenous cyclophosphamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.	**No:** Go to #2

Renewal Criteria		
2. Has the patient's SLE disease activity improved as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index	**Yes:** Approve for 6 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *5/18 (DM)*
Implementation: *TBD*