

## Medical Policy



An independent licensee of the  
Blue Cross Blue Shield Association

### Title: Benlysta® (belimumab)

- BCBSKS will review Prior Authorization requests.

#### Prior Authorization Form:

[http://www.bcbsks.com/CustomerService/Forms/pdf/15-17\\_predeterm\\_request\\_frm.pdf](http://www.bcbsks.com/CustomerService/Forms/pdf/15-17_predeterm_request_frm.pdf)

#### Link to Drug List (Formulary):

[http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug\\_list.shtml](http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml)

#### Professional

Original Effective Date: July 1, 2011

Revision Date(s): January 1, 2012;  
September 5, 2016

Current Effective Date: September 5, 2016

#### Institutional

Original Effective Date: February 1, 2012

Revision Date(s): February 1, 2012,  
September 5, 2016

Current Effective Date: September 5, 2016

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

### DESCRIPTION

The intent of the Benlysta (belimumab) Prior Authorization (PA) program is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended product labeling. The PA program will consider belimumab appropriate for adult patients with active

and/or anti-dsDNA -positive, systemic lupus erythematosus (SLE) who are receiving the standard of care therapy. The PA criteria will not approve belimumab for patients with the following: severe active lupus nephritis or severe active central nervous system lupus, current therapy with other biologic agents or intravenous cyclophosphamide within the previous 6 months, or current therapy for treatment of a chronic infection. The initial criteria will also allow for a patient who has any FDA approved diagnosis that is not already addressed in the criteria set with a requested dosage that is within FDA limits. Renewal criteria will have similar requirements to initial criteria with the exception that the patient will have to have improvement or stabilization in at least one SLE diagnostic criterion. The dose of belimumab will be limited to the FDA labeled dosage (e.g. 10 mg/kg intravenously at 2-week intervals for the first 3 doses and at 4-week intervals thereafter for SLE) in both initial and renewal criteria.

### Target Drug

Brand (generic)	
Benlysta® (belimumab)	120 mg injection 400 mg injection

### FDA Approved Indications and Dosage

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

Limitation of use: efficacy has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. It has not been studied in combination with other biologics or intravenous cyclophosphamide so is not recommended in these situations.

The FDA approved dosage regimen is 10 mg/kg administered intravenously at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

**POLICY****Prior Authorization Criteria for Approval****Initial Evaluation**

**Benlysta® (belimumab)** will be approved when ALL of the following are met:

1. ONE of the following:
  - A. There is documentation that the patient is currently being treated with the requested agent  
**OR**
  - B. The prescriber states that the patient is using the requested agent AND is at risk if therapy is changed  
**OR**
  - C. ALL of the following:
    - i. The patient has a diagnosis of active systemic lupus erythematosus (SLE) disease  
**AND**
    - ii. The patient is 18 years of age or older  
**AND**
    - iii. BOTH of the following:
      - a. The patient has a history of a positive autoantibody test results [positive antinuclear antibody (ANA >1:80) and/or anti-dsDNA (>30 IU/mL)]  
**AND**
      - b. The patient has a history of 3 other SLE diagnostic criteria (i.e. malar rash, discoid rash, photosensitivity, oral ulcers, nonerosive arthritis, serositis (e.g. pleuritis/pericarditis), renal disorder [e.g. persistent proteinuria >0.5 grams/day or cellular casts], hematologic disorder [e.g. hemolytic anemia (with reticulocytosis), leukopenia, lymphopenia, or thrombocytopenia], and/or immunologic disorder (e.g. positive finding of antiphospholipid antibodies or anti-Sm antibodies)  
**AND**
    - iv. ONE of the following:
      - a. The patient is currently on a standard of care SLE treatment regimen comprised of at least one of the following: corticosteroids, antimalarials (hydroxychloroquine, chloroquine), nonsteroidal anti-inflammatory drugs (NSAIDS), aspirin, and/or immunosuppressives (azathioprine, methotrexate, cyclosporine, oral cyclophosphamide, or mycophenolate)  
**OR**

- b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL the standard of care drug classes listed above
  - D. The patient has another FDA labeled diagnosis
- AND**
- 2. The patient does NOT have or has not had severe active lupus nephritis [proteinuria >6 g/24 hour or equivalent or serum creatinine >2.5 mg/dL OR required hemodialysis or high-dose prednisone >100 mg/day] within the past 90 days
- AND**
- 3. The patient does NOT have or has not had severe active central nervous system lupus [e.g. seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis, CNS vasculitis requiring therapeutic intervention] within the past 60 days
- AND**
- 4. The patient has NOT been treated with intravenous cyclophosphamide in the previous 6 months
- AND**
- 5. The patient is NOT currently using another biologic agent
- AND**
- 6. The patient is NOT currently being treated for a chronic infection
- AND**
- 7. The patient does not have any FDA labeled contraindications to the requested agent
- AND**
- 8. The dose is within the FDA labeled dosage (e.g. 10 mg/kg intravenously at 2-week intervals for the first 3 doses and at 4-week intervals thereafter for SLE)

**Length of Approval:** 12 months

### Renewal Evaluation

**Benlysta® (belimumab)** will be approved when ALL of the following are met:

- 1. The patient has been previously approved for Benlysta
- AND**
- 2. ONE of the following:
    - A. The patient is currently on a standard of care SLE treatment regimen comprised of at least one of the following: corticosteroids, antimalarials (hydroxychloroquine, chloroquine), nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and/or immunosuppressives (azathioprine, methotrexate, cyclosporine, oral cyclophosphamide, or mycophenolate)
- OR**
- B. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL the standard of care drug classes listed above

**AND**

3. The patient has had a decrease in symptoms or stabilization in at least one SLE diagnostic criteria (e.g. serositis, oral ulcers, arthritis, photosensitivity, blood disorders, renal involvement, antinuclear antibodies, immunologic phenomena, neurologic disorder, malar rash, discoid rash)

**AND**

4. The patient does NOT have or has not had severe active lupus nephritis [proteinuria >6 g/24 hour or equivalent or serum creatinine >2.5 mg/dL OR required hemodialysis or high-dose prednisone >100 mg/day] within the past 90 days

**AND**

5. The patient does NOT have or has not had severe active central nervous system lupus [e.g. seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis, CNS vasculitis requiring therapeutic intervention] within the past 60 days

**AND**

6. The patient has NOT been treated with intravenous cyclophosphamide in the previous 6 months

**AND**

7. The patient is NOT currently using another biologic agent

**AND**

8. The patient is NOT currently being treated for a chronic infection

**AND**

9. The patient does not have any FDA labeled contraindications to the requested agent

**AND**

10. The dose is within the FDA labeled dosage (e.g. 10 mg/kg intravenously at 2-week intervals for the first 3 doses and at 4-week intervals thereafter)

**Length of Approval:** 12 months

<b>Agent</b>	<b>Contraindication(s)</b>
<b>Benlysta</b> (belimumab)	Previous anaphylaxis to Benlysta (belimumab)

<b>Biologic Agents not allowed as Concomitant Therapy</b>	
<b>Actemra</b> (tocilizumab)	<b>Orencia</b> (abatacept)
<b>Arcalyst</b> (rilonacept)	<b>Remicade</b> (infliximab)
<b>Cimzia</b> (certolizumab)	<b>Rituxan</b> (rituximab)
<b>Cosentyx</b> (secukinumab)	<b>Simponi</b> (golimumab)
<b>Enbrel</b> (etanercept)	<b>Simponi ARIA</b> (golimumab)
<b>Entyvio</b> (vedolizumab)	<b>Stelara</b> (ustekinumab)
<b>Humira</b> (adalimumab)	<b>Tysabri</b> (natalizumab)
<b>Ilaris</b> (canakinumab)	<b>Xeljanz</b> (tofacitinib)
<b>Kineret</b> (anakinra)	

## RATIONALE

### **Systemic Lupus Erythematosus (SLE)** <sup>2-5</sup>

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory autoimmune disease of unknown cause.<sup>4</sup> It has a broad range of clinical and serological manifestations and can affect any organ. Clinical symptoms of SLE include fatigue, fever, myalgia, changes in weight, skin and mucus membrane lesions and ulcers, and vascular disease. SLE can also include, cardiac, renal, pulmonary, and neurologic involvement. Due to its multisystem involvement and likelihood of changes in presentation, the diagnosis of SLE may be difficult.<sup>4</sup>

The American College of Rheumatology published criteria to aid in diagnosing patients with SLE. The criteria requires the patient has, at any time in his or her medical history, at least four of the following diagnostic criteria: malar rash, discoid rash, photosensitivity, oral ulcers, nonerosive arthritis, serositis (e.g. pleuritis/pericarditis), renal disorder [e.g. persistent proteinuria >0.5 grams/day or cellular casts], hematologic disorder [e.g. hemolytic anemia (with reticulocytosis), leukopenia, lymphopenia, or thrombocytopenia], and/or immunologic disorder (e.g. positive finding of antiphospholipid antibodies or anti-Sm antibodies).<sup>4</sup>

In the 2012 revised American College of Rheumatology (ACR) SLE classification criteria, a person is classified as having SLE in the presence of biopsy-proven lupus nephritis with antinuclear antibodies (ANA) or anti-dsDNA antibodies or if 4 of the ACR diagnostic criteria, including at least 1 clinical and 1 immunologic criterion have been established.<sup>4</sup> When SLE is suspected standard laboratory evaluations include CBC with differential, serum creatinine, and urinalysis with microscopy.

Nonspecific symptomatic treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, and topical therapies may be used initially in SLE patients. Additional conventional SLE therapies include antimalarial drugs, such as hydroxychloroquine and quinacrine, and many nonspecific immunosuppressive medications, such as glucocorticoids, azathioprine, methotrexate, mycophenolate mofetil, and cyclophosphamide. The goal has been the suppression and rebooting of an overactive immune system and thus disease amelioration. However, because of the nonspecific nature and broad immunologic impact of these therapies, the effects have not been optimal and not without a price with regard to infections and other adverse events. In addition, many of these therapies have been empirically introduced in the clinic without the support of good-quality randomized controlled trials.

The American College of Rheumatology (ACR)<sup>4</sup> and The European League Against Rheumatism (EULAR)<sup>5</sup> have published guidelines for the management of adults with SLE. The guidelines are based on available evidence-based information for the diagnosis and management of SLE with the goal of improving the quality of care for patients by primary care physicians. The recommendations are based on both evidence-based research, as well as expert consensus. Neither set of guidelines provides specific recommendations for drug selection and use.

There is substantial evidence that B cells play a central role in the pathogenesis of SLE.

B-lymphocyte stimulator (BLyS; BAFF) is a cytokine essential for B-cell growth and survival. It binds to any of three receptors on B cells: TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor), B-cell maturation antigen (BCMA), and BLyS receptor

3 (BR3 or BAFF-R). BLYS is a member of the TNF ligand family and is expressed by various cells, including monocytes, macrophages, dendritic cells and activated neutrophils.

A proliferation inducing ligand (APRIL), the TNF ligand family member with a similar structure to BLYS, also binds to TACI and BCMA.

Animal models where BLYS is overexpressed result in the development of autoantibodies and immune complex disease of the kidney, which suggests the importance of BLYS in autoimmune disease. Ex vivo studies with serum and synovial fluid from patients with autoimmune disease, including SLE, rheumatoid arthritis, and multiple sclerosis, have demonstrated that BLYS levels are significantly higher than those observed in normal healthy controls.

The ability to slow disease progression in animal models of autoimmune disease by inhibiting the action of BLYS provided the rationale for the development of an antibody that targets BLYS for the treatment of autoimmune diseases.

### **Safety and Efficacy**

The safety and efficacy of belimumab was evaluated in two randomized, double blind, placebo-controlled, phase III studies involving patients age 18 and older with SLE (BLISS-52 and BLISS-76 study). The design of these studies was based on the results of a phase II study which identified that patients who were autoantibody-positive had a better response to belimumab. As a result, BLISS-52 and BLISS-76 limited the study population to only include autoantibody-positive SLE patients. Patients were on a standard of care SLE treatment regimen comprising of at least one of the following: corticosteroids, antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or immunosuppressives (azathioprine, methotrexate, or mycophenolate).<sup>6</sup> Patients with severe active lupus nephritis and severe central nervous system (CNS) lupus were excluded. Patients using other biologics including B-cell targeted therapies such as rituximab or intravenous cyclophosphamide in the previous six months were also excluded.<sup>6</sup>

BLISS-52 (N=865) and BLISS-76 (N=826) had similar designs with the exception of duration. BLISS-76 was 76 weeks in duration and BLISS-52 was 52 weeks in length. Eligible patients had active SLE disease which was defined as a Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score >6. Patients were randomly assigned to receive belimumab 1 mg/kg, 10 mg/kg, or placebo in addition to standard of care. The study medication was administered on Days 0, 14, 28, and then every 28 days for 48 weeks in BLISS-52 and 72 weeks in BLISS-76.<sup>1</sup>

The primary endpoint was a SLE Responder Index (SRI) that defined response as meeting the following criteria at Week 52 compared to baseline:<sup>1</sup>

- >4 point reduction in 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.<sup>1</sup>

In both BLISS-52 and BLISS-76, the proportion of SLE patients achieving a SRI response was significantly higher in the belimumab 10 mg/kg group than placebo while the effect on SRI was not consistently significantly different for the belimumab 1 mg/kg group.<sup>1,2</sup>

**Table 1. Efficacy results expressed as SLE Responder Index improvement and SLEDAI reduction in Phase III belimumab trials (BLISS 52 and BLISS 76).<sup>2</sup>**

End point measure	BLISS-52			BLISS-76		
	Placebo (%)	Belimumab 1 mg/kg (n = 288)	Belimumab 10 mg/kg (n = 290)	Placebo (%)	Belimumab 1 mg/kg	Belimumab 10 mg/kg
SLE Responder Index at week 52	43.6	51.4% (p = 0.013)	57.6% (p = 0.0006)	33.8	40.6% (p = 0.10)	43.2% (p = 0.021)
Reduction in SELENA-SLEDAI by 4 points	46.0	53.1% (p = 0.019)	58.3% (p = 0.0024)	35.6	42.8% (p = 0.087)	46.9% (p = 0.0062)

Sub-group analyses of SRI response rate in patients of African descent were performed. In BLISS-52 and BLISS-76 combined, the SRI response rate in black patients (N=148) in the belimumab groups was less than the placebo group (22/50 or 44% for placebo, 15/48 or 31% for belimumab 1 mg/kg, and 18/50 or 36% for belimumab 10 mg/kg). In a phase II trial, black patients (N= 106) in the belimumab groups did not appear to have a different response than the rest of the study population.<sup>1</sup> Therefore, the effect of racial differences on the efficacy of belimumab for the treatment of SLE needs further evaluation.

## **CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

### CPT/HCPCS

J0490 Injection, belimumab, 10 mg

## **REVISIONS**

01-01-2012	Policy added to the bcbsks.com web site.
09-05-2016	Published 08-04-2016. Effective 09-05-2016
	Description section updated to include addition of FDA Approved Indications and Dosage information.



	<p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ Added "Initial Evaluation"</li> <li>▪ Added Items 1, 1 A, 1 B, and 1 C to read "1. ONE of the following:       <ul style="list-style-type: none"> <li>A. There is documentation that the patient is currently being treated with the requested agent OR</li> <li>B. The prescriber states that the patient is using the requested agent AND is at risk if therapy is changed OR</li> <li>C. ALL of the following:"           <ul style="list-style-type: none"> <li>▪ Added Item 1 C iii to read "iii. BOTH of the following:"</li> <li>▪ In Item 1 C iii a added "a history of a" to read "The patient has a history of a positive autoantibody test results..."</li> <li>▪ Added Item 1 C iii b to read "The patient has a history of 3 other SLE diagnostic criteria (i.e. malar rash, discoid rash, photosensitivity, oral ulcers, nonerosive arthritis, serositis (e.g. pleuritis/pericarditis), renal disorder [e.g. persistent proteinuria &gt;0.5 grams/day or cellular casts], hematologic disorder [e.g. hemolytic anemia (with reticulocytosis), leukopenia, lymphopenia, or thrombocytopenia], and/or immunologic disorder (e.g. positive finding of antiphospholipid antibodies or anti-Sm antibodies)"</li> <li>▪ In Item 1 C iv a added "antimalarials" to read "The patient is currently on a standard of care SLE treatment regimen comprised of at least one of the following: corticosteroids, antimalarials..."</li> <li>▪ In Item 1 C iv b added "ALL" to read "The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL the standard of care drug classes listed above"</li> <li>▪ Added Item D to read "The patient has another FDA labeled diagnosis"</li> <li>▪ In Item 2 and 3 add "or has not had" to read "The patient does NOT have or has not had severe..."</li> <li>▪ Added Item 7 to read "The patient does not have any FDA labeled contraindications to the requested agent"</li> <li>▪ In Item 8 added "(e.g." and "for SLE)" to read "The dose is within the FDA labeled dosage (e.g. 10 mg/kg intravenously at 2-week intervals for the first 3 doses and at 4-week intervals thereafter for SLE)"</li> <li>▪ Added Renewal Evaluation section as follows: "Renewal Evaluation Benlysta® (belimumab) will be approved when ALL of the following are met:               <ul style="list-style-type: none"> <li>1. The patient has been previously approved for Benlysta AND</li> <li>2. ONE of the following:                   <ul style="list-style-type: none"> <li>A. The patient is currently on a standard of care SLE treatment regimen comprised of at least one of the following: corticosteroids, antimalarials (hydroxychloroquine, chloroquine), nonsteroidal anti-inflammatory drugs (NSAIDS), aspirin, and/or immunosuppressives (azathioprine, methotrexate, cyclosporine, oral cyclophosphamide, or mycophenolate) OR</li> <li>B. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL the standard of care drug classes listed above AND</li> </ul> </li> <li>3. The patient has had a decrease in symptoms or stabilization in at least one SLE diagnostic criteria (e.g. serositis, oral ulcers, arthritis, photosensitivity, blood disorders, renal involvement, antinuclear antibodies, immunologic phenomena, neurologic disorder, malar rash, discoid rash) AND</li> </ul> </li> </ul> </li> </ul> </li> </ul>
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<p>4. The patient does NOT have or has not had severe active lupus nephritis [proteinuria &gt;6 g/24 hour or equivalent or serum creatinine &gt;2.5 mg/dL OR required hemodialysis or high-dose prednisone &gt;100 mg/day] within the past 90 days AND</p> <p>5. The patient does NOT have or has not had severe active central nervous system lupus [e.g. seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis, CNS vasculitis requiring therapeutic intervention] within the past 60 days AND</p> <p>6. The patient has NOT been treated with intravenous cyclophosphamide in the previous 6 months AND</p> <p>7. The patient is NOT currently using another biologic agent AND</p> <p>8. The patient is NOT currently being treated for a chronic infection AND</p> <p>9. The patient does not have any FDA labeled contraindications to the requested agent AND</p> <p>10. The dose is within the FDA labeled dosage (e.g. 10 mg/kg intravenously at 2-week intervals for the first 3 doses and at 4-week intervals thereafter)</p> <p>Length of Approval: 12 months"</p> <ul style="list-style-type: none"> <li>▪ Added Contraindications and Biologic Agents not allowed as Concomitant Therapy charts.</li> </ul>
Rationale section added
In Coding section:
<ul style="list-style-type: none"> <li>▪ Removed HCPCS Code: Q2044</li> </ul>
References updated

## **REFERENCES**

1. Benlysta Prescribing Information. GlaxoSmithKline. December 2015.
2. Goldberg A, Katzap E. Belimumab for the Treatment of Systemic Lupus Erythematosus. *International Journal of Clinical Rheumatology*. 2010;5(4):407-413.
3. FDA Arthritis advisory committee meeting briefing document BLA 125370. October 2010. Available at: [www.fda.gov/.../CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM233581.pdf](http://www.fda.gov/.../CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM233581.pdf). Accessed April 12, 2011.
4. American College of Rheumatology and Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Guidelines for referral and management of systemic lupus erythematosus in adults. *Arthritis Rheum*. 1999;42:1785–96.
5. Bertias G, Ioannidis J, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus (SLE) report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2008;67:195–205.
6. Navarra S, Guzmán R, Gallacher A, Hall S, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet*. 377(9767):721-31.
7. Wiglesworth A, Ennis K, Kockler, D. Belimumab: A BLYS-Specific Inhibitor for Systemic Lupus Erythematosus. *Annals of Pharmacotherapy*. 2010;44:1955-1961.
8. Bartels, Christie. Systemic Lupus Erythematosus (SLE) Treatment & Management. *Medscape*. Available at <http://emedicine.medscape.com/article/332244-treatment>. Accessed 3/18/14.