BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

BENLYSTA® (belimumab)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Benlysta (belimumab) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Rheumatologist or Nephrologist

2. Individual has a confirmed diagnosis using EULAR/ACR criteria of **ONE** of the following:
    a. Individual age of 5-years or older with active, autoantibody positive systemic lupus erythematosus (SLE) despite use for at least 3-months of at least two standard therapies for SLE such as corticosteroids, azathioprine, hydroxychloroquine, methotrexate, and mycophenolate

b. Individual age of 18-years or older with active lupus nephritis (LN) despite use for at least 3-months of at least two standard therapies for LN such as corticosteroids, azathioprine, cyclophosphamide, and mycophenolate

3. **For subcutaneous dosing:** Individual is 18-years of age or older

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has received and completed **ALL** of the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. **For Systemic Lupus Erythematosus:**
      i. Positive for anti-nuclear antibody (ANA) greater than or equal to 1:80 or anti-double stranded DNA (anti-dsDNA) greater than or equal to 30 IU/mL
      ii. Disease is active as indicated by **ONE** of the following:
         1. SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index) of 6 or greater
         2. British Isles Lupus Assessment Group (BILAG) A organ domain score ≥1 OR BILAG B organ domain score ≥2
   b. **For Lupus Nephritis:**
      i. Positive ANA greater than or equal to 1:80 or anti-dsDNA greater than or equal to 30 IU/mL
      ii. Disease is active as indicated by **ONE** of the following:
         1. SELENA-SLEDAI of 6 or greater
         2. BILAG A organ domain score ≥1 OR BILAG B organ domain score ≥2
      iii. Biopsy showing International Society of Nephrology (ISN)/Renal Pathology Society (RPS) LN Class III, Class IV, or Class V
      iv. Urinary protein to creatinine ratio (UPCR) of greater than or equal to 1 (corresponding to 1 g/day proteinuria)

6. Individual will continue standard therapy for SLE or LN as clinically appropriate which can include any of the following (alone or in combination): corticosteroids, immunosuppressives (azathioprine, methotrexate, and mycophenolate), and antimalarials (hydroxychloroquine, chloroquine, quinacrine), or NSAIDS

7. Individual does **NOT** have **ANY** of the following:
   a. Evidence of severe active lupus nephritis (proteinuria greater than 6 g/dL over 24 hours, serum creatinine greater than 2.5 mg/dL, or on hemodialysis) or severe active central nervous system lupus (such as seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis)
   b. Evidence of chronic infection(s)
   c. Concurrent use of live vaccines

8. There is no concomitant use with rituximab, other biologics, or intravenous cyclophosphamide

9. An assessment of risk of depression and suicide has been performed

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Benlysta (belimumab) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Rheumatologist or Nephrologist

2. Individual's condition responded while on therapy with response defined as:
    a. **For SLE and LN: TWO** of the following:
        i. Improvement in involved organ systems (such as mucocutaneous, musculoskeletal, immune)
        ii. Able to reduce corticosteroid dose by at least 25% over baseline
        iii. No new organ involvement or evidence of disease progression
        iv. Reduced flares or a prolonged time to flare
    b. **Additional response for LN**: **BOTH** of the following:
        i. UPCR of 0.7 or less
        ii. eGFR that is no worse than 20% below the pre-flare value or at least 60 mL /min/ 1.73 m2

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual will continue standard therapy for SLE or LN as clinically appropriate which can include any of the following (alone or in combination): corticosteroids, immunosuppressives (azathioprine, methotrexate, and mycophenolate), and antimalarials (hydroxychloroquine, chloroquine, quinacrine), or NSAIDS

6. Individual does **NOT** have **ANY** of the following:
    a. Evidence of severe active lupus nephritis (proteinuria greater than 6 g/dL over 24 hours, serum creatinine greater than 2.5 mg/dL, or on hemodialysis) or severe active central nervous system lupus (such as seizures, psychosis, organic brain syndrome, cerebrovascular accident, cerebritis)
    b. Evidence of chronic infection(s)
    c. Concurrent use of live vaccines

7. There is no concomitant use with rituximab, other biologics, or intravenous cyclophosphamide

8. Individual has not developed any contraindications or significant adverse drug effects that may exclude continued use such as:
    a. Anaphylaxis or severe hypersensitivity reaction to Benlysta

b. Serious infections
c. Progressive multifocal leukoencephalopathy (PML)
d. Severe depression and/or suicidal behaviors or other mood changes

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Benlysta (belimumab) is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of patients aged 5 years and older with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. The efficacy of Benlysta (belimumab) has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Benlysta (belimumab) has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of Benlysta (belimumab) is not recommended in these situations.

Belimumab is a human IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B) that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. Benlysta (belimumab) does not bind B cells directly, but by binding with BLyS, Benlysta (belimumab) inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

Belimumab significantly reduces circulating CD19+, CD20+, naïve, activated B-cells, and the SLE B-cell subset. Belimumab also reduces IgG and anti-double strand DNA antibodies (anti-dsDNA). Belimumab increases complement C3 and C4.

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown cause that can affect virtually every organ, the most common pattern is a mixture of constitutional complaints with skin, musculoskeletal, mild hematologic, and serologic involvement. Some patients will have predominately hematologic, renal, or central nervous system manifestations. The disease may be characterized by periods of remissions and of chronic or acute relapses and the symptoms may vary from mild to severe depending upon the type of organs involved. Renal involvement is clinically apparent in approximately 50 percent of SLE patients. Neuropsychiatric involvement of SLE consists of a broad range of neurologic and psychiatric manifestations including cognitive dysfunction, organic brain syndromes, delirium, psychosis, seizures, headache, and/or peripheral neuropathies. Other less common problems are movement disorders, cranial neuropathies, myelitis, and meningitis.
SLE treatment regimen medications include any of the following (alone or in combination): corticosteroids, immunosuppressives (including azathioprine, methotrexate, and mycophenolate), antimalarials (hydroxychloroquine, chloroquine, quinacrine), and NSAIDs.

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Kidney involvement is common in SLE, most patients will have clinical evidence of kidney disease, usually an abnormal urinalysis, at some point in the course of their disease. Lupus nephritis (LN) typically develops early in the disease. Abnormal urinalysis with or without an elevated plasma creatinine concentration is present in a large proportion of patients at the time of diagnosis of LN. The most frequently observed abnormality in patients with LN is proteinuria.

The diagnosis of LN is ideally confirmed by a kidney biopsy. A kidney biopsy should be performed in most patients with SLE who have clinical or laboratory evidence of kidney involvement (e.g., abnormal proteinuria, active urine sediment, elevated serum creatinine and/or decreased glomerular filtration rate) to establish the correct diagnosis and determine the histologic subtype of LN.

Based upon the results from the kidney biopsy, a LN classification system was developed. The International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification system divides glomerular disorders associated with SLE into six different patterns (or classes) based upon kidney biopsy histopathology.

A widely used classification system of LN divides glomerular disorders associated with SLE into six different patterns or classes based upon kidney biopsy findings including minimal mesangial LN (class I), mesangial proliferative LN (class II), focal proliferative LN (class III), diffuse proliferative LN (class IV), membranous lupus nephropathy (class V), and advanced sclerosing LN (class VI).

Treatment of LN varies according to the specific ISN/RPS class as well as other pathologic features. Combined immunosuppressive therapy is typically indicated in patients with focal (Class III) and diffuse (Class IV) proliferative LN and in many patients with lupus membranous nephropathy (Class V). Therapy may include corticosteroids, mycophenolate, cyclophosphamide, azathioprine, and belimumab.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Classification system of LN:
Divides glomerular disorders associated with SLE into six different patterns or classes based upon kidney biopsy findings:

Minimal mesangial LN	Class I
Mesangial proliferative LN	Class II
Focal proliferative LN	Class III
Diffuse proliferative LN	Class IV
Membranous lupus nephropathy	Class V
Advanced sclerosing LN	Class VI

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2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria for Systemic Lupus Erythematosus (SLE):

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

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If absent, do not classify as SLE
If present, apply additive criteria

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Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

<u>Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI)</u>:

- Endpoint consists of some subjective data.
- In clinical trials of belimumab (Benlysta), response was defined as a ≥ 4-point reduction in the SELENA-SLEDAI scale; however, the ACR has defined a clinically meaningful improvement as a ≥ 7-point reduction.

- The scoring system measures disease activity in patients with SLE and consists of 24 clinical and laboratory items.
- The scoring system is based on the presence or absence of the 24 individual items in the previous 10 days and is weighted based on the organ system; for example, mucocutaneous and immunology items are each multiplied by 2, whereas central nervous system (CNS) items are multiplied by 8.
- The weighted scores are then summed, and possible final scores range from 0-105, where higher scores indicate greater disease activity.

SELENA-SLEDAI Scoring Definitions:

Organ System	Score	Description
CNS	8	Seizure – recent onset
	8	Psychosis – altered ability to function in normal activity due to severe disturbance in perception of reality
	8	Organic Brain Syndrome
	8	Visual disturbance – retinal and eye changes of SLE
	8	Cranial nerve disorder – new onset sensory or motor neuropathy
	8	Lupus headache – severe persistent headache
	8	CVA – new onset of CVA(s)
Vascular	8	Vasculitis – ulceration, gangrene, tender finger nodules, etc.
Musculoskeletal	4	Arthritis – > 2 joints with pain and signs of inflammation
	4	Myositis – proximal muscle aching/weakness
Renal	4	Urinary casts – heme-granular or RBC casts
	4	Hematuria – > 5 RBCs per high power field
	4	Proteinuria – New onset or recent increase of > 0.5 g / 24 hours
	4	Pyuria – > 5 WBCs per high power field; Excludes infection
Mucocutaneous	2	Rash – new or ongoing inflammatory lupus rash
	2	Alopecia – new or ongoing abnormal, patchy or diffuse hair loss
	2	Mucosal ulcers – new or ongoing oral/nasal ulcerations
Cardiovascular / Respiratory	2	Pleurisy – classic and severe pleuritic chest pain, pleural rub or effusion or new pleural thickening
	2	Pericarditis – classic and severe pericardial pain, rub or effusion
Immunologic	2	Low complement –CH50, C3 or C4 below lower limit of normal
	2	Increased DNA binding – > 25% binding by Farr assay
Constitutional	1	Fever – > 38°C, excluding infectious causes
Hematologic	1	Thrombocytopenia – < 100,000 platelets / mm^3
	1	Leukopenia – < 3,000 WBCs / mm^3, excluding drug causes

<u>British Isles Lupus Activity Group (BILAG) assessment</u>:

- An organ-specific assessment consisting of 86-items based on a healthcare provider's intention to treat.
- The assessor scores organ manifestations on a 4-point scale, where 1 = improved, 2 = same, 3 = worse, and 4 = new within the last month.
- The areas assessed include general, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, vasculitis, renal and hematologic.

- Multiple manifestations and laboratory findings within an organ system are combined into a single score for that system (using a computer program), and the resulting score is classified as:
  - A = very active disease
  - B = moderate activity
  - C = mild stable disease
  - D = resolved activity
  - E = organ was never involved
- The ACR defined a clinically meaningful improvement in the BILAG score to be a ≥ 7-point reduction

Physicians Global Assessment (PGA):

- The PGA is a visual analog scale that is scored from 0 to 3
- In SLE, a score of:
  - 0 = absence of disease activity
  - 1 = mild lupus disease activity
  - 2 = moderate activity
  - 3 = severe activity
- An increase of ≥ 10%, or 0.3 points, is considered to be clinically meaningful disease activity worsening

Systemic Lupus Erythematosus Responder Index (SRI):

- The SRI uses:
  - SELENA-SLEDAI score as an objective measure of reduction in global disease activity
  - BILAG index to ensure no significant worsening in any specific organ system
  - PGA to ensure that improvements in disease activity are not accompanied by worsening of the patient's condition overall
- The SRI is a novel, composite endpoint that attempts to capture clinically meaningful improvement without a significant worsening in overall disease activity in patients with SLE, where response is defined as meeting each of the following criteria at Week 52 compared with baseline:
  - ≥ 4-point reduction in the SELENA-SLEDAI score (defined below), and
  - No new BILAG A organ domain score or 2 new BILAG B organ domain score, and
  - No worsening (< 0.30-point increase) in PGA score

Resources:

Benlysta (belimumab) product information, revised by manufacturer GlaxoSmithKilne LLC. 07-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed January 24, 2023.

Wallace DJ, Gladman DD. Clinical manifestations and diagnosis of systemic erythematosus in adults. In: UpToDate, Pisetsky DS, Curtis MR (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2022. Topic last updated November 04, 2022. Accessed January 24, 2023.

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Bomback AS, Appel GB. Lupus nephritis: Diagnosis and classification. In: UpToDate, Glassock RJ, Pisetsky DS, Lam AQ, Curtis MR (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2022. Topic last updated October 19, 2022. Accessed January 24, 2023.

Falk RJ, Dall'Era M, Appel GB. Lupus nephritis: Therapy of lupus membranous nephropathy. In: UpToDate, Glassock RJ, Rovin BH, Lam AQ, Curtis MR (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2022. Topic last updated September 27, 2021. Accessed January 24, 2023.

Falk RJ, Dall'Era M, Appel GB. Lupus nephritis: Initial and subsequent therapy for local or diffuse lupus membranous nephritis. In: UpToDate, Glassock RJ, Rovin BH, Lam AQ, Curtis MR (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2022. Topic last updated August 30, 2022. Accessed January 24, 2023.

Falk RJ, Dall'Era M, Appel GB. Lupus nephritis: Treatment of relapsing focal or diffuse lupus nephritis. In: UpToDate, Glassock RJ, Rovin BH, Lam AQ, Curtis MR (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2022. Topic last updated January 04, 2022. Accessed January 24, 2023.

Falk RJ, Dall'Era M, Appel GB. Lupus nephritis: Treatment of relapsing focal or diffuse lupus nephritis resistant to initial therapy. In: UpToDate, Glassock RJ, Rovin BH, Lam AQ, Curtis MR (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2022. Topic last updated January 05, 2022. Accessed January 24, 2023.