BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

LUPKYNIS™ (voclosporin) 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/or 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.

Medical Necessity Requirements for LUPKYNIS (voclosporin)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in chronic inflammatory disease, or is in consultation with a Rheumatologist, Immunologist, or Nephrologist

Indication
- Active lupus nephritis (LN) caused by systemic lupus erythematosus (SLE)

ORIGINAL EFFECTIVE DATE: 02/18/2021 | ARCHIVE DATE: | LAST REVIEW DATE: 02/19/2026 | LAST CRITERIA REVISION DATE: 02/19/2026

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Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- Diagnoses of systemic lupus erythematosus (SLE) used European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria
- Diagnosis of active lupus nephritis used International Society of Nephrology/Renal Pathology Society (ISN/RPS) renal biopsy classification is **ONE** of the following:
  - Class III or IV lupus nephritis (alone or in combination with Class V lupus nephritis)
  - Class V lupus nephritis
- Urine protein to creatinine (UPCR) ratio is **ONE** of the following:
  - Class III or IV lupus nephritis (alone or in combination with Class V lupus nephritis): Greater than or equal to 1.5 mg/mg
  - Class V lupus nephritis: Greater than or equal to 2 mg/mg
- Active lupus nephritis disease is indicated by **ONE** of the following:
  - Safety of Estrogens in Lupus Erythematosus, National Assessment SLE Disease Activity Index (SELENA SLEDAI) score of 6 or greater
  - British Isles Lupus Activity Group (BILAG) A organ domain score greater than or equal to 1 OR BILAG B organ domain score greater than or equal to 2
- Positive antinuclear antibody (ANA) greater than or equal to 1:80 or anti double stranded DNA (anti dsDNA) greater than or equal to 30 IU/mL

Alternative Therapies

- Failure (trial for at least three months duration), contraindication, intolerance, or is not a candidate for **TWO** of the following:
  - Hydroxychloroquine
  - Corticosteroid and mycophenolate
  - Corticosteroid and cyclophosphamide
  - Mycophenolate and either cyclosporine or tacrolimus
- Corticosteroid and mycophenolate will be continued

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- Does not have **ANY** of the following:
  - Estimated glomerular filtration rate (eGFR) less than or equal to 45 mL/min/1.73 m²
  - Baseline blood pressure greater than 165/105 mmHg
  - Hypertensive emergency

  - Severe hepatic impairment (Child Pugh Class C)
  - Concurrent use of live attenuated vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, TY21a typhoid)
- No concomitant use with cyclophosphamide, Benlysta (belimumab), or Saphnelo (anifrolumab fnia)
- No FDA label contraindications such as:
  - Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin)
  - Known serious or severe hypersensitivity reaction to Lupkynis (voclosporin) or any of its excipients
- Not currently taking drugs causing severe adverse reactions or significant drug interactions requiring discontinuation such as moderate or strong CYP3A4 inducers (e.g., carbamazepine, enzalutamide, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort)

Documentation Requirements
- A completed request form must be submitted including:
  - Chart notes
  - Lab results (e.g., urine protein to creatinine, estimated glomerular filtration rate, antinuclear antibody, anti double stranded DNA)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy.

Prescriber Qualifications
- Continues to be seen by a physician specializing in chronic inflammatory disease, or is in consultation with Rheumatologist, Immunologist, or Nephrologist

Clinical Response
- Positive clinical response defined as **BOTH** of the following:
  - Urine protein to creatinine (UPCR) ratio is 0.5 or less
  - Effect on renal function is **ONE** of the following:
    1. Estimated glomerular filtration rate is at least 60 mL/min/1.73 m²
    2. Estimated glomerular filtration rate is no worse than 20 percent below baseline
    3. No treatment or disease related eGFR associated events (e.g., increased serum creatinine, decreased renal clearance, renal impairment, renal failure)

Adherence
- Adherence to prescribed therapy regimen with Lupkynis (voclosporin), corticosteroid, and mycophenolate has been documented

PHARMACY COVERAGE GUIDELINE

LUPKYNIS™ (voclosporin)
Generic Equivalent (if available)

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- Does **NOT** have **ANY** of the following:
  - Estimated glomerular filtration less than or equal to 45 mL/min/1.73 m²
  - Severe hepatic impairment (Child Pugh Class C)
  - Concurrent use of live attenuated vaccines
- No concomitant use with cyclophosphamide, Benlysta (belimumab), or Saphnelo (anifrolumabfnia)
- No newly developed contraindications or significant adverse drug effects including:
  - Nephrotoxicity (acute or chronic)
  - Blood pressure above 165/105 mmHg uncontrolled by medication or dose adjustment
  - Hypertensive emergency
  - Neurotoxicity (e.g., posterior reversible encephalopathy syndrome, seizures)
  - Severe hyperkalemia
  - QT prolongation
  - Pure red cell aplasia
  - Concomitant use of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin)
  - Concomitant use of moderate or strong CYP3A4 inducers (e.g., carbamazepine, enzalutamide, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort)

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in lupus nephritis
- Lab values confirming safe use (e.g., urine protein to creatinine, estimated glomerular filtration rate)

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

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

PHARMACY COVERAGE GUIDELINE

LUPKYNIS™ (voclosporin) Generic Equivalent (if available)

Description:

Lupkynis (voclosporin) is a calcineurin-inhibitor immunosuppressant indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN). Safety and efficacy of Lupkynis (voclosporin) have not been established in combination with cyclophosphamide. Use of Lupkynis (voclosporin) is not recommended in this situation.

The mechanism of voclosporin suppression of calcineurin has not been fully established. Activation of lymphocytes involves an increase in intracellular calcium concentrations that bind to the calcineurin regulatory site and activate calmodulin binding catalytic subunit and through dephosphorylation activates the transcription factor, Nuclear Factor of Activated T-Cell Cytoplasmic (NFATc). The immunosuppressant activity results in inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens.

Studies also support a non-immunological role for calcineurin inhibition in kidney function to stabilize actin cytoskeleton and stress fibers in podocytes leading to increased podocyte integrity in glomeruli.

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.

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. Immunosuppressive therapy is not usually used to treat minimal mesangial (Class I), mesangial proliferative (Class II), or advanced sclerosing (Class VI) LN.

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
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
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

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

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 / mm³
	1	Leukopenia – < 3,000 WBCs / mm³, 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:

Lupkynis (voclosporin) product information, revised by Aurinia Pharma U.S., Inc. 04-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 27, 2025.

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ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03021499: A Randomized, Controlled Double-blind Study Comparing the Efficacy and Safety of Voclosporin (23.7mg Twice Daily) With Placebo in Achieving Renal Response in Subjects With Active Lupus Nephritis. Available from: http://clinicaltrials.gov. Last update posted March 27, 2023. Last verified March 2023. Accessed October 28, 2025.

Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis. Kidney Int. 2024;105(1S):S1–S69. Accessed October 28, 2025.

Menn-Josephy H, Hodge L, Birardi V, Leher H. Efficacy of Voclosporin in Proliferative Lupus Nephritis with High Levels of Proteinuria. Clin J Amer Soc Nephrol 2024 March;19(3): 309-318, DOI: 10.2215/CJN.0000000000000297. Accessed October 29, 2025.

Aringer M, Costenbader K, Daikh D, et al.: 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis & Rheumatology 2019 Sept; 71 (9): 1400–1412. DOI 10.1002/art.40930. Accessed October 28, 2025.