PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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LUPKYNIS™ (voclosporin)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Lupkynis (voclosporin) is considered ***medically necessary*** and will be approved when **ALL** of 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 is 18 years of age or older

3. A confirmed of diagnosis of systemic lupus erythematosus (SLE), using EULAR/ACR criteria, with confirmed active lupus nephritis (LN) using the International Society of Nephrology/Renal Pathology Society (ISN/RPS) biopsy classification

4. ISN/RPS renal biopsy classification is **ONE** of the following:
    a. Class III or IV LN (alone or in combination with Class V LN)
    b. Class V LN

5. Urine protein to creatinine (UPCR) ratio is **ONE** of the following:
    a. Class III or IV LN (alone or in combination with Class V LN): equal to or greater than 1.5 mg/mg
    b. Class V LN: equal to or greater than 2 mg/mg

6. LN disease is active as indicated by **ONE** of the following:
    a. Safety of Estrogens in Lupus Erythematosus, National Assessment- SLE Disease Activity Index (SELENA-SLEDAI) of 6 or greater
    b. British Isles Activity Group (BILAG) A organ domain score equal to or greater than 1 OR BILAG B organ domain score equal to or greater than 2

7. Individual has a positive ANA greater than or equal to 1:80 or anti-dsDNA greater than or equal to 30 IU/mL

8. Documented failure (after least 3-months use), contraindication per FDA label, intolerance, or not a candidate to **TWO** of the following:
    a. Glucocorticosteroid and mycophenolate
    b. Glucocorticosteroid and cyclophosphamide
    c. Mycophenolate and either cyclosporine or tacrolimus

9. If approved will also use glucocorticosteroid and mycophenolate

10. There are **NO** FDA-label contraindications, such as:
    a. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin)

11. Blood pressure is less than 165/105 mmHg

12. Estimated glomerular filtration rate (eGFR) is equal to or greater than 45 mL/min/1.73 m^2

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13. Will not be used in severe hepatic impairment (Child-Pugh Class C)
14. Will not be used concurrently with cyclophosphamide
15. Will not be used with live vaccines
16. There are no significant interacting drugs

Initial approval duration: 6 months
If there is no therapeutic benefit at this time Lupkynis (voclosporin) **will not** be renewed

- **Criteria for continuation of coverage (renewal request):** Lupkynis (voclosporin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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
    a. Response is defined as **ALL** of the following:
        i. UPCR of 0.5 or less
        ii. Effect on renal function is **ONE** of the following:
            1. eGFR is at least 60 mL /min/ 1.73 m^2 or more
            2. eGFR is no worse than 20% below baseline
            3. No treatment or disease related eGFR-associated events (such as increased blood/serum creatinine, decreased renal clearance, decreased glomerular filtration rate, renal impairment, or renal failure)
3. Individual has been adherent with the medication and glucocorticosteroid and mycophenolate
4. Blood pressure is less than 165/105 mmHg
5. Estimated glomerular filtration rate (eGFR) is equal to or greater than 45 mL/min/1.73 m^2
6. Will not be used in severe hepatic impairment (Child-Pugh Class C)
7. Will not be used concurrently with cyclophosphamide
8. Will not be used with live vaccines
9. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Nephrotoxicity, acute and/or chronic
        ii. Blood pressure above 165/105 mmHg that is uncontrolled by medication or Lupkynis (voclosporin) dose adjustment

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iii. Neurotoxicity, including posterior reversible encephalopathy syndrome (PRES) and seizures
iv. Hyperkalemia
v. QT prolongation
vi. Pure red cell aplasia

10. There are no significant interacting drugs

Renewal duration:12 months if there is documentation of response as defined in #2 above
If there is no therapeutic benefit at this time Lupkynis (voclosporin) **will not** be renewed

- 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:

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:

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

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Membranous lupus nephropathy	Class V
Advanced sclerosing LN	Class VI

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.

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

- 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

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British Isles Lupus Activity Group (BILAG) assessment:

- 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 Pharmaceuticals, Inc. 01-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed January 07, 2022.

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