Drug Monograph

Drug Name: **Lupkynis™ (voclosporin) Capsule**
Drug Class: **Calcineurin-Inhibitor Immunosuppressant**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Lupkynis is available as an oral capsule containing 7.9 mg of voclosporin.
Manufacturer:	Distributed by: Aurinia Pharma U.S., Inc., Rockville, MD 20850.
Summary of Findings:	The efficacy of Lupkynis was studied in a randomized, double-blind, placebo-controlled trial with 357 patients with active lupus nephritis. Patients were randomized in a 1:1 ratio to receive either Lupkynis 23.7 mg twice daily (with dosing adjustments based on estimated glomerular filtration rate and blood pressure) or placebo. Patients in both arms received background treatment with mycophenolate mofetil and corticosteroids. The primary efficacy endpoint was the proportion of patients achieving complete renal response at Week 52. A higher proportion of patients in the Lupkynis arm than the placebo arm achieved the primary endpoint (Odds Ratio 2.7; 95% CI: 1.6, 4.3; p<0.001). Lupkynis was favored in every secondary endpoint, including renal response at Week 24, partial renal response at Week 4, Week 52, and time to urine protein to creatinine ratio (UPCR) reduction.
Status Recommendation:	☐ Clinical Edit ☒ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting up to 1.5 million people in the U.S. It is much more common in women than in men (9 out of 10) and often strikes during the child-bearing years. In adults who have lupus, as many as 5 out of 10 will have kidney disease of some sort, a common type being lupus nephritis (LN). The symptoms of lupus nephritis may include foamy urine, edema, and hypertension. It is diagnosed through urine and blood tests and a kidney biopsy. Goals of treating LN are to: reduce inflammation in the kidneys, decrease immune system activity, and modulate the immune system to block antibody production. Medications used include: corticosteroids, immunomodulators (cyclophosphamide or mycophenolate mofetil [MMF]) and hydroxychloroquine. In addition medications may be added to specifically control blood pressure such as: angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, beta-blockers (BB), or calcium channel blockers (CCB). Between 10-30% of people who have lupus nephritis develop kidney failure. On January 22, 2021, the FDA approved Lupkynis as the first oral treatment for LN and the second for LN following Benlysta® (belimumab) in December 2020.

Dosage Form [3]

Lupkynis is available as an oral capsule containing 7.9 mg of voclosporin.

Manufacturer [3]

Distributed by: Aurinia Pharma U.S., Inc., Rockville, MD 20850.

Indication(s) [3]

Lupkynis is indicated in combination with a background immunosuppressive therapy regimen (MMF and corticosteroids) for the treatment of adult patients with active lupus nephritis.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Voclosporin is a calcineurin inhibitor immunosuppressant. The mechanism of suppression 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 in animal models 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.

Pharmacokinetics:

Absorption	t_{max}=1.5 hours
Metabolism	Hepatic (CYP3A4)
Excretion	Feces (92.7%), Urine (2.1%)
Half-life	30 hours

Clinical Trials Experience

STUDY 1 DESIGN (NCT 03021499)	Randomized, double-blind, placebo-controlled trial (n=357)

INCLUSION CRITERIA	• Subjects with evidence of active nephritis, defined as follows:
	  ○ Kidney biopsy result within 2 years prior to screening indicating Class III, IV-S, IV-G (alone or in combination with Class V), or Class V lupus nephritis (LN) with a doubling or greater increase of UPCR within the last 6 months to a minimum of ≥1.5 mg/mg for Class III/IV or to a minimum of ≥2 mg/mg for Class V at screening. Biopsy results over 6 months prior to screening must be reviewed with a medical monitor to confirm eligibility, OR
	  ○ Kidney biopsy result within 6 months prior to screening indicating Class II, Iv-s, IV-G (alone or in combination with Class V) LN with a UPCR of ≥1.5 mg/mg at screening, OR
	  ○ Kidney biopsy result within 6 months prior to screening indicating Class V LN and a UPCR of ≥2 mg/mg at screening
	• Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline.

EXCLUSION CRITERIA	• Patient with baseline eGFR ≤45 ml/min/1.73 m^2 at screening
	• Current medical history of:
	  ○ Congenital or acquired immunodeficiency
	  ○ Clinically significant drug or alcohol abuse within 2 years prior to screening
	  ○ Malignancy within 5 years of screening, with the exception of basal and squamous cell carcinomas treated by complete excision
	  ○ Lymphoproliferative disease or previous total lymphoid irradiation
	  ○ Severe viral infection or known HIV infection
	• Active tuberculosis (TB), or known history of TB/evidence of old TB if not taking prophylaxis with isoniazid
	• Other known clinically significant active medical conditions, such as: severe cardiovascular disease, liver dysfunction or chronic obstructive pulmonary disease or asthma requiring oral steroids or any other overlapping autoimmune condition for which the condition or the treatment of the condition may affect the study assessments or outcomes

TREATMENT REGIMEN	Patients were randomized in a 1:1 ration to receive either Lupkynis 23.7 mg twice daily or placebo. Patients in both arms received background treatment with MMF and corticosteroids as follows: 1)

<table>
<tr><td></td><td>Oral MMF at a target dose of 2 g/day, dose increases up to 3 g/day were allowed; 2) IV methylprednisolone on Day 1 and Day 2 at a dose of 500 mg/day (body weight ≥45 kg) or 250 mg/day (body weight <45 kg) followed by a reducing taper of oral corticosteroids [oral prednisone 25 mg/day (body weight ≥45 kg) or 20 mg/day (body weight <45 kg); tapered to achieve a target dose of 2.5 mg by Week 16]. Dosage was adjusted based on eGFR and BP in a pre-defined dosage protocol.</td></tr>
<tr><td>RESULTS</td><td>The primary efficacy endpoint was the proportion of patients achieving complete renal response at Week 52. Complete renal response was defined as follows (both must be met):
1. Urine protein to creatinine ratio (UPCR) of ≤0.5 mg/mg, and
2. eGFR ≥60 ml/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20% or no treatment- or disease-related eGFR-associated event (defined as blood creatinine increased, creatinine renal clearance decreased, glomerular filtration rate decreased, serum creatinine increased, renal impairment, renal failure, or renal failure acute) at time of assessment. (These criteria correspond to the components of primary endpoint in chart below)
In order to be considered a responder, the patient must not have received more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during Weeks 44 through 52. Patients who received rescue medication or withdrew from the study were considered non-responders.

Complete Renal Response at Week 52
<table>
<tr><th></th><th>Lupkynis (N=179)</th><th>Placebo (N=178)</th><th>Odds Ratio</th></tr>
<tr><td colspan="4">Primary Endpoint</td></tr>
<tr><td>Complete Renal Response at Week 52 [n (%)]</td><td>73 (40.8)</td><td>40 (22.5)</td><td>2.7 (95% CI: 1.6, 4.3); p<0.001</td></tr>
<tr><td colspan="4">Components of Primary Endpoint (See descriptions of criteria above chart)</td></tr>
<tr><td>Criterion 1 [n (%)]</td><td>81 (45.3)</td><td>41 (23.0)</td><td>3.1 (95% CI: 1.9, 5.0)</td></tr>
<tr><td>Criterion 2 [n (%)]</td><td>147 (82.1)</td><td>135 (75.8)</td><td>1.5 (95% CI: 0.8, 2.5)</td></tr>
</table>
A higher proportion of patients in the Lupkynis arm than the placebo arm achieved complete renal response at Week 52.

Secondary endpoints: A higher proportion of patients in the Lupkynis arm than the placebo arm achieved complete renal response at Week 24 (32% vs. 19.7%; odds ratio: 2.2; 95% CI: 1.3, 3.7). Time to UPCR of ≤0.5 mg/mg was shorter in the Lupkynis arm than the placebo arm (median time of 169 days vs. 372 days; hazard ratio: 2.0; 95% CI: 1.5, 2.7).</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
</table>

Contraindications [3,4]

- Patients concomitantly using strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) because these medications can significantly increase exposure to Lupkynis which may increase the risk of acute and/or chronic nephrotoxicity.
- Patients who have had a known serious or severe hypersensitivity reaction to Lupkynis or any of its excipients.

Warnings and Precautions [3,4]

- Immunosuppressants increase the risk of developing lymphomas and other malignances, particularly of the skin.
- Immunosuppressants increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections.
- Lupkynis, like other calcineurin-inhibitors, can cause acute and/or chronic nephrotoxicity. Monitor estimated glomerular filtration rate (eGFR) regularly during treatment, and consider dose reduction or discontinuation in patients with decreases in eGFR from baseline.
- Hypertension is a common adverse reaction of Lupkynis therapy and may require antihypertensive therapy. Some antihypertensive drugs can increase the risk for hyperkalemia. Certain calcium-channel blocking agents may increase voclosporin blood concentrations and require dosage reduction of Lupkynis.
- Calcineurin-inhibitors may cause a spectrum of neurotoxicities. The most severe neurotoxicities include posterior reversible encephalopathy syndrome, delirium, seizure, and coma; others include tremors, paresthesias, headache, mental symptoms and changes in motor and sensory functions. Consider dosage reduction or discontinuation of Lupkynis if neurotoxicity occurs.
- Hyperkalemia has been reported with calcineurin-inhibitors. Concomitant use of agents associated with hyperkalemia may increase the risk for hyperkalemia.
- Lupkynis prolongs the QT_c interval in a dose-dependent manner after single dose administration at a dose higher than the recommended lupus nephritis therapeutic dose. Certain circumstances may increase the risk of the occurrence of torsade de points and/or sudden death association with the use of drugs that prolong the QTc interval, including: 1) bradycardia, 2) hypokalemia or hypomagnesemia, 3) concomitant use of other drugs that prolong the QTc interval, 4) presence of congenital prolongation of the QT interval.
- Avoid the use of live attenuated vaccines during treatment with Lupkynis (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).
- Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another calcineurin-inhibitor immunosuppressant.

Adverse Effects [3,4]

Most common, ≥3 % and ≥2% Higher Than Placebo	Lupkynis 23.7 mg twice a day (n=267) %	Placebo (n=266) %
Glomerular filtration rate decreased	26	9
Hypertension	19	9
Diarrhea	19	13

Headache	15	8
Anemia	12	6
Cough	11	2
Urinary tract infection	10	6
Abdominal pain upper	7	2
Dyspepsia	6	3
Alopecia	6	3
Renal impairment*	6	3
Abdominal pain	5	2
Mouth ulceration	4	1
Fatigue	4	1
Tremor	3	1
Acute kidney injury*	3	1
Decreased appetite	3	1

Drug Interactions [3,4]

- Strong and Moderate CYP3A4 Inhibitors: Voclosporin is a sensitive CYP3A4 substrate. Co-administration with strong or moderate CYP3A4 inhibitors increases voclosporin exposure, which may increase the risk of Lupkynis adverse reactions. Co-administration of Lupkynis with strong CYP3A4 inhibitors is contraindicated.
- Strong and Moderate CYP3A4 Inducers: Co-administration with strong or moderate CYP3A4 inducers decreases voclosporin exposure, which may decrease the efficacy of Lupkynis. Avoid co-administration of Lupkynis with strong or moderate CYP3A4 inducers.
- Certain P-gp Substrates: Voclosporin is a P-gp inhibitor. Co-administration of voclosporin increases exposure of P-gp substrates, which may increase the risk of adverse reactions of these substrates.
- The effect of Lupkynis on OATP1B1 substrates (e.g., statins) has not been studied clinically. However, voclosporin is an OAT1B1 inhibitor in vitro, and information suggests an increase in the concentration of these substrates is possible. Monitor for adverse reactions of OATP1B1 substrates when used concomitantly.

Dosage and Administration [3,4]

- Before initiating Lupkynis, establish an accurate baseline eGFR and check blood pressure (BP)
  - Use is not recommended in patients with a baseline eGFR ≤45 ml/min/1.73 m^2 unless benefit exceeds the risk; these patients may be at increased risk for acute and/or chronic nephrotoxicity.
  - Do not initiate Lupkynis in patients with baseline BP > 165/105 mmHG or with hypertensive emergency.
- Recommended starting dose: 23.7 mg orally twice daily.
  - Use in combination with mycophenolate mofetil (MMF) and corticosteroids.
  - Must be swallowed whole on an empty stomach.
  - Instruct patients to avoid eating grapefruit or drinking grapefruit juice while taking Lupkynis.
- Modify the dose based on eGFR
  - Assess eGFR every 2 weeks for the first month, and every four weeks thereafter
  - If eGFR <60 ml/min/1.73 m^2 and reduced from baseline by >20% and <30%, reduce

dose by 7.9 mg twice a day.
    - If e GFR <60 ml/min/1.73 m^2 and reduced from baseline by ≥30%, discontinue Lupkynis. Re-assess eGFR within two weeks; consider re-initiating Lupkynis at a lower dose (7.9 mg twice daily) only if eGFR has returned to ≥80% of baseline.
    - For patients that had a decrease in dose due to eGFR, consider increasing the dose by 7.9 mg twice a day for each eGFR measurement that is ≥80% of baseline; do not exceed the starting dose.
- Monitor BP every 2 weeks for the first month after initiating Lupkynis, and as clinically indicated thereafter. For patients with BP >165/105 mmHG or with hypertensive emergency, discontinue Lupkynis and initiate antihypertensive therapy.
- If the patient has not experienced therapeutic benefit by 24 weeks, consider discontinuation of Lupkynis.
- Consider the risks and benefits of Lupkynis treatment beyond one year in light of the patient's treatment response and risk of worsening nephrotoxicity.
- Dosage adjustments:
    - Patients with severe renal impairment: the recommended dose is 15.8 mg twice daily.
    - Patients with mild and moderate hepatic impairment: the recommended dose is 15.8 mg twice daily.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Voclosporin	Lupkynis	Aurinia	23.7 mg orally twice daily	$11,850 at initial dosing
Belimumab	Benlysta	Human Genome Sciences	10 mg/kg/dose IV every 2 weeks for 3 doses, then every 4 weeks thereafter OR 400 mg SubQ once weekly for 4 doses then 200 mg once weekly thereafter	$3,983.12 at 200 mg SubQ weekly
Cyclosporine	Gengraf, Neoral, Sandimmune	Various	2.5 mg/kg/day orally in 2 divided doses	$670.64 at 100 mg twice daily
Tacrolimus	Prograf	Astellas Pharma, various	0.1 mg/kg/dose orally once daily on an empty stomach	$1,304.81 at 7 mg twice daily

** Wholesale Acquisition Cost

Conclusion

LN is a kidney disease that results as a complication of SLE. About 10% of patients with LN will go on to develop end-stage renal disease, so early diagnosis and treatment is key. The American College of Rheumatology and Kidney Disease Improving Global Outcome (KDIGO) practice guidelines recommend for Class III and IV LN include MMF at a dose of 2 to 3 grams

total daily (preferred) or cyclophosphamide for 6 months with glucocorticoids as induction therapy, followed by maintenance therapy with azathioprine, MMF or calcineurin inhibitor (tacrolimus and cyclosporine use in LN is considered off-label), and a low-dose steroid. The efficacy of Lupkynis was studied in a randomized, double-blind, placebo-controlled trial with 357 patients with active lupus nephritis. Patients were randomized in a 1:1 ratio to receive either Lupkynis or placebo. The primary efficacy endpoint was the proportion of patients achieving complete renal response at Week 52. A higher proportion of patients in the Lupkynis arm than the placebo arm achieved the primary endpoint (Odds Ratio 2.7; 95% CI: 1.6, 4.3; p<0.001). Lupkynis was favored in every secondary endpoint, including renal response at Week 24, partial renal response at Week 4, Week 52, and time to urine protein to creatinine ratio (UPCR) reduction. The most common adverse events in trials were: decreased eGFR, hypertension, diarrhea, headache, anemia, cough, and urinary tract infection. Lupkynis does not appear to exhibit the cardiovascular and metabolic adverse effects seen in other CNIs, such as tacrolimus.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) National Institute of Diabetes and Digestive and Kidney Diseases. Lupus and Kidney Disease (Lupus Nephritis). Available at: https://www.niddk.nih.gov/health-information/kidney-disease/lupus-nephritis#:~:text=The%20symptoms%20of%20lupus%20nephritis%20may%20include%20foamy,face.%20You%20may%20also%20develop%20high%20blood%20pressure. Accessed February 5, 2021.
2) Lupkynis [new drug review]. IPD Analytics. Available at: https://secure.ipdanalytics.com/User/Pharma/RxStrategy/Search?q=Lupkynis. Accessed February 5, 2021.
3) Clinical Pharmacology [drug reference database]. Available at: https://www.clinicalkey.com/pharmacology/. Accessed February 5, 2021.
4) Lupkynis [package insert]. Rockville, MD: Aurinia Pharma U.S., Inc.; January 2021.
5) U.S. National Library of Medicine. [clinical trial] Aurinia Renal Response in Active Lupus with Voclosporin. Available at: https://clinicaltrials.gov/ct2/show/NCT03021499?term=NCT+03021499&draw=2&rank=1. Accessed February 5, 2021.

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