NEW DRUG APPROVAL

Brand Name	Lupkynis™
Generic Name	voclosporin
Drug Manufacturer	Aurinia Pharmaceuticals Inc.

New Drug Approval

FDA Approval Date: January 22, 2021

Review Designation: Priority

Type of Review: Type 1 - New Molecular Entity

Dispensing Restriction: Specialty Pharmacy

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that causes inflammation and organ damage throughout the body; patients commonly experience chronic fatigue, joint pain, skin rash, and swelling in the face and/or feet. SLE can cause damage to organs, such as the brain, lungs, and kidneys. It is estimated that systemic lupus erythematosus (SLE) affects up to 1.5 million people in the United States and up to 5 million people globally. Lupus nephritis (LN) is a type of kidney disease caused by SLE, and it affects approximately 40% of patients with SLE, with higher prevalence seen in non-Caucasians and those with childhood-onset SLE.

Lupus nephritis (LN) is a kidney disease that results as a complication of SLE. It affects approximately 50% of people at the time of SLE diagnosis. An additional 10%–20% of patients will develop LN during the first 10 years of an SLE diagnosis. About 10% of patients with LN will go on to develop end-stage renal disease (ESRD), so early diagnosis and treatment is key. Active LN is an indicator of poor prognosis with between 10% and 25% of patients developing end-stage renal disease (ESRD). Black and Hispanic patients are more likely to develop LN earlier, leading to outcomes such as ESRD and death.

There is increased prevalence of LN in poorer socioeconomic areas likely due to a lack of medical insurance and access to healthcare (e.g., emergency room care, rheumatology specialists).

NEW DRUG APPROVAL

Efficacy

The efficacy and safety of Lupkynis™ was evaluated in two randomized, controlled, double-blinded trials: AURA-LV (Phase 2) and AURORA (Phase 3). See Table 1 for a summary of the study designs and patient populations.

Table 1: AURA-LV (NCT02141672) and AURORA (NCT03021499): Study Design Summary

	AURA-LV	AURORA
Study Design	• Phase 2 randomized, controlled, double-blind	• Phase 3 randomized, controlled, double-blind
Study Population	• 265 participants 18 to 75 years of age with a diagnosis of SLE and kidney biopsy within 6 months with a histologic diagnosis of LN Classes III, IV, V, alone or in combination ○ Mean age = 31.7 years ○ Mean baseline urine protein creatine ratio (UPCR) = 4.69 ○ 86.8% female (n = 230) ○ 40% White (n = 108), 27% Asian (n = 72), 22% Asian-Indian subcontinent (n = 60), 5% Black (n = 14) • Class III, IV: UPCR ≥1.5 mg/mg • Class V: UPCR ≥2 mg/mg • eGFR ≤45 mL/min/1.73 m^2, those currently requiring dialysis, or those with previous kidney transplant or planned transplant were excluded from the study	• 357 participants 18 to 75 years of age with a diagnosis of SLE and kidney biopsy with a histologic diagnosis of LN Classes III, IV, V, alone or in combination ○ Mean age = 31 years ○ Mean baseline UPCR = 4 ○ 87.7% female (n = 313) ○ 36% White (n = 129), 30% Asian (n = 109), 20% mixed race (n = 74), 12% Black (n = 45) • Class III, IV: UPCR ≥1.5 mg/mg • Class V: UPCR ≥2 mg/mg • eGFR ≤45 mL/min/1.73 m^2 were excluded from the study
Interventions	• Low-dose voclosporin: 23.7 mg twice daily (n = 89), or • High-dose voclosporin: 23.7 mg twice daily for 2 weeks, then 39.5 mg twice daily (n = 88), or • Placebo (n = 88) • All participants received MMF 2 g/day and tapered low-dose oral corticosteroids	• Voclosporin 23.7 mg twice daily (n = 179), or placebo (n = 178) • All participants received MMF 2 g/day and tapered low-dose oral corticosteroids
Endpoints	• **Primary endpoint**: Complete renal remission (CRR) at Week 24, defined as: ○ UPCR ≤0.5 mg/mg, and ○ eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of ≥20% • **Secondary endpoint**: CRR at Week 48	• **Primary endpoint**: Renal response at Week 52, defined as: ○ UPCR ≤0.5 mg/mg, and ○ eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of ≥20% • **Secondary endpoints**: Renal response at Week 24, partial renal response at Week 24, Week 52, time to UPCR ≤0.5, time to 50% reduction in UPCR

NEW DRUG APPROVAL

Efficacy Results	• Both low-dose and high-dose voclosporin were superior to placebo with CRR at Week 24 (27%–32% voclosporin vs. 19% placebo) and Week 48 (39%–49% voclosporin vs. 24% placebo). • All participants receiving low-dose voclosporin and in remission at Week 24 sustained response to Week 48; 75% of participants in the high-dose group maintained their CRR at Week 48. • Participants in the voclosporin groups also saw earlier time to partial remission (≥50% decrease in UPCR and no use of rescue medications) and decrease in UPCR. • Participants with Class V LN did not show benefit with either dose of voclosporin.	• AURORA met its primary endpoint with 40.8% in the voclosporin group with renal response vs. 22.5% placebo group at Week 52 (OR 2.65; *P* <0.001). • Voclosporin also achieved all secondary endpoints (voclosporin vs. placebo): ○ Renal response at Week 24: 32.4% vs. 19.7% (odds ratio [OR] 2.23; *P* = 0.002) ○ Partial renal response at Week 24: 70.4% vs. 50% (OR 2.43; *P* <0.001) ○ Partial renal response at Week 52: 69.8% vs. 51.7% (OR 2.02; *P* <0.001) ○ Time to UPCR ≤0.5 (hazard ratio [HR] 2.02; *P* <0.001) ○ Time to 50% reduction in UPCR: (HR 2.05; *P* <0.001)
Safety Results	• Most adverse events (AEs) occurred in the first 24 weeks of the study; there were more AEs in the high-dose voclosporin group but more severe AEs in the low-dose voclosporin group, including 10 of the 13 deaths occurring in the study. • 11 of the 13 deaths that occurred were not due to study drug; these deaths occurred at study sites outside of the United States in patients with more severe disease, poor nutrition, and limited access to standard medical care.	• AEs were similar between groups (20.8% voclosporin vs. 21.3% placebo) with infection reported most in both groups (10.1% voclosporin vs. 11.2% placebo). • There were six deaths in the trial – one in the voclosporin group and five in the placebo group.

Source: Lupkynis Prescribing Information, NCT02141672, NCT03021499

Safety

ADVERSE EVENTS

The most commonly reported adverse reactions (≥3%) were glomerular filtration rate decreased, hypertension, diarrhea, headache, anemia, cough, urinary tract infection, abdominal pain upper, dyspepsia, alopecia, renal impairment, abdominal pain, mouth ulceration, fatigue, tremor, acute kidney injury, and decreased appetite.

WARNINGS & PRECAUTIONS

- Nephrotoxicity (acute and/or chronic): May occur due to Lupkynis™ or concomitant nephrotoxic drugs. Monitor renal function; consider dosage reduction.
- Hypertension: May require antihypertensive therapy; monitor relevant drug interactions.
- Neurotoxicity: Including risk of posterior reversible encephalopathy syndrome (PRES); monitor for neurologic abnormalities; reduce dosage or discontinue Lupkynis™.
- Hyperkalemia: Risk may be increased with other agents associated with hyperkalemia; monitor serum potassium levels.
- QT Prolongation: Consider obtaining electrocardiograms and monitoring electrolytes in patients at high risk.
- Immunizations: Avoid live vaccines.
- Pure Red Cell Aplasia: Consider discontinuation.

NEW DRUG APPROVAL

CONTRAINDICATIONS

- Patients concomitantly using strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin).
- Known serious or severe hypersensitivity reaction to Lupkynis™ or any of its excipients.

Clinical Pharmacology

MECHANISMS OF ACTION

Lupkynis™ is a calcineurin-inhibitor immunosuppressant. 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

Dose & Administration

ADULTS

23.7 mg orally, twice a day.

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Dosage adjustments of voclosporin are recommended based on eGFR. Assess eGFR at baseline, then every 2 weeks for the first month and every 4 weeks thereafter.

Patients with severe renal impairment: the recommended dose is 15.8 mg twice daily.

HEPATIC IMPAIRMENT

Mild and Moderate hepatic impairment (Child-Pugh A and Child-Pugh B): Reduce to 15.8 mg PO twice daily.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 7.9 mg