

Brand name: Lupkynis

Generic name: Voclosporin

Manufacturer: Aurinia Pharmaceuticals, Inc.¹

Drug class: Calcineurin-inhibitor, immunosuppressant^{1,2}

Uses:

Labeled, FDA approved uses: Active lupus nephritis, in combination with a background immunosuppressive therapy regimen^{1,2}

Unlabeled, non-FDA approved uses: None

Mechanism of action: Voclosporin is a known calcineurin-inhibitor, but the mechanism of this suppression has not been fully established; the 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 of voclosporin results in the inhibition of lymphocyte proliferation, T-cell cytokine production, and expression of T-cell activation surface antigens.¹

Pharmacokinetics^{1,2,3,4}:

T _{max}	1.5 hrs
V _d	2154 L
t _{1/2}	24.9 – 36.5 hrs
Clearance	63.6 L/hr
Protein binding	97%
Bioavailability	Not reported

Metabolism: Predominately metabolized by CYP3A4; voclosporin is the major circulating component and pharmacological activity is attributed to the parent molecule; the major metabolite in human blood represented 16.7% of total exposure and is about 8-fold less potent than the parent molecule¹

Elimination: Following single oral administration of radiolabeled voclosporin 70 mg, 92.7% of the radioactivity was recovered in feces (including 5% as unchanged voclosporin), and 2.1% was recovered in urine (including 0.25% as unchanged voclosporin).¹

Efficacy:

National Library of Medicine. Aurania Renal Response in Active Lupus with Voclosporin Trial. (2017, January 16 – 2019, November 20). Aurinia Pharmaceuticals, Inc. Identifier: NCT03021499.

Study design: A 52-week, randomized (1:1), double-blind, parallel, placebo-controlled trial
Description of study: Purpose: To assess the efficacy of voclosporin, added to the standard of care treatment, compared with placebo in achieving renal response after 52 weeks of therapy in

subjects with active lupus nephritis (LN). **Methods:** A total of 357 patients with LN were randomized to receive voclosporin 23.7 mg twice daily or placebo. Patients in both arms received background treatment with mycophenolate mofetil (MMF) and corticosteroids. Throughout the study, patients were prohibited from using immunosuppressants (other than MMF and hydroxychloroquine/chloroquine) and from changing/commencing ARBs or ACE inhibitors. Patients with baseline eGFR ≤ 45 mL/min/1.73 m² were not enrolled in this study. Dosage was adjusted based on eGFR and BP in a pre-defined dosage adjustment protocol. **Outcomes and Results:** The median age of patients was 31 years (range 18 to 72). The mean (SD) daily dose of voclosporin was 41.3 (± 9.7) mg/day. The primary efficacy endpoint was the proportion of patients achieving complete renal response at Week 52. A higher proportion of patients in the voclosporin arm than the placebo arm achieved complete renal response at Week 52. A higher proportion of patients in the voclosporin arm than the placebo arm achieved complete renal response at Week 24.

Limitations: This study was designed and conducted by Aurinia Pharmaceuticals, Inc., the manufacturer of voclosporin. This study has not yet been published and raw data is available only through the clinical trial summary and package insert, meaning methodology, baseline patient characteristics, and results cannot be fully summarized or analyzed. Additionally, patients that received rescue medication were removed from the study and considered non-responders; however, this is not reflective of clinical practice as rescue medications might be administered concomitantly.

Conclusion: This study showed that voclosporin, in combination with current standard of treatment, allowed patients to receive complete renal response in LN; this conclusion is evidenced by the higher proportion of patients in the voclosporin arm than the placebo arm achieved complete renal response at Week 24 (32.4% vs. 19.7%; odds ratio: 2.2; 95% CI: 1.3, 3.7). However, until this study is published with details including the full inclusion/exclusion criteria and baseline characteristics, these results should be interpreted with caution in clinical practice.

Rovin B, Solomons N, Pendergraft W, et al; AURA-LV Study Group. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis (AURA-LV Trial). *Kidney Int.* 2019;95(1):219-231.

Study design: A 48-week, randomized, multicenter, double-blind, placebo-controlled trial

Description of study: **Purpose:** To assess if the calcineurin inhibitor (CNI) voclosporin, when added to the standard treatment of care, increased complete renal remission (CRR) rates in patients with active lupus nephritis (LN). **Methods:** A total of 265 subjects (aged 18-75 years of age) from 79 centers in 20 countries were recruited and randomized to treatment for 48 weeks. Eligible subjects were randomized at baseline to receive low-dose voclosporin (VCS) (23.7 mg twice daily), high-dose VCS (39.5 mg twice daily) or low- or high-dose matched placebo in a ratio of 2:2:1:1 in combination with mycophenolate mofetil (2 g/d) and rapidly tapered low-dose oral corticosteroids for induction of remission in LN. The primary endpoint was CRR at 24 weeks; the secondary endpoint was CRR at 48 weeks. **Outcomes and results:** CRR at week 24 was achieved by 29 (32.6%) subjects in the low-dose voclosporin group, 24 (27.3%) subjects in the high-dose voclosporin group, and 17 (19.3%) subjects in the placebo group (OR 2.03 for low-dose voclosporin versus placebo). The significantly greater CRR rate in the low-dose voclosporin group persisted at 48 weeks, and CRRs were also significantly more common in the high-dose voclosporin group compared to placebo at 48 weeks. There were more serious adverse events in

both voclosporin groups, and more deaths in the low-dose group compared to placebo and high-dose voclosporin groups (11.2%, 1.1%, and 2.3%, respectively).⁵

Limitations: Several authors of this study did have affiliations with Aurinia Pharmaceuticals, the manufacturer of voclosporin. This study did have several differences in the baseline characteristics of study participants after randomization, including differences in sex and race of patients that could favor results in certain treatment groups.

Conclusion: The results of this study suggest that treatment with voclosporin, in addition to the current standard of care, results in an approved renal response; as evidenced by CRR achieved by 32.6% of subjects in the low-dose group (odds ratio [OR] 2.03; 95% CI: 1.01– 4.05; P = 0.046) and by 27.3% in the high-dose VCS group (OR 1.59; 95% CI: 0.78–3.27; P = 0.204) compared with 19.3% in the placebo group. However, this study found significant concerns for adverse events including death. The outcomes of death resulted very early during treatment and was noted with both the lower and higher doses of voclosporin but may be a result of imbalances in disease severity during randomization (a higher percent of patients in the low dose voclosporin arm had more severe disease at baseline). As a result, the decision to start voclosporin therapy must be carefully considered prior to initiation.

Contraindications: The concomitant use of strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, etc.) is contraindicated because these medications can significantly increase exposure to voclosporin, which may increase the risk of acute and/or chronic nephrotoxicity.¹ Additionally, voclosporin is contraindicated in patients who have severe hypersensitivity to voclosporin or any of its excipients.^{1,2}

Precautions:

Lymphoma and other malignancies: Immunosuppressants, including voclosporin, are known to increase the risk of developing lymphomas and skin malignancies. This risk increases based on the intensity and duration of treatment; it is advised to examine patients for skin changes during treatment with voclosporin.^{1,3}

Serious infections: Immunosuppressants, including voclosporin, increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious or fatal outcomes; it is recommended to monitor for development of infection during treatment with voclosporin.^{1,3}

Nephrotoxicity: Calcineurin-inhibitors, including voclosporin, can cause acute and/or chronic nephrotoxicity. During treatment, monitor eGFR regularly and consider dose reduction or discontinuation in patients with decreased eGFR from baseline. It is encouraged to avoid administering concomitant drugs with a known risk of nephrotoxicity.^{1,2,3}

Hypertension: A common adverse effect of treatment with voclosporin is hypertension and patients may require antihypertensive medications during therapy. Monitor blood pressure regularly during therapy and treat new-onset hypertension exacerbations and pre-existing hypertension.^{1,2,3}

Neurotoxicity: Like other calcineurin-inhibitors, voclosporin may cause a spectrum of neurotoxicity, including posterior reversible encephalopathy syndrome, delirium, seizure, and coma. Monitor for these symptoms and consider dosage reduction or discontinuation if neurotoxicity occurs.^{1,2,3}

Hyperkalemia: During treatment with voclosporin, hyperkalemia has been reported, especially in combination with other agents that increase this risk (potassium-sparing diuretics, ACE/ARB inhibitors, etc.); monitor serum potassium periodically during treatment.^{1,2,3}

QTc prolongation: Voclosporin prolongs the QTc interval in a dose-dependent manner after single dose administration at a higher than therapeutic dose; the use of voclosporin in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.^{1,2}

Live attenuated immunizations: Avoid the use of live attenuated vaccines during treatment with voclosporin (intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).¹

Pure red cell aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another calcineurin-inhibitor immunosuppressant; this was not seen during treatment with voclosporin in clinical trials but should be monitored for during therapy.¹

Adverse effects^{1,2,3,4:}

Common, occurring in $\geq 10\%$ of patients:

Cardiovascular:

Hypertension (19%)

Gastrointestinal:

Diarrhea (19%)

Hematologic:

Anemia (12%)

Immunologic:

Infectious disease (62%)

Serious infectious disease (10.1%)

Neurologic:

Headache (15%)

Migraine (62%)

Renal:

Decreased creatine clearance (26-31%)

Urinary tract infections (10%)

Respiratory:

Cough (11%)

Rare but serious, occurring in $< 10\%$ of patients:

Cardiovascular:

Hypertension, serious (1.9%)

Endocrine:

Hyperkalemia (1.9%)

Immunologic:

Opportunistic infection (1.1%)

Neurologic:

Serious migraine (3.4%)

Posterior reversible encephalopathy (incidence not reported)

Seizure (incidence not reported)

Renal:

Acute kidney injury (3%)
Kidney disease (9.7%)
Serious kidney disease (4.9%)
Renal impairment (6%)

Other:

Cancer (1.5%)

Drug interactions^{1,2,4}:

Strong and moderate CYP3A4 inhibitors: Co-administration will increase the concentration of voclosporin and will significantly increase the risk of nephrotoxicity; use with strong inhibitors is contraindicated, and dose reductions should be made when used with moderate inhibitors. Additionally, avoid grapefruit juice while taking voclosporin.

Strong and moderate CYP3A4 inducers: Co-administration will decrease exposure and decrease efficacy of voclosporin.

Certain P-gp substrates: Voclosporin is a P-gp inhibitor; co-administration will increase exposure of these substrates and possible adverse events.

OATP1B1 substrates: The effect of voclosporin on OATP1B1 substrates (such as statins) has not been studied clinically but information suggests an increase in the concentration of these substrates is possible. It is recommended to monitor for adverse reactions during co-administration with voclosporin.

Dosing/administration^{1,2,3,4}:

Usual dose: Establish an accurate baseline eGFR and blood pressure prior to initiation. Do not initiate treatment in patient with blood pressure greater than 165/105 mmHg or with hypertensive emergency. Use not recommended with baseline eGFR of 45 mL/min/1.73m² or less unless benefit outweighs risk. Discontinuation should be considered if no benefit is seen by 24 weeks of treatment.

Initial dose: 23.7 mg (3 capsules) orally twice daily on an empty stomach

Assess estimated GFR (eGFR) every 2 weeks for first month and every 4 weeks thereafter and modify dosage based on eGFR as needed.

Renal impairment doses:

Baseline eGFR 45 mL/minute/1.73 m² or less:

Voclosporin has not been studied in this patient population; use is not recommended unless benefit exceeds increased risk for acute or chronic nephrotoxicity. If a decision is made to initiate therapy, the recommended starting dose is 15.8 mg by mouth twice daily.

Dose Adjustments After Therapy Initiation:

If eGFR less than 60 mL/minute/1.73 m² and reduced by more than 20% and less than 30% from baseline:

Reduce dose by 7.9 mg twice a day; reassess eGFR within 2 weeks. If eGFR still reduced from baseline by more than 20%, then reduce dose again by 7.9 mg twice a day.

If eGFR less than 60 mL/minute/1.73 m² and reduced by 30% or more from baseline:

Discontinue voclosporin. Reassess eGFR within 2 weeks. If eGFR has returned to 80% or more of baseline, then may consider restarting voclosporin at 7.9 mg twice daily.

Hepatic impairment dose: In patients with mild and moderate hepatic impairment, the recommended dose is 15.8 mg twice daily.

Use in special circumstances:

Pregnancy: Avoid use in pregnant women due to the alcohol content of the drug formulation.¹

Lactation: Advise against breastfeeding during voclosporin therapy and for at least 7-days after the last dose of voclosporin.¹

Pediatric use: The safety and efficacy of voclosporin in pediatric patients has not been established.¹

Geriatric use: Voclosporin clinical trials did not include a sufficient number of patients aged 65 years and older; in general, dose selection for elderly patients should be cautious and started at the lower end reflecting decreased hepatic and renal function.¹

Overdosage: Accidental overdose has been reported with voclosporin therapy and symptoms include tremor, headache, nausea, and vomiting, infections, tachycardia, urticaria, lethargy, and increases in blood urea nitrogen, serum creatine, and aminotransferase levels. If overdose occurs, treatment includes general supportive measures and symptomatic treatment; contact a medical toxicologist for specific overdose management recommendations.¹

Conclusion: Lupkynis (voclosporin) is an effective treatment for active lupus nephritis, (LN) in combination with a background immunosuppressive therapy regimen. Clinical studies have shown that voclosporin, in combination with current standard of treatment, allowed patients to receive complete renal response in LN. However, more studies need to be completed as there is no data to support the use or document adverse effects beyond 1-year of therapy. Voclosporin has a considerable risk of both common and rare, but serious events. As a result, the decision to start voclosporin therapy must be carefully considered prior to initiation. If treatment is initiated, dosage should be adjusted according to careful monitoring of eGFR. Overall, Lupkynis (voclosporin) is an effective treatment option for patients with active lupus nephritis but patients should be monitored for development of serious adverse events including serious infections, renal toxicity, and hypertension.

References:

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3. National Library of Medicine. Aurinia Renal Response in Active Lupus with Voclosporin (AURORA) Trial. (2017, January 16 – 2019, November 20). Aurinia Pharmaceuticals, Inc. Identifier: NCT03021499.
4. Voclosporin, Drug Monograph. Clinical Pharmacology [electronic database]. Accessed March 3, 2021.
5. Rovin B, Solomons N, Pendergraft W, et al; AURA-LV Study Group. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis (AURA-LV Trial). *Kidney Int*. 2019;95(1):219-231.

6. Voclosporin (Lexi-Drugs). In: Dosing, Patient & Therapy Management. Lexicomp [electronic database]. Wolters Kluwer. Accessed March 3, 2021.
7. U.S. Food & Drug Administration. Drug trials snapshot: Lupkynis. Updated February 10, 2021.

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