PDL DRUG REVIEW

Proprietary Name: Lupkynis®
Common Name: voclosporin
PDL Category: SLE Agents

Comparable Products	Preferred Drug List Status
Benlysta	Non-Preferred

Summary

Pharmacology/Usage: Voclosporin, the active ingredient of Lupkynis®, is a calcineurin-inhibitor immunosuppressant. The mechanism of action 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.

Indication: In combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN). The safety and efficacy of Lupkynis® have not been established in combination with cyclophosphamide. Use of Lupkynis® is not recommended in this situation.

There is no pregnancy category for this product; however, the risk summary indicates to avoid use of Lupkynis® in pregnant women due to the alcohol content of the drug formulation. The available data on use in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with systemic lupus erythematosus (SLE). The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Capsules: 7.9mg. Inactive ingredients include alcohol.

Swallow capsules whole; do not open, crush, or divide.

Recommended Dosage: Prior to starting treatment:

- Establish an accurate baseline estimated glomerular filtration rate (eGFR). Use of Lupkynis® is not recommended in patients with a baseline eGFR ≤45ml/min/1.73m^2 unless the benefit exceeds the risk. These patients may be at increased risk for acute and/or chronic nephrotoxicity.
- Check blood pressure at baseline. Do not start treatment in patients with BP >165/105mmHg or with hypertensive emergency. Then, monitor BP every 2 weeks for the first month after initiating Lupkynis®, and

as clinically indicated thereafter. For patients with BP >165/105mmHg or with hypertensive emergency, discontinue Lupkynis® and start antihypertensive therapy.

Take 23.7mg PO BID on an empty stomach consistently as close to a 12-hour scheduled as possible in combination with mycophenolate mofetil (MMF) and corticosteroids. Avoid eating grapefruit or drinking grapefruit juice while taking Lupkynis®. If a dose is missed, take the missed dose as soon as possible within 4 hours after missing the dose. Beyond the 4-hour time frame, wait until the usual scheduled time to take the next regular dose. Do not double the next dose. If the patient does not experience therapeutic benefit by 24 weeks, consider discontinuation of Lupkynis®. Safety and efficacy have not been established beyond one year. Consider the risks and benefits of longer durations of treatment in light of the patient's treatment response and risk of worsening nephrotoxicity.

Modify Lupkynis® dosage based on eGFR:

- Assess eGFR every 2 weeks for the first month, and then every 4 weeks thereafter.
- If eGFR <60ml/min/1.73m^2 and reduced from baseline by >20% and <30%, reduce the dose by 7.9mg BID. Re-assess eGFR within 2 weeks; if eGFR is still reduced from baseline by >20%, reduce the dose again by 7.9mg BID.
- If eGFR <60ml/min/1.73m^2 and reduced from baseline by ≥30%, discontinue Lupkynis®. Re-assess eGFR within 2 weeks; consider restarting Lupkynis at a lower dose (7.9mg BID) 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 7.9mg BID for each eGFR measurement that is ≥80% of baseline; do not exceed the starting dose.

As discussed above, the use of Lupkynis® is not recommended in patients with a baseline eGFR ≤45ml/min/1.73m^2 unless the benefit exceeds the risk. If used in patients with severe renal impairment at baseline, the recommended starting dose is 15.8mg BID. In patients with mild and moderate hepatic impairment, the recommended dose is 15.8mg BID. Lupkynis® is not recommended to be used in patients with severe hepatic impairment.

Drug Interactions: 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 (e.g. ketoconazole, itraconazole, clarithromycin) is contraindicated. Reduce Lupkynis® dosage when co-administered with moderate CYP3A4 inhibitors (e.g. verapamil, fluconazole, diltiazem). Reduce the Lupkynis® dose to 15.8mg QAM and 7.9mg QPM. Avoid food or drink containing grapefruit when taking Lupkynis®.

Voclosporin is a sensitive CYP3A4 substrate. Co-administration with strong or moderate CYP3A4 inducers decreases voclosporin exposure, which may decrease the efficacy of Lupkynis®. Avoid the co-administration of Lupkynis® with strong or moderate CYP3A4 inducers.

Voclosporin is a P-gp inhibitor. Co-administration of voclosporin increases exposure of P-gp substrates. For certain P-gp substrates with a narrow therapeutic window, reduce the dosage of the substrate as recommended in its prescribing information, if needed.

The effect of Lupkynis® on OATP1B1 substrates (e.g. statins) has not been studied clinically. However, voclosporin is an OATP1B1 inhibitor in vitro and information suggests an increase in the concentration of these substrates is possible. Thus, monitor for adverse reactions of OATP1B1 substrates when used concomitantly with Lupkynis®.

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). Inactivated vaccines noted to be safe for administration may not be sufficiently immunogenic during treatment with Lupkynis®.

Box Warning: Lupkynis® has a box warning regarding malignancies and serious infections. The warning notes that there is an increased risk for developing malignancies and serious infections with Lupkynis® or other immunosuppressants that may lead to hospitalization or death.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Lupkynis®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included glomerular filtration rate decreased (15%), hypertension (10%), diarrhea (6%), headache (7%), anemia (6%), cough (9%), urinary tract infection (4%), abdominal pain upper (5%), dyspepsia (3%), alopecia (3%), renal impairment (3%), abdominal pain (3%), mouth ulceration (3%), fatigue (3%), tremor (2%), acute kidney injury (2%), and decreased appetite (2%).

Immunosuppressants, including Lupkynis®, increase the risk of developing lymphomas and malignancies, especially of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Assess patients for skin changes and advise to avoid or limit sun exposure and to avoid artificial light by wearing protective clothing and using a broad spectrum sunscreen with a high protection factor (SPF 30 or higher).

Immunosuppressants, including Lupkynis®, increase the risk of developing bacterial, viral, fungal, and protozoal infections. These infections may lead to serious, including fatal, outcomes. Monitor for the development of infection. Consider the risks and benefits for the individual patient, and use the lowest effective dose needed to maintain response.

Lupkynis®, like other calcineurin-inhibitors, can cause acute and/or chronic nephrotoxicity. Monitor eGFR regularly during treatment and consider dose reduction or discontinuation in patients with decreases in eGFR from baseline. Consider risks and benefits of Lupkynis® treatment in light of the patient's treatment response and risk of worsening nephrotoxicity, including in the following situations:

- Longer treatment duration beyond one year. Safety and efficacy of Lupkynis® have not been established beyond one year
- Coadministration with drugs associated with nephrotoxicity. The risk for acute and/or chronic nephrotoxicity is increased when Lupkynis® is concomitantly administered with drugs associated with nephrotoxicity.

Hypertension is a common adverse reaction of Lupkynis® therapy and may require antihypertensive therapy. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension.

Lupkynis®, like other calcineurin-inhibitors, may cause a spectrum of neurotoxicities. Monitor for neurologic symptoms and consider dosage reduction or discontinuation of Lupkynis® if neurotoxicity occurs.

Hyperkalemia, which may be serious and require treatment, has been reported with calcineurin-inhibitors including Lupkynis®. Concomitant use of agents associated with hyperkalemia (e.g. potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) may increase the risk for hyperkalemia. Monitor serum potassium levels periodically during treatment.

Lupkynis® prolongs the QTc interval in a dose-dependent manner after single dose administration at a dose higher than the recommended lupus nephritis therapeutic dose. The use of Lupkynis® in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including bradycardia; hypokalemia or hypomagnesemia; concomitant use of other drugs that prolong the QTc interval; and the presence of congenital prolongation of the QT interval.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another calcineurin-inhibitor immunosuppressant. All of these patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. If PRCA is diagnosed, consider discontinuation of Lupkynis®.

Contraindications: In patients

- Concomitantly using strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin)
- Who have had a known serious or severe hypersensitivity reaction to the Lupkynis® or any of its excipients

Manufacturer: Aurinia Pharma US, Inc

Analysis: The safety and efficacy of Lupkynis® were assessed in a 52-week, randomized, double-blind, placebo-controlled study that included adults (N=357) diagnosed with systemic lupus erythematosus and with International Society of Nephrology/Renal Pathology Society (ISN/RPS) biopsy-proven active Class III or IV lupus nephritis (LN) (alone or in combination with Class V LN) or Class V LN. Patients with Class III or IV LN (alone or in combination with Class V LN) were required to have a urine protein to creatinine (UPCR) ratio of ≥1.5mg/mg; patients with Class V LN were required to have a UPCR of ≥2mg/mg.

Patients were randomized to receive Lupkynis® 23.7mg BID or placebo and in both arms received background treatment with MMF (oral at a target dose of 2g/day) and corticosteroids (IV followed by a reducing taper of oral). Throughout the study, patients were prohibited from using immunosuppressants (other than MMF and hydroxychloroquine/chloroquine) and from changing/commencing angiotensin II receptor blockers (ARBS) or angiotensin converting enzyme (ACE) inhibitors. The median age of included adults was 31 years (range 18 to 72), while most were women (88%). The distribution by kidney biopsy class was Class III or IV (60.8%), Class III or IV in combination with Class V (24.9%), and Class V (14.3%). Mean eGFR upon entry was 91ml/min/1.73m^2 and mean UPCR on entry was 4mg/mg.

The primary endpoint was the proportion of patients achieving complete renal response at week 52. Complete renal response was defined as follows (and both must be met):

- UPCR of ≤0.5mg/mg, and
- eGFR ≥60ml/min/1.73m^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.

In order to be considered a responder, the patient must not have received more than 10mg 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.

Results suggested that a significantly higher proportion of patients in the Lupkynis® arm than in the placebo arm achieved complete renal response at week 52. Results can be seen in the table below, which was adapted from the prescribing information.

Endpoints	Lupkynis® (N=179)	Placebo (N=178)	Odds Ratio
Primary Endpoint			
Complete Renal Response at week 52, [n (%)]	73 (40.8%)	40 (22.5%)	2.7; p<0.001
Components of the Primary Endpoint			
UPCR ≤0.5mg/mg, [n (%)]	81 (45.3%)	41 (23.0%)	3.1
eGFR ≥60ml/min/1.73m^2 or no confirmed ↓ from baseline in eGFR of >20% or no treatment- or disease-related eGFR-associated AE, [n (%)]	147 (82.1%)	135 (75.8%)	1.5

A higher proportion of patients in the Lupkynis® arm than placebo arm achieved complete renal response at week 24 (32.4% vs 19.7%; OR 2.2). Time to UPCR of ≤0.5mg/mg was shorter in the Lupkynis® arm than the placebo arm (median time of 169 days vs 372 days; HR 2.0).

Place in Therapy: Lupkynis®, an oral calcineurin-inhibitor immunosuppressant, is indicated in combination with a background immunosuppressive therapy regimen (mycophenolate mofetil [MMF] and corticosteroids) for the treatment of adults with active lupus nephritis. The safety and efficacy of Lupkynis® have not been established in combination with cyclophosphamide. Use of Lupkynis® is not recommended in this situation. A baseline eGFR must be established before the start of treatment and use is not recommended in patients with a baseline eGFR ≤45ml/min/1.73m^2. In addition, blood pressure must be checked at baseline and treatment should not be started in patients with BP >165/105mmHg or with hypertensive emergency.

In the randomized, double-blind clinical trial assessing the safety and efficacy of Lupkynis®, a significantly higher proportion of patients in the Lupkynis®/MMF/corticosteroid arm than the placebo/MMF/corticosteroid arm achieved complete renal response at week 52. Other comparator studies were not found.

While in one phase 3 study the combination of Lupkynis® plus MMF/corticosteroids was significantly more effective than MMF/corticosteroids for the primary endpoint of achieving complete renal response, there is no evidence at this time to suggest that Lupkynis® is safer or more effective than the other medications. It is recommended that Lupkynis® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Lupkynis [package insert]. Rockville, MD: Aurinia Pharma US, Inc; 2021.