Prescribing Information (UNITED KINGDOM)

Lupkynis ▼ (voclosporin) 7.9 mg soft capsules

Please refer to the full Summary of Product Characteristics (SmPC) before prescribing.

Indication: Lupkynis is indicated in combination with mycophenolate mofetil (MMF) for the treatment of adult patients with active class III, IV or V (including mixed class III/V and IV/V) lupus nephritis (LN). **Dose:** The recommended dose is 23.7 mg (three 7.9 mg soft capsules), twice daily. **Method of administration:** Lupkynis treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of lupus nephritis. Oral use. The soft capsules must be swallowed whole and can be taken with or without food. It is recommended not to take Lupkynis with grapefruit or grapefruit juice. Lupkynis should be used in combination with MMF. Physicians should evaluate the efficacy of treatment at a time point of at least 24 weeks and make an appropriate risk-benefit analysis for continuation of therapy. ***Dose adjustment based on eGFR*:** It is recommended to establish a baseline estimated glomerular filtration rate (eGFR) before starting treatment, and assess every two weeks for the first month, and every four weeks thereafter. If eGFR remains ≥ 60 mL/min/1.73 m^2 no dose modification is required. If reduced eGFR (i.e. two consecutive assessments within 48 hours) and below 60 mL/min/1.73 m^2, dose adjustment is required. At a ≥ 30% reduction from baseline in eGFR, stop treatment. Restart upon eGFR recovery at 7.9 mg (1 capsule) twice daily and increase as tolerated based on renal function. At a > 20% and < 30% reduction, reduce dose by 7.9 mg (1 capsule) twice daily. Retest within two weeks; if eGFR decrease has not recovered, reduce dose by further 7.9 mg (one capsule) twice daily. At ≤ 20% reduction, maintain current dose and monitor. Patients requiring dose reduction should be reassessed for eGFR recovery within two weeks. For patients that had a decrease in dose due to eGFR reduction, consider increasing the dose by 7.9 mg twice a day for each eGFR measurement that is ≥ 80% of baseline; do not exceed starting dose. ***Co-administration with moderate cytochrome P450 (CYP)3A4 inhibitors:*** (e.g., verapamil, fluconazole, diltiazem), reduce dose to 15.8 mg in the morning and 7.9 mg in the evening. ***Hepatic impairment:*** In patients with mild and moderate hepatic impairment (Child-Pugh Class A and B, respectively), the recommended starting dose is 15.8 mg twice daily. The effect of Lupkynis in patients with severe hepatic impairment (Child-Pugh Class C) has not been assessed and so Lupkynis is not recommended. ***Renal impairment:*** Careful monitoring of renal function is recommended. In patients with baseline eGFR 30 to < 45 mL/min/1.73 m^2, it is recommended to use Lupkynis only if the benefit outweighs the risk, and at a starting dose of 23.7 mg twice daily. Lupkynis has not been studied in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and is not recommended unless the benefit outweighs the risk. If used, the recommended starting dose is 15.8 mg twice daily. ***Elderly:*** Data are limited in LN patients > 65 years, and there are no data in patients aged > 75 years. Lupkynis is not recommended in patients > 75 years of age. ***Paediatric population:*** The safety and efficacy of Lupkynis in children and adolescents aged 5 to 18 years have not yet been established. No data are available. There is no relevant use of Lupkynis in children below the age of 5 years in lupus nephritis.

Contraindications: Hypersensitivity to active substance or excipients. Co-administration with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin). **Special warnings and precautions:** Immunosuppressants increase the risk of developing ***lymphomas and other malignancies***, particularly of the skin. Patients should avoid or limit unprotected exposure to sunlight and UV light. ***Serious infections*:** Immunosuppressants, may increase the risk of bacterial, viral, fungal, and protozoal infections, including serious or fatal opportunistic infections. Monitor closely for infections during treatment. If an infection occurs, assess the benefit-risk of continuing Lupkynis. ***Renal toxicity*:** As with other calcineurin-inhibitors, acute worsening of renal function or eGFR decreases have been seen in patients treated with Lupkynis. In the first four weeks of treatment, haemodynamic reductions in eGFR have been observed. This can be managed by dose adjustments. Monitor eGFR regularly. Cases of ***pure red cell aplasia*** (PRCA) have been reported in patients treated with a different calcineurin inhibitor. All of these patients had risk factors for PRCA, such as a parvovirus B19 infection, a primary disease or concomitant treatments associated with PRCA. If PRCA is diagnosed, consider discontinuation of Lupkynis. ***Hyperkalaemia***, which may be serious and require treatment, has been reported with calcineurin inhibitors, including Lupkynis. Concomitant use of medicinal products associated with hyperkalaemia (e.g., potassium-sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers) may increase the risk of hyperkalaemia. Monitor serum potassium levels periodically during treatment. Lupkynis can cause or worsen systemic ***hypertension***. Monitor blood pressure every two weeks for the first month after initiating treatment, and as clinically indicated thereafter. In the event of clinically concerning elevated blood pressure, please consult the SmPC for recommendations for management of hypertension. ***QT prolongation:*** The use of Lupkynis in combination with other medicinal products 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 medicinal products that prolong the QTc interval, including bradycardia; hypokalaemia or hypomagnesaemia; concomitant use of other medicinal products that prolong the QTc interval; and the presence of congenital prolongation of the QT interval. ***Neurotoxicity:*** Patients receiving immunosuppressive therapies, including Lupkynis, are at increased risk of neurotoxicity. Patients should be monitored for new-onset or worsening of neurological symptoms; reduction or discontinuation of Lupkynis should be considered if these occur. ***Vaccination:*** Immunosuppressants may affect the response to vaccination, and vaccination during treatment with Lupkynis may be less effective. The use of live attenuated vaccines should be avoided. ***Concomitant use with other medicinal products:*** Co-administration of Lupkynis with moderate or strong CYP3A4 inducers is not recommended. The safety and efficacy of Lupkynis have not been established in combination with cyclophosphamide. ***Excipients: Ethanol:*** This medicinal product contains a small amount alcohol and will not have any noticeable effects. ***Sorbitol:*** This medicinal product contains sorbitol. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. ***Soya lecithin (potential residue from manufacturing process):*** This medicinal product may contain trace amounts of soya lecithin. Patients who have experienced anaphylactic reactions to soya or peanut, must not use this medicinal product. **Interaction with other medicinal products and other forms of interaction:** Lupkynis is metabolised by CYP3A4 and is an inhibitor of P-glycoprotein (P-gp) and organic-anion-transporting polypeptide (OATP)1B1 and OATP1B3. ***Potential to affect Lupkynis exposure*: *CYP3A4 inhibitors:*** Co-administration of Lupkynis with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is contraindicated. Reduce the dose to 15.8 mg in the morning and 7.9 mg in the evening when co-administered with moderate CYP3A4 inhibitors (e.g., verapamil, fluconazole, erythromycin, diltiazem, grapefruit,grapefruit juice). Mild CYP3A4 inhibitors may increase Lupkynis exposure, but no in vivo study has been performed. No dose adjustment is required when Lupkynis is co-administered with mild CYP3A4 inhibitors but additional monitoring of eGFR is recommended when initiating a mild CYP3A4 inhibitor. ***CYP3A4 inducers:*** Strong and moderate CYP3A4 inducers (e.g., carbamazepine, phenobarbital, rifampicin, St John's Wort, efavirenz) are not recommended to be dosed concomitantly with Lupkynis. Mild inducers of CYP3A4 may result in decreased exposure and effect, but the clinical relevance is unknown. ***Potential for Lupkynis to affect exposure to other medicinal products*. *P-gp substrates:*** Lupkynis is an inhibitor of P-gp. Concomitant administration of Lupkynis with multiple doses of digoxin increased digoxin exposure. Caution must be exercised in case of co-administration of Lupkynis with sensitive P-gp substrates, especially those with narrow therapeutic index (e.g., digoxin, dabigatran etexilate, fexofenadine) and monitor patients as outlined in respective product labelling. ***OATP1B1/OATP1B3 substrates:*** Lupkynis is an OATP1B1/OATP1B3 inhibitor. Lupkynis increased the exposure of simvastatin and the active metabolite simvastatin acid. Monitor patients for adverse events such as myopathy and rhabdomyolysis when OATP1B1/OATP1B3 substrates (e.g., simvastatin, atorvastatin, pravastatin, rosuvastatin) are used concomitantly with Lupkynis. ***BCRP substrates:*** Lupkynis inhibits breast cancer resistance protein (BCRP) *in vitro*. A clinically relevant inhibition of intestinal BCRP cannot be excluded and Lupkynis may increase the concentration of these substrates *in vivo*. Monitor use of BCRP substrates where small concentration changes may lead to serious toxicity (e.g., rosuvastatin) when used concomitantly with Lupkynis. ***MMF:*** Co-administration of Lupkynis with MMF had no clinically significant impact on mycophenolic acid blood concentrations. ***CYP3A4 substrates:*** Multiple administrations of Lupkynis orally (0.4 mg/kg twice daily) had no clinically relevant effect on the pharmacokinetics of the sensitive CYP3A4 substrate midazolam. **Pregnancy:** No or limited data

from the use of Lupkynis in pregnant women. Animal studies have shown reproductive toxicity. Lupkynis is not recommended during pregnancy and in women of childbearing potential not using contraception. **Breast-feeding:** In a study in 12 lactating subjects, the highest estimated voclosporin dose ingested by a fully breastfed infant was 1.4% of maternal weight-adjusted dose. The effect of voclosporin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Lupkynis therapy considering the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Fertility:** No data on the effect on human fertility. In animal studies, Lupkynis-related changes in the male reproductive tract were observed. **Summary of the safety profile:** The most frequently reported adverse reactions with use of Lupkynis are decreased eGFR (26.2%) and hypertension (19.1%). The most frequently reported serious adverse reactions were infections (10.1%), acute kidney injury (3%) and hypertension (1.9%). In the first 4 weeks of treatment with Lupkynis, haemodynamic reductions in eGFR are commonly experienced, which subsequently stabilise, even if treatment is continued. Adverse events reported during clinical trials are as follows, where the frequency is defined as: very common, ≥1/10; common, ≥ 1/100 to <1/10. ***Very common:*** upper respiratory tract infection, anaemia, headache, hypertension, cough, diarrhoea, abdominal pain and decreased glomerular filtration rate. ***Common:*** pneumonia, influenza, herpes zoster, gastroenteritis, urinary tract infection, hyperkalaemia, decreased appetite, seizure, tremor, nausea, gingival hyperplasia, dyspepsia, mouth ulceration, alopecia, hypertrichosis, acute kidney disease, acute kidney injury and fatigue. ***Serious adverse reactions*** reported during clinical trials are pneumonia, gastroenteritis, urinary tract infection, serious opportunistic infections, fatal infections, renal toxicity (including decreased eGFR, renal impairment, acute kidney injury, hyperkalaemia) and serious hypertension. Prescribers should consult the SmPC for other adverse reactions. **Overdose:** Cases of accidental overdose have been reported with Lupkynis; symptoms included tremor and tachycardia. Symptoms of overdose with other calcineurin inhibitors (but not observed with Lupkynis) include headache, nausea and vomiting, infections, urticaria, lethargy, changes in electrolyte levels and increases in blood urea nitrogen, and alanine aminotransferase. No specific antidote to Lupkynis therapy is available. If overdose occurs, general supportive measures and symptomatic treatment should be conducted, including temporarily stopping Lupkynis and assessing blood urea nitrogen, serum creatinine, eGFR and alanine aminotransferase levels. **Legal Classification:** Prescription Only Medicine (POM) **Basic NHS price:** Lupkynis capsules: 7.9mg soft capsule, 180 pack size=£1000. **Marketing Authorisation (MA) number:** PLGB 50697/0032

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Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search MHRA Yellow Card in Google Play or the Apple App store.

Adverse events should also be reported to Otsuka Pharmaceuticals (UK) Ltd. by email to OPUKSafety@otsuka.co.uk or by calling 0808 168 6726